8ª GIORNATA DELLO SPECIALIZZANDO IN NEUROLOGIA

Università del Piemonte Orientale
Università Vita - Salute San Raffaele
Università degli Studi di Udine
ALMA MATER STUDIORUM Università di Bologna
Università degli Studi di Torino
Università degli Studi di Brescia
Università degli Studi di Padova
Università degli Studi di Ferrara
Università degli Studi di Genova
Università degli Studi di Pavia
Università degli Studi di Verona
UNIMORE Università degli Studi di Modena e Reggio Emilia
Università degli Studi di Trieste
Università dell'Insubria
Università degli Studi di Parma
Università degli Studi di Milano Bicocca

Università degli Studi di Milano
Università degli Studi di Chieti
Università degli Studi di Pisa
Università degli Studi di Firenze
Università degli Studi di Roma "Tor Vergata"
Università dell'Aquila
Università di Roma "La Sapienza"
Università degli Studi di Perugia
Università Campus Biomedico di Roma
Università degli Studi di Siena
Università Politecnica delle Marche
UNIVERSITÀ CATTOLICA del Sacro Cuore
UNIVERSITÀ degli STUDI di CATANIA

Università degli Studi di Bari
Università degli Studi di Catanzaro
Università degli Studi di Napoli Federico II
Università degli Studi di Palermo
Università degli Studi di Cagliari
Università degli Studi di Messina
Università della Campania Luigi Vanvitelli
Università degli Studi di Salerno

MILANO ROMA CATANIA

11 giugno 2019

Prefazione

Le Scuole di Specializzazione in Neurologia dell'Università degli Studi di Milano, dell'Università Cattolica di Roma e dell'Università degli Studi di Catania, nelle loro rispettive sedi, organizzano l'**11 giugno 2019** l'**8ª Giornata dello Specializzando in Neurologia**. Partecipano all'evento anche le 16 Scuole di Specializzazione del Nord, le 10 del Centro e le 8 del Sud Italia. La giornata dello Specializzando è realizzata grazie al supporto e patrocinio della Società Italiana di Neurologia (SIN).

Scopo di questa 8ª giornata, ormai a carattere nazionale e in continuità con le precedenti edizioni, è quello di porre al centro dell'incontro lo Specializzando, indipendentemente dall'anno di corso, attraverso la presentazione dei risultati delle sue ricerche di base o cliniche nei diversi filoni della Neurologia, con la formula della "Comunicazione orale", " Flash Poster", "Poster" o "Hot Topics" ovvero sessioni interattive per promuovere lo scambio e la partecipazione attiva degli Specializzandi.

La giornata è introdotta, nelle tre sedi, da Letture Magistrali tenute da Professori delle Scuole di Specializzazione su tematiche particolarmente interessanti ed innovative della Neurologia.

L'auspicio è che questa 8ª giornata degli Specializzandi di Neurologia delle Università italiane possa rappresentare un modello di efficienza ed eccellenza clinico-didattica e illustri un percorso che, coniugando la ricerca clinica e di base con la moderna medicina translazionale, mantenga sempre come cardine l'alta formazione didattica e clinica presente nelle nostre Scuole di Specializzazione.

Cordialmente

Prof. Giovanni Meola

Direttore della Scuola di Specializzazione in Neurologia dell'Università degli Studi di Milano

Coordinatore Nazionale della 8ª Giornata dello Specializzando in Neurologia

9.30 Registrazione dei partecipanti

10.00 Introduzione
G. Meola *(Milano)*
G. Mancardi *(Genova)*

10.10 Saluto del Magnifico Rettore Prof. Elio Franzini

10.20 **Lettura Magistrale**
La diagnosi della Malattia di Alzheimer: dalla ricerca alla pratica clinica
Moderatore: N. Bresolin *(Milano)*
C. Ferrarese *(Milano)*

11.00-13.30
Sessione di comunicazioni orali
Moderatori: M. Filippi *(Milano)* - A. Schenone *(Genova)*

11.00 **Features, frequency, short and long term outcome of recurrent TIA: a prospective observational cohort study**
Matteo Foschi, L. Pavolucci, A. Amato, E. Favaretto, L. Spinardi, F. Rondelli, D. Degli Esposito , M. Filippini, P. Cortelli, M. Guarino *(Bologna, Ravenna)*

11.15 **Maneuvering Between Scylla and Charybdis, management of antithrombotic therapy in thrombocytopenic patients with ischemic stroke**
Matteo Grazzini, C. Finocchi, M. Bandettini, M. Balestrino *(Genova)*

11.30 **Longitudinal evolution of white matter damage in Parkinson's disease**
Pietro Giuseppe Scamarcia, F. Agosta, E. Spinelli, T. Stojkoviç, I. Stankovic, V. Markovic, I. Petroviç, E. Stefanova, V. Kostic, M. Filippi *(Milano, Belgrado SRB)*

11.45 **Neurofascin is a novel gene causing hereditary ataxia**
Edoardo Monfrini *(Milano)*

12.00 **Spasmodic dysphonia as a presenting symptom of Spinocerebellar ataxia type 12**
Jessica Rossi, F. Cavallieri, G. Giovannini, C. Budriesi, A. Gessani, M. Carecchio, D. Di Bella, E. Sarto, J. Mandrioli, S. Contardi, S. Meletti *(Modena, Milano)*

12.15 **Can we use genetics to discriminate between Multiple Sclerosis and adult-onset post-infectious neurological syndromes?**
Riccardo Currò, F. Martinelli-Boneschi, F. Clarelli, G. Berzero, S. Santoro, M. Sorosina, L. Ferré, S. Peroni, G. Comi, A. Guglielmi, E. Vegezzi, I. Callegari, A. Cortese, F. Esposito, E. Marchioni *(Pavia, Milano)*

12.30 **Spinal cord atrophy in neuromyelitis optica is spatially related to cord lesions and disability**
Laura Cacciaguerra, P. Valsasina, V. Martinelli, M. Rocca, M. Filippi *(Milano)*

12.45 **Spinal cord involvement in multiple sclerosis is highly predictive of disability and disease phenotype**
Raffaello Bonacchi, M. Rocca, E. Pagani, A. Meani, L. Cacciaguerra, P. Preziosa, E. De Meo, M. Filippi *(Milano)*

13.00 **Relationship between retinal inner nuclear layer, age and disease activity in progressive Multiple Sclerosis**
Maria Cellerino, C. Cordano, G. Boffa, G. Bommarito, M. Petracca, E. Sbragia, G. Novi, C. Lapucci, E. Capello, A. Uccelli, M. Inglese *(Genova, San Francisco, New York USA)*

13.15 **Diagnosing autoimmune encephalitis in clinical practice: application and analysis of diagnostic algorithm in a single-center cohort**
Antonino Giordano, R. Fazio, S. Gelibeter, G. Magnani, M. Volonté, V. Martinelli, M. Filippi *(Milano)*

13.30 Pranzo

14.15-15.15
Sessione di flash poster
Moderatori: G. Mancardi *(Genova)* - G. Meola *(Milano)*

14.15 **Idiopathic diffuse superficial siderosis in CNS: a case report with application of rational investigation**
Giuseppe Fiamingo *(Pavia)*

14.20 **Emergent stenting after IV rt-PA in acute ischemic stroke: efficacy and safety of loading dose of antiplatelets**
Laura Filippi, C. Finocchi, M. Balestrino, N. Mavilio, L. Castellan, M. Bandettini di Poggio *(Genova)*

14.25 **Scenery of Idiopathic Generalized Epilepsy in the adult age: data from a Third Level Epilepsy Centre**
Elisa Micalizzi *(Pavia)*

14.30 **Multiplex Ligation-Dependent Probe Amplification in undiagnosed autosomal recessive Limb Girdle Muscular Dystrophies**
Eleonora Mauri, F. Magri, D. Ronchi, S. Corti, N. Bresolin, G. Comi *(Milano)*

14.35 **Relative incremental value of 18F-FDG-PET and CSF biomarkers in Mild Cognitive Impairment (MCI) suspected for Alzheimer's disease**
Federico Massa, L. Farotti, P. Eusebi, E. Capello, M. Dottorini, C. Tranfaglia, M. Bauckneht, S. Morbelli, L. Parnetti, F. Nobili *(Genova, Perugia)*

14.40 **Does the side of onset of motor symptoms in parkinsonian patients have an impact on the global clinical phenotype?**
Giulia Lazzeri, G. Franco, F. Arienti, E. Monfrini, E. Frattini, I. Trezzi, L. Borellini, F. Cogiamanian, G. Ardolino, N. Bresolin, A. Di Fonzo *(Milano)*

14.45-15.15

Sessione Poster

Area Cerebrovascolare, Cefalee e Epilessia
Moderatori: L. Pantoni *(Milano)* - C. Tassorelli *(Pavia)*

1. **Actilyse-induced hypofibrinogemia with subsequent intracerebral haemorrhage: a little-known, preventable cause of post-thrombolysis bleeding**
   Nicolò Bruschi, C. Finocchi, M. Bandettini, M. Balestrino *(Genova)*
2. **An atypical case of reversible hypertensive encephalopathy**
   Gloria Valcamonica, S. Lanfranconi, I. Ghione, P. Basilico, I. Trezzi, N. Bresolin, S. Bonato *(Milano)*
3. **Room tilt illusion and persistent hiccups as presenting symptoms of a left PICA stroke: a case report**
   Umberto Pensato, V. Mastrangelo, R. D'angelo, R. Rinaldi, M. Guarino, P. Cortelli *(Bologna)*
4. **Posterior reversible encephalopathy syndrome (PRES) in a patient treated with IMAB362, an experimental drug for gastric cancer**
   Alessandro Cagol, C. Dato, C. Starvaggi Cucuzza, F. Martinelli Boneschi, L. Bet, G. Meola *(Milano)*
5. **Reversible vasoconstriction syndrome clinical and radiological spectrum: a case series**
   Federico Mazzacane, E. Rognone, I. Canavero, V. Genovese, E. Leuci, M. Zaccarelli, A. Morotti *(Pavia)*
6. **Posterior circulation embolic stroke after foam sclerotherapy for treatment of varicose veins**
   Giulia Barbiera, A. Cagol, L. Bet, G. Meola *(Milano)*
7. **Shabu abuse and ischemic stroke in an Asian adult**
   Davide Villa, G. Valcamonica, I. Ghione, S. Lanfranconi, D. Gagliardi, N. Bresolin, S. Bonato *(Milano)*

8. **Acute confusional migraine: a case report and literature review**
   Claudia Montabone, E. Virgilio, L. Bolamperti, D. Mittino, R. Cantello *(Novara)*
9. **Gender differences in the clinical presentation of Cluster Headache**
   Lara Ahmad, M. Allena *(Pavia)*
10. **Response predictors in chronic migraine: medication overuse and depressive symptoms negatively impact onabotulinumtoxin-a treatment**
    Francesca Schiano di Cola, S. Caratozzolo, P. Liberini, R. Rao, A. Padovani *(Brescia)*
11. **Treatment of Established Status Epilepticus: data from an observational study of the adult Status Epilepticus population of Modena**
    Niccolò Orlandi, G. Giovannini, A. Vaudano, J. Rossi, M. Cioclu, S. Meletti *(Modena)*

Area Neuromuscolare, Malattie Demielinizzanti e Demenze
Moderatori: G.P. Comi *(Milano)* - S. Corti *(Milano)* - E. Scarpini *(Milano)*

12. **Longitudinal functional changes in a cohort of adult nusinersen- treated spinal muscular atrophy patients at the Padova Neuromuscular Center**
    Luca Caumo, V. Bozzoni, L. Bello, C. Semplicini, G. Cester, J. Gabrieli, F. Causin, G. Sorarù', E. Pegoraro *(Padova)*
13. **Functional tests in Myotonic Dystrophy type 1: a three-year longitudinal study.**
    Virginia Bozzoni, L. Bello, S. Tripodi, L. Caumo, G. Sorarù, E. Pegoraro *(Padova)*
14. **Contactin-1-mediated Chronic Inflammatory Demeyelinating Polineuropathy treated with Rituximab: a case report**
    Claudia Cutelle', C. Balducci, V. Francioni, A. Stabile, L. Marzorati, M. Frigo, L. Brighina, D. Vallauri, G. Padovano, E. Nobile-Orazio, C. Giannotta, I. Appollonio, C. Ferrarese, G. Cavaletti *(Monza, Milano)*
15. **Bendamustine-Rituximab (BR) combined therapy for treatment of immuno-mediated neuropathies associated to hematological disorders**
    Angela Zuppa, F. Massa, C. Demichelis, C. Briani, S. Ferrari, A. Schenone, L. Benedetti *(Genova, Padova, Verona)*
16. **Modulation of selected miRNAs in ALS models for the development of novel therapeutics**
    Gianluca Costamagna, M. Rizzuti, G. Filosa, L. Calandriello, V. Melzi, N. Bresolin, G. Comi, M. Nizzardo, S. Corti *(Milano)*
17. **Clinical spectrum of SOD1-mutated ALS patients**
    Ignacio Juan Keller Sarmiento, C. Tiloca, F. Verde, S. Peverelli, C. Morelli, S. Messina, B. Poletti, L. Maderna, A. Ratti, V. Silani, N. Ticozzi *(Milano)*
18. **Towards digital neuroepidemiology. Assessing seasonal dynamics of Guillain-Barre' syndrome with Google Trends data**
    Marco Vabanesi, A. Giordano, G. Dalla Costa, F. Cerri, G. Comi, V. Martinelli, R. Fazio, M. Filippi *(Milano)*

19. **Clinical case of a patient affected by Familial Mediterranean Fever who developed a form of relapsing-remitting Multiple Sclerosis. Which is the best therapy?**
Mattia Pozzato, A. Cagol, C. Starvaggi Cucuzza, L. Bet, F. Martinelli Boneschi, G. Meola *(Milano)*
20. **18F-3,4-dihydroxyphenylalanine positron emission tomography features in brain tumefactive demyelinating lesions.**
Elvira Sbragia, C. Lapucci, S. Raffa, M. Bauckneht, S. Morbelli, F. Nobili, G. Mancardi, M. Inglese, L. Roccatagliata *(Genova)*
21. **Selective cerebellar atrophy associates with depression and fatigue in the early phases of relapsing remitting Multiple Sclerosis**
Andrea Lazzarotto, M. Margoni, S. Franciotta, S. Zywicki, A. Miscioscia, A. Riccardi, D. Poggiali, M. Anglani, A. Favaretto, P. Gallo *(Padova)*
22. **Theory of mind deficits mediate the impact of cognitive deficits on quality of life in Multiple Sclerosis**
Riccardo Fabrizio Meli, G. Sanzone, L. Filippi, E. Sbragia, A. Laroni, G. Mancardi, A. Uccelli, M. Pardini *(Genova)*

Area Neuroimmunologia e neuroinfettivologia
Moderatori: R. Cantello *(Novara)* - L. Parrino *(Parma)*

23. **Neuro-Behçet: the clinical experience of the Luigi Sacco Hospital Neurological Unit**
Giacomo Querzola, F. Mele, S. Rosa, L. Pantoni *(Milano)*
24. **Occult breast tumor mimics Miller-Fisher syndrome**
Clara Lunardon, C. Varrasi, I. Campini, R. Cantello *(Novara)*
25. **Bilateral facial nerve palsy unveiling "the great imitator"**
Fiammetta Pirro, I. Appollonio, C. Ferrarese *(Monza, Milano)*
26. **Non-ataxic acute polyradiculoneuritis associated to serum antiGD1b antibodies and IgM lambda monoclonal component: a case report**
Chiara Starvaggi Cucuzza, A. Cagol, M. Cavalli, L. Bet, F. Martinelli Boneschi, G. Meola *(Milano)*
27. **A case of relapsing hypersomnia: when hydrogen breath test for small intestinal bacterial overgrowth can be useful for management of Kleine-Levin syndrome**
Giorgia Bernabé, A. Melpignano, I. Trippi, R. Ciliento, C. Mutti, L. Parrino *(Parma)*
28. **Late-onset anti-VGKC autoimmune encephalitis: a case report**
Andrea Bellomo, L. Pantoni *(Milano)*
29. **Faciobrachial Dystonic Seizures in Anti-LGI1 Encephalitis: a Case Report**
Matilde Lazzari, G. Strigaro, C. Varrasi, R. Cantello *(Novara)*

Area Disordini del Movimento
Moderatore: A. Priori *(Milano)*

30. **Validation of the dymus screening questionnaire to assess dysphagia in Parkinson's disease and atypical parkinsonian disorders**
Alessia Putorti, M. Avenali, C. Dagna, R. De Icco, M. Gandolfi, C. Solaro, D. Restivo, M. Bartolo, F. Meneghello, G. Sandrini, C. Tassorelli, Dypak Sirn Group *(Pavia, Verona, Moncrivello, Zingonia di Ciserano, Catania, Venezia)*
31. **Impaired cortical plasticity in functional movement disorders: a target for therapeutic intervention?**
Francesca Bianchi, A. D'Arrigo, B. Demartini, O. Gambini, A. Priori, L. Campiglio *(Milano)*
32. **Drug-induced negative myoclonus: a case report**
Lisa Lerjefors, M. Mainardi, A. Antonini, M. Carecchio *(Padova)*
33. **Dystonic postures in Fragile X Associated Tremor/Ataxia Syndrome**
Anna Vera Milner, L. Magistrelli, C. Comi, R. Cantello *(Novara)*

15.15-16.30
Sessione Hot Topics (interaction 1)
Moderatore: A. Padovani *(Brescia)*

15:15 *Discussant:* M. Versino *(Pavia)*
Vertigine acuta in PS: i pro e i cons per la neuronite vestibolare
F. Turco *(Varese)*

15:40 *Discussant:* M. Zucconi *(Milano)*
RBD come marker di neurodegenerazione: I pro e I cons
L. Baldelli *(Bologna)*

16:05 *Discussant:* I. Appollonio *(Milano)*
Speranze e fallimenti delle terapie "disease modifying" nella Malattia di Alzheimer
B. Storti *(Milano)*

16.30 Pausa caffè

16.45-18.00
Sessione Hot Topics (interaction 2)
Moderatore: S. Meletti *(Modena)*

16.45 *Discussant:* J. Mandrioli *(Modena)*
I neurofilamenti nelle malattie degenerative
E. Zucchi (Modena)

17.10 *Discussant:* V. Silani *(Milano)*
SLA: una malattia sistemica?
E. Colombo *(Milano)*

17.35 *Discussant:* A. Schenone *(Genova)*
Malattie neuromuscolari: effetti neurotossici della terapia oncologica di precision
C. Demichelis *(Genova)*

18.15 Premiazione miglior Comunicazione orale, miglior Poster, miglior Hot Topic
G. Mancardi *(Genova)*

18.25 Conclusioni della giornata
G. Meola *(Milano)*

9.30 Registrazione dei partecipanti

10.00 Introduzione
S. Servidei *(Roma)*

10.10 **Lettura Magistrale**
Neurofisiologia dell'invecchiamento cerebrale
P.M. Rossini *(Roma)*

10.50-13.30
Sessione di comunicazioni orali 1
Moderatori: P. Calabresi *(Perugia)* - M. Silvestrini *(Ancona)*

10.50 **Update on mutational spectrum of Primary Familial Brain Calcification**
Ilenia Andreini, I. Taglia, A. Mignarri , C. Battisti , A. Federico, M. Dotti *(Siena, Grosseto)*

11.00 **A possible role of Palmitoylethanolamide combined with Luteoline in Frontotemporal Dementia treatment: a clinical and neurophysiological study**
Martina Assogna, C. Motta, S. Bonnì, E. Casula, I. Borghi, M. Minei, F. Di Lorenzo, A. Martorana, G. Koch *(Roma)*

11.10 **Cases of dementia with confabulations: Alzheimer or not Alzheimer?**
Elisabetta Belli *(Pisa)*

11.20 **Neuronal ceroidolipofuscinosis: clinical and genetic heterogeneity in relation with innovative therapeutic opportunities**
Stefania Dallagiacoma, A. Malandrini, I. Di Donato, M.T. Dotti *(Siena)*

11.30 **Gait ataxia, pyramidal involvement and leukoencephalopathy: what's underneath?**
Chiara Manfredi, I. Di Donato, A. Covelli, A. Cerase, F. Santorelli, M. Dotti *(Siena, Pisa)*

11.40 **Validation of the Italian version of HIV-Dementia Scale: a screening tool for the detection of subcortical cognitive deficits**
Roberta Rinaldi, C. Montanucci, P. Eusebi, N. Salvadori, V. Lisetti, P. Calabresi, L. Parnetti *(Perugia)*

11.50 **Sleep microstructure and cognitive decline in Mild Cognitive Impairment: a novel biomarker**
Alessandro Schirru, L. Carnicelli, M. Maestri Tassoni, F. Giorgi, G. Tognoni, U. Bonuccelli, E. Bonanni *(Pisa)*

12.00 **Sensory involvement in Motor Multifocal Neuropathy explored with sudoscan: a single-centre experience**
Francesco Barbato, A. Romano, G. Bisogni , A. Di Paolantonio, P. Rossini, M. Sabatelli, S. Servidei, G. Granata, M. Luigetti *(Roma)*

12.10 **Atypical presentation and response to therapy in Sporadic Late-Onset Nemaline Myopathy (SLONM)**
Giovanni Colacicco, G. Primiano, C. Sancricca, G. Severa, S. Servidei *(Roma)*

12.20 **Necrotizing autoimmune myopathy revealing an undetected mitocondrial myopathy**
Antonio Covelli, I. Di Donato, E. Cardaioli, P. Brunori, A. Malandrini, M. T. Dotti *(Siena, Perugia)*

12.30 **A Dynein gene mutation associated with sporadic non-progressive Spinal Muscular Atrophy Lower Extremity Predominant (SMALED1)**
Eleonora Torchia, D. Tiziano, G. Primiano, C. Sancricca, S. Servidei *(Roma)*

12.40 **Diagnostic challenge in rapidly progressive dementia: a case report**
Maria Rosaria Bagnato, A. Castelli, M. Pierantozzi, C. Bonomi, M. Conti, L. Boffa, N. Mercuri *(Roma)*

12.50 **Anti-NMDA-receptor encephalitis: two cases with atypical course and good response to early immunotherapy**
Virginia Cancelloni, C. Battisti, A. Cerase, M. Dotti *(Siena)*

13.00 **Specificity and sensitivity of a single CSF-restricted IgG band cut-off as a marker of Multiple Sclerosis**
Francesco Antonio Losavio, M. Lucchini, M. Loiodice, V. Nociti, C. De Fino, V. Di Carlo, T. De Michele, M. Mirabella *(Roma)*

13.10 **Melkersson-Rosenthal Syndrome in an Italian family: evidence of autosomal dominant transmission?**
Eleonora Rollo, G. Tasca *(Roma)*

13.20 **Two cases of LGI1-antibodies encephalitis: clinical characteristics and the role of immunotherapy**
Maria Teresa Sollazzo, C. Battisti, R. Marconi, M. Dotti *(Siena, Grosseto)*

13.30 Pranzo

14.15-15.25

Sessione di comunicazioni orali 2

Moderatori: M.T. Dotti *(Siena)* - S. Sacco *(L'Aquila)*

14.15 **Anticoagulant-related intracerebral hemorrhage: 6-year data from a population-based stroke registry**
Enrico Colangeli, M. Gentile, R. Ornello, C. Tiseo, G. Perrotta, C. Scarpato, S. Sacco *(L'Aquila)*

14.25 **Carotid dissection with eagle syndrome: a case report**
Ciro Scarpato, G. Perrotta, R. Ornello, C. Tiseo, E. Colangeli, B. Orlandi, F. De Santis, F. Notturno, S. Sacco *(L'aquila, Avezzano)*

14.35 **Symptomatic intracranial atherosclerotic disease: an ultrasound 2-year follow-up pilot study**
Giuseppe Reale *(Roma)*

14.45 **Cryptogenic Stroke - clinical features, diagnosis, prognosis and therapy**
Giuseppe Reale *(Roma)*

14.55 **Prevalence of Right-to-left Shunt (RLS) and volumetric brain changes in patients with episodic and chronic migraine**
Paolo Cerrone, F. Pistoia, M. Quarantelli, I. Frattale, A. Carolei, C. Marini, A. Splendiani, S. Sacco *(L'Aquila, Napoli)*

15.05 **Synaptic vesicle protein 2A tumoral expression predicts levetiracetam adverse events**
Carmen Calvello, M. Romoli, M. Mandarano, M. Romozzi, P. Eusebi, C. Bedetti, E. Nardi Cesarini, A. Verzina, E. Loreti, A. Sidoni, P. Giovenali, P. Calabresi, C. Costa *(Perugia)*

15.15 **Onset of Creutzfeldt-Jakob disease mimicking an acute cerebrovascular event**
Eleonora Sabatelli *(Roma)*

15.25-16.40

Sessione Hot Topics (interaction 1)

Moderatori: G. Siciliano *(Pisa)* - N.B. Mercuri *(Roma)*

DEMENZE

Malattia di Alzheimer: una entità clinica vs. un'entità biologica

15.25 Entità clinica
A. Plutino *(Ancona)*

15.35 Entità biologica
M. Carraro *(Firenze)*

15.45 Discussione

EPILESSIA
Sospensione precoce della terapia in fase di remissione: Pros vs. Cons

15.50 Pros
C. Calvello *(Perugia)*
16.00 Cons
F. Dono *(Chieti)*
16.10 Discussione

MALATTIE CEREBROVASCOLARI
Stroke criptogenetici: terapia anticoagulante vs antiaggregante

16.15 Terapia anticoagulante
A. Fallacara *(Roma)*
16.25 Terapia antiaggregante
G. Perrotta *(L'Aquila)*
16.35 Discussione

16.40 Pausa caffè

17.00-18.15

Sessione Hot Topics (interaction 2)
Moderatori: G. Siciliano *(Pisa)* - N.B. Mercuri *(Roma)*

SCLEROSI MULTIPLA
Utilizzo precoce di terapie di seconda linea nelle forme remittenti - recidivanti: Pros vs Cons

17.00 Pros
F. Parodi *(Siena)*
17.10 Cons
R. Reniè *(Roma)*
17.20 Discussione

MALATTIE NEUROMUSCOLARI
Miastenia gravis: trattamento precoce con farmaci biologici: Pros vs Cons

17.25 Pros
A. Gargani *(Pisa)*
17.35 Cons
G. Spagni *(Roma Cattolica)*
17.45 Discussione

DISTURBI DEL MOVIMENTO
DBS nella malattia di Parkinson in fase precoce: Pros vs Cons

17.50 Pros
R. Cerroni *(Roma)*
18.00 Cons
D. Genovese *(Roma)*
18.10 Discussione

18.15 Premiazione miglior Comunicazione Orale, miglior Poster, miglior Hot Topic
S. Servidei *(Roma)*

18.25 Conclusioni della giornata
S. Servidei *(Roma)*

9.30 Registrazione dei partecipanti

10.00 Introduzione
M. Zappia *(Catania)*

10.10 Saluti delle Autorità

10.20 **Lettura Magistrale**
Biomarkers nella malattia di Parkinson e Parkinsonismi
A. Quattrone *(Catanzaro)*

11.00-12.45
Sessione di comunicazioni orali (1)
Moderatore: G. Tedeschi *(Napoli)* - A. Gambardella *(Catanzaro)*

11.00 **Does Acute Peripheral Trauma Contribute to Idiopathic Adult-onset Dystonia?**
Tommaso Ercoli, M. Mascia, G. Defazio *(Cagliari)*

11.15 **Retinal thickness and microvascular pattern in early Parkinson's disease**
Cristina Rascunà, C. Terravecchia, A. Russo, G. Mostile, C. Cicero, A. Luca, N. Castellino, A. Longo, T. Avitabile, M. Reibaldi, M. Zappia, A. Nicoletti *(Catania)*

11.30 **Prevalence of Huntington's Disease in Sardinia, Italy**
Maria Margherita Sechi, M. Murru, A. Muroni, G. Defazio *(Cagliari)*

11.45 **Usefulness of 24-hour Ambulatory EEG Monitoring in the Diagnosis of Typical Absences**
Alessia Giugno, F. Fortunato, M. Sturniolo, I. Sammarra, A. Pascarella, A. Quattrone, M. Mancini, M. Cretella, F. Pucci, A. Labate, A. Gambardella *(Catanzaro)*

12.00 **Prevalence of Hippocampal Malrotation in patients with Temporal Lobe Epilepsy: an update**
Ilaria Sammarra, A. Giugno, F. Fortunato, A. Pascarella, A. Quattrone, A. Gambardella, A. Labate *(Catanzaro)*

12.15 **Incidence of early post-stroke seizures during reperfusion therapies in patients with acute ischemic stroke: an observational, prospective study**
Giovanni Mastroianni, V. Belcastro, E. Ferlazzo, S. Gasparini, G. Ferrigno, S. Lattanzi, P. Banfi, M. Versino, F. Carimati, S. Vidale, G. Grampa, F. Brigo, G. Gigli, F. Bax, G. Merlino, M. Valente, U. Aguglia *(Catanzaro, Como, Ancona, Varese, Verona, Udine)*

12.30 **Intrathecal administration of Nusinersen in adult population: a real life safety assessment**
Giammarco Milella, E. D'Errico, A. Fraddosio, I. Tempesta, A. Mastronardi, A. Morea, G. Scaglione, M. Trojano, I. Simone *(Bari)*

12.45 **Default mode networks abnormalities predict the cutaneous allodynia in patients with episodic migraine without aura**
Fabrizio Scotto di Clemente *(Napoli)*

13.00 Pranzo

13.30-14.00
Sessione poster
Moderatore: I.L. Simone *(Bari)*

1. **Seizures in Alzheimer Disease: a case report helping in differential diagnosis**
   Angela Mariaelena Alicino, R. Leone, M. Parisi, L. Bollo, G. Candida, M. Narracci, T. Francavilla, M. Guido, G. Libro, R. Pellicciari, M. Trojano, I. Simone *(Bari)*
2. **Fahr's disease: identification of an uncommon SLC20A2 mutation**
   Sebastiano Arena, S. Toscano, G. Mostile, C. Rascunà, G. Portaro, A. Nicoletti, M. Zappia *(Catania)*
3. **Malic enzyme 2 gene and the possible susceptibility to genetic generalized epilepsies (GGEs): a case report**
   Giulia Battaglia, L. Giuliano, G. Mainieri, A. Guccione, V. Sofia, M. Zappia *(Catania)*
4. **Intra-hospital delay in acute ischemic stroke: impact of standardized-interdisciplinary local protocol**
   Giusy Candida, M. Petruzzellis, G. Scaglione, A. Manni, M. Trojano, I. Simone *(Bari)*
5. **Limphocyte subpopulation changes In chimeric and humanized B-cell-depleting antibodies for Multiple Sclerosis**
   Nicola Capasso, N. Capasso, A. Nozzolillo, R. Lanzillo, A. Carotenuto, M. De Angelis, M. Petruzzo, F. Saccà, C. Russo, V. Brescia Morra, M. Moccia *(Napoli)*
6. **Homozygosity for the Glu89Gln mutation in TTR gene: first report of an Italian Family**
   Francescopaolo Cucinotta, L. Gentile, G. Fabrizi, F. Taioli, C. Stancanelli, M. Aguennouz, M. Russo, G. Vita, A. Toscano, A. Mazzeo *(Messina, Verona)*
7. **OnabotulinumtoxinA affects visual cortical excitability in chronic migraineurs: preliminary results of a study with sound induced flash illusions**
   Salvatore Ferlisi, S. Di Marco, L. Pilati, A. Torrente, S. Scardina, E. Di Marco, F. Ferraro, G. La Bianca, G. Cosentino, M. Gangitano, F. Brighina *(Palermo)*

8. **Mandragora intoxication mimicking acute stroke: a case report**
   Ludovica Ferraù, F. Grillo, C. Dell'Area, R. Musolino, A. Toscano *(Messina)*
9. **Recurrent vertebro-basilar strokes: a suggestive case of Primary Angiitis of the Central Nervous System**
   Giulia Fiume, F. Giammello, F. Grillo, A. Toscano, R. Musolino *(Messina)*
10. **Efficacy and Safety of Perampanel in a "Real World" Context**
    Francesco Fortunato, I. Sammarra, A. Giugno, A. Quattrone, A. Pascarella, A. Labate, A. Gambardella *(Catanzaro)*
11. **Musicogenic epilepsy: case report**
    Antonella Guccione, A. Guccione, L. Giuliano, G. Mainieri, G. Battaglia, V. Sofia , M. Zappia *(Catania)*
12. **Severe cognitive fluctuations and hallucinations as clinical presentation of Alzheimer's disease: a challenging diagnosis that mimics other primary dementias**
    Salvatore Gulizia, A. Luca, R. Manna, C. D'agate, A. Nicoletti, M. Zappia *(Catania)*
13. **Probable sporadic Creutzfeldt-Jakob disease misdiagnosed as depression and anxiety**
    Nicola Davide Loizzo, L. Bollo, A. Alicino, G. Candida, I. Simone, M. Trojano *(Bari)*
14. **An uncommon association between juvenile myoclonic epilepsy and multiple sclerosis: a case report**
    Roberta Manna, S. Lo Fermo, V. Sofia, G. Mainieri, A. Luca, S. Gulizia, M. Zappia *(Catania)*
15. **An uncommon neurological presentation of breast cancer**
    Roberta Manna, V. Sofia, R. Terranova, A. Luca, M. Zappia *(Catania)*
16. **Vemurafenib for BRAFV600E-mutated pilocytic astrocytoma in young adulthood: a case report**
    Milena Narracci, M. Narracci, E. D'Errico, T. Perillo, M. Trojano, I. Simone *(Bari)*
17. **Subacute central-variant posterior reversible encephalopathy syndrome: a case report**
    Angelo Pascarella, A. Giugno, M. Mancini, A. Quattrone, A. Gambardlla, A. Labate *(Catanzaro)*
18. **Elucidation of a novel triggering mechanism of Multiple Sclerosis mediated by non-typeable Haemophilus influenzae**
    Martina Petruzzo, R. Lanzillo, C. Criscuolo, A. Lamberti, M. Cavaliere, P. Salvatore, R. Colicchio, C. Pagliuca, E. Scaglione, G. Mantova, F. Real-Fernandez, P. Rovero, F. Lolli, H. Rusche, R. Berisio, F. Nuti, M. Mancini, A. Papini, V. Brescia Morra *(Napoli, Sesto Fiorentino, Firenze, Parigi F)*
19. **Differences in 3D Spatio-Temporal and Kinematic Gait Parameters between Idiopathic Normal Pressure Hydrocephalus associated with Parkinsonism and Parkinson's Disease Patients**
    Giacomo Portaro, G. Mostile, V. Dibilio, F. Contrafatto, P. Cunsolo, G. Raudino, F. Certo, A. Nicoletti, G. Barbagallo, M. Zappia *(Catania)*

20. **Giant pontine telangiectasia presenting as headache**
Domenico Santangelo, G. Demonte, T. Garcea, A. Gambardella, F. Bono *(Catanzaro)*
21. **Effects of OnabotulinumtoxinA on headache disability and comorbid depression in chronic migraine patients**
Serena Scardina, A. Torrente , S. Ferlisi, F. Ferraro, S. Di Marco, L. Pilati, E. Di Marco, G. La Bianca, M. Gangitano, G. Cosentino, F. Brighina *(Palermo, Pavia)*
22. **Is protein s deficiency a possible arterial thrombosis risk factor?**
Rossana Sgobio, M. Petruzzellis, S. Lamberti, D. Mezzapesa, M. Savarese, B. Tartaglione, L. Pascazio, S. D'Alessandro, A. Lalla, G. Milella, G. Falcicchio, M. La Cava, F. Caputo, M. Trojano, I. Simone *(Bari)*
23. **Accumulation of proteinaceous material in skeletal muscle fibers of a young man with Spinal Muscular Atrophy type III: common finding or rare association?**
Irene Tempesta, L. Bollo, A. Alicino, M. Ucci, A. Manni, G. Scaglione, G. Milella, A. Amati, F. Girolamo, M. Trojano, I. Simone *(Bari)*
24. **Exploratory Analysis of Electrocortical Signal Complexity in Patients with Progressive Supranuclear Palsy and Corticobasal Syndrome**
Roberta Terranova, G. Mostile, L. Giuliano, A. Luca, G. Donzuso, G. Portaro, C. Rascunò, V. Sofia, A. Nicoletti, M. Zappia *(Catania)*
25. **Lower limbs neuropathy due to non-Hodgkin's lymphoma of the iliopsoas muscle mimicking a chronic inflammatory demyelinating polyneuropathy (CIDP)**
Maria Ucci, R. Sgobio, L. Pascazio, M. Savarese, P. Milzi, D. Mezzapesa, M. Petruzzellis, B. Tartaglione, S. Lamberti, M. Trojano, I. Simone *(Bari)*
26. **Homeostatic-like plasticity is impaired In Multiple Sclerosis**
Vanessa Ziccone, C. Terranova, M. Buccafusca, A. Quartarone, P. Girlanda, V. Rizzo *(Messina)*

14.00-15.45

Sessione di comunicazioni orali (2)

Moderatori: A. Nicoletti *(Catania)* - G. Salemi *(Palermo)*

14.00 **Clinical features in a cohort of Italian MuSK-MG patients in a long term follow-up**
Carmen Bonanno, S. Messina, G. Nicocia, A. Lupica, A. Toscano, C. Rodolico *(Messina)*

14.15 **Clinical features of an italian cohort of patients with very late-onset Myasthenia gravis**
Giulia Nicocia, A. Lupica, S. Messina, C. Bonanno, T. Brizzi, S. Sinicropi, G. Vita, A. Toscano, C. Rodolico *(Messina)*

14.30 **Mitochondrial Encephalomyopathies: a single centre experience**
Alessia Pugliese, A. Toscano, O. Musumeci *(Messina)*

14.45 **Visual cortical excitability in fibromyalgic patients: a study with sound induced flash illusions**
Angelo Torrente, G. Damerino, R. Aronica, S. Ferlisi, S. Scardina, S. Di Marco, L. Pilati, G. La Bianca, N. Bolognini, G. Guggino, F. Brighina *(Palermo, Milano)*

15.00 **Anti-ri-associated Paraneoplastic Ophtalmoplegia-Ataxia Syndrome in a woman with breast cancer**
Manuela Mancini, A. Quattrone, M. Casaletto, A. Pascarella, A. Giugno, A. Labate, A. Gambardella *(Catanzaro)*

15.15 **Immunoadsorption as relapse therapy in NMOSD patients: relationship between clinical outcome and MOG-IgG and AQP4-IgG titer**
Luca Bollo, P. Iaffaldano, M. Mastrapasqua, M. Ruggieri, A. Manni, R. Sgobio, D. Paolicelli, I. Simone, A. Frigeri, M. Trojano *(Bari)*

15.30 **Initial Treatment Choice in a large Italian cohort of Relapsing Remitting Multiple Sclerosis patients**
Aurora Zanghì, E. D'Amico, C. Chisari, S. Toscano, S. Arena, S. Lo Fermo, F. Patti, M. Zappia *(Catania)*

15.45-17.45

Sessione Hot Topics

Moderatore: A. Toscano *(Messina)*

Sclerosi Multipla. Strategia di trattamento: induction vs escalation

15.45 Induction
S. Toscano *(Catania)*

15.55 Escalation
A. Manni *(Bari)*

16.05 Discussione

Emicrania. Trattamento con i nuovi farmaci: sono utili?

16.15 Pros
M. Silvestro *(Napoli)*

16.25 Cons
S. Ferlisi *(Palermo)*

16.35 Discussione

Miastenia. Immunosoppressione precoce: utilità e limiti

16.45 Pros e Cons
C. Bonanno *(Messina)*
17.05 Discussione

Tremore essenziale: sindrome o malattia

17.15 Sindrome
F. Abate *(Salerno)*
17.25 Malattia
T. Ercoli *(Cagliari)*
17.35 Discussione

17.45 Premiazioni e conclusioni

Contributi scientifici
Area Nord
Sede di Milano

Università del Piemonte Orientale

Università Vita - Salute San Raffaele

Università degli Studi di Udine

ALMA MATER STUDIORUM Università di Bologna

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Università degli Studi di Pavia

Università degli Studi di Verona

UNIMORE Università degli Studi di Modena e Reggio Emilia

Università degli Studi di Trieste

Università dell'Insubria

Università degli Studi di Parma

Università degli Studi di Milano Bicocca

Università degli Studi di Milano

FROM REM SLEEP BEHAVIOR DISORDER TO NEURODEGENERATION: CLINICAL SPECTRUM AND ETHICAL ISSUES

Luca Baldelli, L. Sambati, G. Calandra-Buonaura, F. Provini, P. Cortelli

Department of Biomedical and NeuroMotor Sciences (DiBiNeM) - University of Bologna – Bologna

REM sleep behavior disorder (RBD) is a REM sleep parasomnia characterized by loss of the physiological muscular atonia, associated to the possibility for the patients of «acting out» their dreams. It can be idiopathic (iRBD), when occurring in absence of signs of neurological diseases, or secondary to other neurological conditions. However, patients with idiopathic RBD show often subtle subjective or objective clinical abnormalities consistent with the same pathological findings of synucleinopathies such as Parkinson Diseases, Dementia with Lewy Bodies and Multiple System Atrophy; healthy ageing alone cannot account for these results. Consistent evidence demonstrated how iRBD can be the prodromal stage of a neurodegenerative disease preceding by years or decades the onset of an overt synucleinopathy up to the 65% of cases [1]. From this standpoint several issues arise, which modern-day neurologists need to cope with. First, while iRBD conversion into an synucleinopathy is well established, there is unclear evidence describing towards what specific disease will the patients convert and what markers should be indicative of that. Nonetheless, long-term followed-up iRBD patients (>10 years) seem to defy its neurodegenerative, underlining how iRBD diagnosis is not absolutely predictive of the development of a neurodegenerative disease, but rather suggests an increased susceptibility or that the patient will develop such a disorder in the future [2]. The neurologists treating these patients should then consider the difference between disclosing a diagnosis and disclosing the risk of a diagnosis; whether to disclose this risk to patients; and if deciding to disclose the risk, the appropriate timing of such a conversation. An appropriate prognostic counseling should generally include disclosure of phenoconversion risk to iRBD patients giving at the same time tailored information based on the patients' background. It should encourage, in the lack of a disease modifying therapy, follow-ups for the earliest identification of alterations allowing their appropriate management in case of development, promoting a good quality of life. Telling the truth about the future risk of neurodegenerative disease with RBD while being honest about the uncertainty of the risk would promote patients' autonomy and would engender their trust in the physician [3].

References: Postuma, R.B., et al., Risk and predictors of dementia and parkinsonism in idiopathic REM sleep behaviour disorder: a multicentre study. Brain, 2019. 142(3): p. 744-759
Vertrees, S. and G.P. Greenough, Ethical considerations in REM sleep behavior disorder. Continuum (Minneap Minn), 2013. 19(1 Sleep Disorders): p. 199-203
Högl, B., et al., RBD: Future Directions in Research and Clinical Care and Counseling, in Rapid-Eye-Movement Sleep Behavior Disorder, C.H. Schenck, B. Högl, and A. Videnovic, Editors. 2019, Springer International Publishing: Cham. p. 649-663

FEATURES, FREQUENCY, SHORT AND LONG TERM OUTCOME OF RECURRENT TIA: A PROSPECTIVE OBSERVATIONAL COHORT STUDY

Matteo Foschi[1], L. Pavolucci[2], A. Amato[3], E. Favaretto[3], L. Spinardi[4], F. Rondelli[1], D. Degli Esposti[5], M. Filippini[3], P. Cortelli[6], M. Guarino[1]

[1] Neurology Unit - S. Orsola - Malpighi University Hospital - Bologna
[2] Neurology Unit – "S. Maria delle Croci" Hospital, AUSL Romagna, ambito di Ravenna - Ravenna
[3] Angiology and Blood Coagulation Unit - S. Orsola - Malpighi University Hospital - Bologna
[4] Neuroradiology Department - S. Orsola - Malpighi University Hospital - Bologna
[5] Cardiothoracic and Vascular Department - S. Orsola - Malpighi University Hospital - Bologna
[6] Department of Biomedical and Neuromotor Sciences - IRCCS Instituto delle Scienze Neurologiche di Bologna - Bologna

Background: Transient ischemic attack (TIA) is related to an increased risk of subsequent stroke (about 10% at 1-month) with >50% of events occurring in the first 2 days after index TIA. About 20% of all patients experiencing TIA symptoms have more than one episode (recurrent TIA). [1] Data estimating early clinical outcome after recurrent TIA are inferable mainly from two large population-based prospective observational studies (PROMAPA and OXVASC). [2,3] Anyway, a clear relationship between specific etiologies and early stroke occurrence after recurrent TIA has not been established, with the sole exception of large artery atherosclerosis (LAA) and capsular warning syndrome (CWS). Additionally, long and very long-term cerebrovascular outcome of patients with recurrent TIA remains not well characterized as well as subsequent general cardiovascular risk.
Objectives: To evaluate frequency, short and long-term outcome, clinical and etiological features of recurrent TIA.
Methods: prospective observational cohort study enrolling all consecutive patients with TIA. Primary endpoints were stroke, and composite outcome (stroke, acute coronary syndrome, vascular death) at 3, 12 and 60-months. Secondary outcome included: TIA recurrence, cerebral hemorrhage, new onset atrial fibrillation, death by other causes. Concordance between index TIA and subsequent stroke etiologies was evaluated. Statistical significance of intergroup differences was tested by Mann-Withney and Fisher Exact tests. Independent predictors of stroke occurrence by Cox proportional-hazards multivariate analyses.
Results: from August-2010 to December-2017, we enrolled 1035 patients, (822 single TIA, 213 recurrent TIA-20%). Concerning the etiology, capsular warning syndrome (CWS) and large-artery atherosclerosis (LAA) showed the strongest relationship with recurrent TIA ($p < 0.001$ and $p = 0.002$ respectively). The risk of stroke was significantly more high in recurrent TIA subgroup at each follow-up ($p < 0.001$) but the most of stroke episodes occurred within the next 48-h after index TIA. Composite outcome (stroke, acute coronary syndrome and vascular death) was also higher in TIA recurrent group at each follow up ($p < 0.001$). TIA with

lesion, dysarthria and leukoaraiosis were independent predictors of stroke risk at 3 and 12-month, after recurrent TIA. Substantial concordance was observed between index TIA and subsequent stroke etiologies. ABCD3 score >6 was able to identify patients with higher risk of stroke recurrence during the entire follow-up (p = 0.02).

Conclusions: To our knowledge, our study was the first with focusing on long and very long-term outcome after recurrent TIA. Recurrent TIA was frequent accounting for >20% of all TIAs and it was associated either with a high early stroke risk that poor long-term prognosis. We found that the routinely use of clinical prognostic score considering TIA recurrence could help to better and promptly stratify the stroke risk in order to reduce the poor clinical outcome.

References: 1) Easton JD, Saver JL, Albers GW, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. The American Academy of Neurology affirms the value of this state.

2) Purroy F, Jiménez Caballero PE, Gorospe A, et al. Stroke Project of the Spanish Cerebrovascular Diseases Study Group. Recurrent transient ischaemic attack and early risk of stroke: data from the PROMAPA study. J Neurol Neurosurg Psychiatry. 2013 Jun;84(6):596-603.

3) Paul NL, Simoni M, Chandratheva A, Rothwell PM. Population-based study of capsular warning syndrome and prognosis after early recurrent TIA. Neurology. 2012 Sep 25;79(13):1356-62.

ROOM TILT ILLUSION AND PERSISTENT HICCUPS AS PRESENTING SYMPTOMS OF A LEFT PICA STROKE: A CASE REPORT

Umberto Pensato, V. Mastrangelo, R. D'angelo, R. Rinaldi, M. Guarino, P. Cortelli

IRCCS Institute of Neurological Sciences of Bologna – Bologna

Aims: to describe a patient who presented with very rare symptoms, such as persistent hiccups and RTI, after an acute ischemic stroke.
Matherials And Methods: The patient signed an informed consent. The patient was clinically evaluated periodically by a neurologist and received the appropriate pharmacological and non-pharmacological treatment.
Results: After a car crash injury, a 65-years-old man presented with left side dysmetria, persistent hiccups and a counter clockwise 90 degrees tilting of visual environment. A brain computer tomography (CT) scan performed three days after presentation showed a large left cerebellar ischemic stroke. The patient was treated conservatively with anti-hypertensive drugs and rehabilitation and he recovered completely. The visual environment illusion occurred every day since the car crash, it used to last for 4-6 hours and persisted for 15 days. Then the patient was able to evoke it and to revert it for further 15 days and, finally, the illusion disappeared permanently. Also the hiccup persisted for 15 days, being present 24/7, eventually resolving without any medical interventions.
Discussion And Conclusions: the binocular vertical visual field distortion in this patient was likely caused by the ischemic cerebellar stroke implicating a discordance between the inputs received by the vestibular cortex. The peculiarity about our case report, consist on the very long duration and recurring nature of this symptom, and on the ability of our patient to evoke and to revert the distortion through quick modifications of the inputs (e.g. after eyes closure). The hiccups, instead, can be correlated to the compression of area postrema due to cerebellar oedema or, less likely, to the arch reflex activation due to the intramural aortic hematoma. In conclusion RTI and persistent hiccups are very rare symptoms which should not be neglected as they are possible red flags of a posterior circulation stroke presentation.

References: Sierra-Hidalgo F, De Pablo-Fernindez E, Marta-n AHS, et al. Clinical and imaging features of the room tilt illusion. J Neurol. 2012. doi:10.1007/s00415-012-6536-0.
Chang FY, Lu CL. Hiccup: Mystery, nature and treatment. J Neurogastroenterol Motil. 2012. doi:10.5056/jnm.2012.18.2.123.
Stracciari A, Guarino M, Ciucci G, Pazzaglia P. Acute upside down reversal of vision in vertebrobasilar ischaemia [1]. J Neurol Neurosurg Psychiatry. 1993. doi:10.1136/jnnp.56.4.423

RESPONSE PREDICTORS IN CHRONIC MIGRAINE: MEDICATION OVERUSE AND DEPRESSIVE SYMPTOMS NEGATIVELY IMPACT ONABOTULINUMTOXIN-A TREATMENT

Francesca Schiano di Cola, S. Caratozzolo, P. Liberini, R. Rao, A. Padovani

Neurology Unit, University and Spedali Civili Clinical and Experimental Sciences Department - Università degli studi di Brescia – Brescia

Background: albeit numerous studies have investigated possible clinical, radiological or biochemical response predictors', the clinical profile of those patients who might most probably benefit from OnabotulinumtoxinA is still missing. Aim of the present study was to identify potential OnabotulinumtoxinA response predictors' among several clinical characteristics and confirm OnabotulinumtoxinA efficacy and safety in chronic migraine (CM) prevention.
Materials and Methods: the study was conducted at the Headache Centre of Spedali Civili of Brescia. 84 consecutive CM patients were enrolled, with a mean age of 45 yrs (SD 8.7) and a mean disease duration of 10.1 yrs (SD 6.6). The mean reported headache-days frequency was 22.5 (SD 5.9) per month, while the mean number of severe headache-days of 15.2 (SD 8.9) and a mean monthly medication intake of 33.2 (SD 5.6). The clinical characteristics analyzed as potential response predictors' were: gender, disease duration, migraine characteristics (location, side constancy, unilateral autonomic and neurovegetative symptoms), previous prophylactic treatments, add-on therapies, withdrawal therapies, systemic and psychiatric (anxiety and depression) comorbidities, medication overuse. Results: a statistically significant reduction from baseline to 3, 6, 9 and 12 months' treatment cycles in total headaches' days ($p<0.0001$), high intensity headaches' days ($p=0.001$) and triptans' consumption ($p=0.03$) per month was found.
Statistically significant response predictors' were: absence of depressive symptoms ($p=0.05$) and absence of medication overuse ($p=0.048$).
Discussion and Conclusion: our results confirm the efficacy and safety of OnabotulinumtoxinA in CM. Depressive comorbidity and medication overuse, among all clinical variables, were the only significant response predictors'. Such findings provide interesting insights into the current state of the art regarding patients' selection for OnabotulinumtoxinA treatment, being, as we currently are, on the verge of a major therapeutic revolution in migraine prophylaxis, with clinicians having to thoroughly judge and tailor among the available therapeutic options now available. Future research might be needed to confirm our findings, in particular for its therapeutic implications; i.e. better patients' selection, careful management and identification of medication overuse and inclusion of pharmacologic and/or non pharmacologic interventions aimed at comorbidities.

THEORY OF MIND DEFICITS MEDIATE THE IMPACT OF COGNITIVE DEFICITS ON QUALITY OF LIFE IN MULTIPLE SCLEROSIS

Riccardo Fabrizio Meli, G. Sanzone, L. Filippi, E. Sbragia, A. Laroni, G. Mancardi, A. Uccelli, M. Pardini

Policlinic Hospital San Martino-IST, Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health - University of Genoa – Genoa

Cognitive deficits are frequent findings in multiple sclerosis (MS) and a significant cause of quality of life (QoL) reduction. To date it is not completely understood which components of cognitive impairment impact the most on QoL reduction. In other neurological conditions, QoL reduction has been associated with impairment in social cognition impairments due to frontal structural damage. Here we thus evaluated if theory of mind (ToM) mediates QoL in MS independently from deficits in other cognitive domains. 87 patients with MS (age 40.3±12.1 education 13.0±4.1 years, 52 females, median EDSS 3.0, range EDSS 2-6.5) were included in the study. All included patients were assessed with Brief International Clinical Assessment for Multiple Sclerosis (BICAMS) (outcome measure: z scores of the average cognitive performance across the battery), the Hamilton Anxiety and Depression Scale (HADS), the Multiple Sclerosis Quality of Life 54 (MSQOL-54), the MS Neuropsychological Screening Questionnaire (MSNQ-S), and the Reading the Mind in the Eyes Test (RMET). The RMET is a test used to evaluate ToM; in this test subjects are shown 36 pictures of actors and asked to recognize the emotions represented. Healthy Parametric tests were used to evaluate the correlations between the aforementioned measures and a mediation analysis was used to explore the possible cascade leading from cognitive deficits to quality of life reduction. In univariate analyses, MSQOL-54 presented significant correlations with BICAMS total score (r=0.39, p=0.005), HADS (r=-0.38, p=0.005), and RMET (r=0.50, p=0.001) scores; the latter three variables all contributed to MSQOL-54 scores in a stepwise regression analysis. Mediation analyses revealed that (i) part of the effect of BICAMS on MSQOL-54 was mediated by changes in RMET scores, (ii) the effect of HADS on MSQOL-54 was not mediated by RMET changes. To better clarify the impact of cognition on ToM in MS, RMET scores were correlated with the three components of the BICAMS; among those only the symbol digit modalities test (SDMT) correlated with RMET performance (r=0.56, p=0.001). We showed in a large sample of MS patients, that RMET deficits are a predictor of QoL reduction. Moreover, we showed that part of the impact of overall cognitive deficits on QoL (and more precisely of the fronto-parietal functions probed by the SDMT) are mediated by change in ToM abilities. Potentially rehabilitative interventions aimed to improve mentalizing could improve QoL in MS.

References: Goretti B, Nicolai C, et al. The brief international cognitive assessment for multiple sclerosis (BICAMS): normative values with gender, age and education corrections in the Italian population, BMC Neurology 2014, 14:171
Baron-Cohen S, Whellwright S, et al. The «reading the mind in the eyes» Test revised version: A study with normal adults and adults with Asperger Syndrome or high-functioning autism. Journal of Child Psychology and Psychiatry, 2001, 42, 241-251.
Solari A, Filippini G, et al. Validation of Italian multiple sclerosis quality of life 54 questionnaire, J Neurol Neurosurg Psychiatry, 1999 Aug;67(2):158-62

BENDAMUSTINE-RITUXIMAB (BR) COMBINED THERAPY FOR TREATMENT OF IMMUNO-MEDIATED NEUROPATHIES ASSOCIATED TO HEMATOLOGICAL DISORDERS

Angela Zuppa[1], F. Massa[1], C. Demichelis[1], C. Briani[2], S. Ferrari[3], A. Schenone[1], L. Benedetti[1]

1 Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI) - University of Genoa – Genoa
2 Department of Neurosciences - University of Padova - Padova
3 Department of Neurosciences, Biomedicine and Movement Sciences - University of Verona - Verona

Rituximab is a recognized therapeutic choice in anti-MAG polyneuropathy (AMPN) but its usefulness in chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) associated with hematological diseases is still controversial. Moreover to date only one case-report described long-term efficacy of combined Bendamustine-Rituximab (BR) in AMPN refractory to Rituximab. Herein we described a six-months combined Bendamustine-Rituximab (BR) treatment schedule (Bendamustine 90 mg/m2 for two consecutive days and Rituximab 375 mg/m2 every 28 days) in eight patients affected by CIDP or by AMPN (four cases respectively) associated to hematological diseases. Bendamustine-Rituximab was the first-line therapy in four cases (three AMPN and one CIDP) because of hematological diseases severity, while in the others it followed an unsuccessful repeated cycle of conventional therapies (intravenous immunoglobulins, steroids, plasma exchange). All patients had an early and progressive clinical improvement - defined by at least 1 point in INCAT scale - during therapy. In one patient affected by CIDP associated to Chronic lymphocytic leukemia (CCL) the most impressive improvement concerned attitudinal and intentional tremor. All patients presented a sustained response with average progression-free-survival (PFS) of 30 months. In AMPN affected patients, anti-MAG antibodies significantly declined already two months after the last infusion. The neurological relapse occurred in two AMPN affected patients after more than three years of follow up along with Waldenstrom Macroglbulinemia reactivation. The patient affected by CIDP associated to CLL, after three years of sustained stability, presented a clinical relapse occurred in absence of hematological disease reactivation. Six-months Rituximab therapy was administered but Rituximab alone allowed a shorter disease remission compared to the previous combination of BR (one year vs three years). To date only one case report described long term efficacy of BR in AMPN refractory to Rituximab. In our eight cases, combination of Bendamustine Rituximab was a valid option in immune mediated neuropathies associated to hematological disorders. In some patients Bendamustine Rituximab allowed to obtain an early response compared to Rituximab alone. Moreover in one patient, BR schedule led to a longer and sustained improvement than Rituximab alone.

References: Rison AR, Beydoun SR. Paraproteinemic neuropathy: a practical review. BMC Neurology 2016 16:13
Gomez A, Hoffman JE. Anti myelin-associated-glycoprotein antibody peripheral neuropathy response to combination chemoimmunotherapy with bendamustine/rituximab in a patient with biclonal IgM k and IgM: case report and review of the literature. Clinical Lymphoma, Myeloma & Leukemia. 2016; 16(7): e101-8. Nobile-Orazio E, Gallia F, Terenghi F, Bianco M. Comparing treatment options for chronic inflammatory neuropathies and choosing the right treatment plan. Expert Rev Neurother. 2017;17:755-765.

ACTILYSE-INDUCED HYPOFIBRINOGEMIA WITH SUBSEQUENT INTRACEREBRAL HAEMORRHAGE: A LITTLE-KNOWN, PREVENTABLE CAUSE OF POST-THROMBOLYSIS BLEEDING

Nicolò Bruschi, C. Finocchi, M. Bandettini, M. Balestrino

I.R.C.C.S. San Martino Hospital – University of Study of Genoa – Genoa

Acquired coagulopathy and fibrinogen depletion due to incomplete recombinant tissue plasminogen activator (rt-PA) fibrin specificity is a relevant pro-haemorragic risk factor in patients who undergo a thrombolytic therapy. We report the case of a 72 years old man treated with intravenously (iv) Actilyse who subsequently developed relevant fibrinogen decrease (4,2 g/L1,5g/L; -64,3%) and severe symptomatic intracerebral hemorrhage (sICH). This report underlines the importance of fibrinogen monitoring in patients treated with rt-PA for acute ischemic stroke.

Background: Iv rt-PA is the recommended treatment for eligible acute stroke patients and is well known to be associated with an increased risk of ICH that mainly occurs within 24-36 h after thrombolysis. According to SITS-MOST data, the proportion of post thrombolysis sICH is 1.7% An interesting haemorragic risk factor seems to be an acquired coagulopathy induced by the thrombolytic drug itself due to incomplete fibrin specificity causing a fibrinogen consumption, which may lead to a pro-hemorrhagic state supporting bleeding complications.

Case: We describe the case of a 72 years old man affected by Diabetes type II and dyslipidemia who was under treatment with Aspirin for a previous ischemic stroke. He was admitted to the emergency room for a wake up stroke with expressive aphasia right facio-brachial hemiparesis leading to a NIHSS score of 8. Fibrinogen level was normal (4,2 g/L) and the MRI showed an extensive diffusion/perfusion (DWI/PWI) mismatch with no FLAIR detectable lesion. In absence of contraindications IV thrombolysis was performed at 10 am with little benefit (NIHSS 7). At 5 pm he developed consciousness impairment, on urgent CT scan there was evidence of severe ICH. He was treated with craniotomy, at blood samples (+10h post IV rt-PA) fibrinogen level dropped to 1,5 g/L (-64,3% from baseline), at discharge NIHSS was 15, he died the following week due to pneumonia.

Conclusions: ICH is the most serious adverse event related to IV rt-PA as it carries a relevant morbidity and mortality. Previous works have shown that post- thrombolysis ICH might be linked to an early rtPA-related coagulopathy that causes a fibrinogen breakdown. We recommend to test pre-post thrombolysis fibrinogen level and to correct it in selected cases with IV Fibrinogen according to the protocol suggested by Vandell et Al: IV fibrinogen supplementation if fibrinogen levels < 1,0 g/L and no sICH; <2,0 g/L and sICH or reduction more than 30%.

References: Vandelli L, Trenti T, Varani M et Al, Fibrinogen concentrate replacement in ischemic stroke patients after recombinant tissue plasminogen activator treatment, Adv Clin Exp Med. 2019;28(2):219-222 Trouillas P, Derex L, Philippeau F, et al. Early fibrinogen degradation coagulopathy is predictive of parenchymal hematomas in cerebral rt-PA thrombolysis: A study of 157 cases. Stroke. 2004;35(6):1323-1328
Vandelli L, Marietta M, Gambini ME, et al. Fibrinogen decrease after intravenous thrombolysis in ischemic stroke patients is a risk factor for intracerebral hemorrhage. J Stroke Cerebrovasc Dis. 2015;24(2):394-400

RELATIONSHIP BETWEEN RETINAL INNER NUCLEAR LAYER, AGE AND DISEASE ACTIVITY IN PROGRESSIVE MULTIPLE SCLEROSIS

Maria Cellerino[1], C. Cordano[2], G. Boffa[1], G. Bommarito[1], M. Petracca[3], E. Sbragia[1], G. Novi[1], C. Lapucci[1], E. Capello[1], A. Uccelli[1], M. Inglese[1]

[1] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health - University of Genova – Genova
[2] Department of Neurology, Multiple Sclerosis Center - UCSF - San Francisco, California
[3] Departments of Neurology, Radiology and Neuroscience - Icahn School of Medicine at Mount Sinai - New York

Background: Despite the advent of new highly-active disease-modifying therapies for relapsing-remitting Multiple Sclerosis (MS), the current therapeutic approach for progressive MS (P-MS) remains challenging. Selective B-cell depletion in primary-P-MS has shown to affect disease progression in patients aged < 51 years, especially those with evidence of inflammatory activity, thus suggesting that the latter criteria could be crucial for treatment beneficial effect. Previous studies suggested that increased thickness of retinal inner nuclear layer (INL) measured with optical coherence tomography (OCT) reflects inflammatory activity within the central nervous system and could be therefore used as a marker for patients' stratification and therapy response monitoring in relapsing MS. However, INL in P-MS has not been extensively addressed yet.
Aims: To investigate whether INL thickness as assessed with OCT differs between P-MS patients according to age and disease activity.
Methods: In this retrospective longitudinal analysis, differences in terms of peripapillary retinal nerve fiber layer (pRNFL), ganglion cell+inner plexiform layer (GCIPL), INL and T1/T2 lesion volumes (T1LV/T2LV) were assessed between 84 P-MS patients and 36 sex- and aged-matched healthy controls (HC) and between patients stratified according to age (cut off 51 years) and evidence of clinical/MRI activity in the previous 12-months.
Results: pRNFL and GCIPL thickness were significantly lower in P-MS patients than in HC (p=0.003 and p<0.0001, respectively). INL was significantly thicker in patients aged<51 years compared to the older ones and HC (38.2 vs 36.5 and 36.7 Î¼m; p=0.038 and p=0.04, respectively) and in those who presented MRI activity (new T2/gadolinium-enhancing lesions) in the previous 12-months compared to the ones who did not and HC (39.5 vs 36.4 and 36.7 Î¼m; p=0.003 and p=0.008, respectively). Recent MRI activity was significantly predicted by grater INL thickness (Nagelkerke R2 0.36, p=0.001).
Conclusions: INL thickness was higher in younger P-MS patients with recent MRI activity, criteria used in previous studies to identify a specific subset of P-MS patients who best responded to DMT. If this finding is confirmed, we suggest that INL thickness might be a useful tool in P-MS patients' stratification for current and experimental treatments choice.
References: Petzold A, Balcer LJ, Calabresi PA et al. Retinal layer segmentation in Multiple Sclerosis: a

systematic review and meta-analysis. Lancet Neurol. 2017;16(10):797-812.
Knier B, Schmidt P, Aly L et al. Retinal inner nuclear layer volume reflects response to immunotherapy in multiple sclerosis. Brain. 2016;139(11):2855-2863.
Hawker K, O'Connor P, Freedman MS et al. Rituximab in patients with primary progressive multiple Sclerosis: Results of a randomized double-blind placebo-controlled multicenter trial. Ann. Neurol. 2009;66(4):460-471.

NEUROMUSCULAR DISORDERS: NEUROTOXICITY IN THE ERA OF ONCOLOGICAL TARGETED THERAPY

Chiara Demichelis[1], C. Lapucci[1], A. Zuppa[1], S. Grisanti[1], C. Genova[2], P. Queirolo[3], A. Schenone[1], M. Grandis[1], L. Benedetti[1]

[1] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genova - Polyclinic San Martino – Genoa
[2] Lung Cancer Unit - Polyclinic San Martino – Genoa
[3] Medical Oncology 2 – Polyclinic San Martino – Genoa

In the last years, many new drugs have been developed targeting different oncology pathways, overall improving both quality of life and survival in several malignancies. However, the increasingly widespread use of these therapies is associated with novel toxicities, mainly immune-related adverse events (irAEs). Different irAEs are now well characterized and, among them, neuromuscular diseases following immune checkpoint inhibitor (ICPi) therapy are increasingly studied. However, there are also neurologic complications related to the use of other targeted therapies, less known and probably underestimated. Herein we describe four oncological patients who developed neuromuscular diseases after administration of different targeted therapies, who came to our observation in the last few months. The first two patients were treated with Nivolumab and Ipilimumab, both monoclonal antibodies targeting the immune checkpoint molecules programmed cell death protein-1 (PD1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), respectively. The first patient, treated for lung adenocarcinoma, developed myasthenia gravis, with high-titre positivity of AChR-Antibodies. Prednisone showed only mild improvement and pyridostigmine was stopped due to gastroenteric side effects; an intravenous immunoglobulins (IVIg) cycle (2g/kg) achieved complete resolution of symptoms. The second one, affected by mesothelioma, developed dysphagia, dysphonia, dysautonomia and progressive respiratory failure. The neurophysiological study was suggestive of Lambert-Eaton Syndrome. He obtained only mild benefit (weaning of NIV during daytime) from a combined treatment with methylprednisolone (120 mg/daily), Plasma Exchange (PE), IVIg (2g/kg, 3 cycle) and Rituximab (2 infusions, 1000 mg each, 15 days apart). The third and the fourth patients were not treated with ICPi, or other monoclonal antibodies. The former, a woman with a melanoma, was treated with the association of Vemurafenib and Cobimetinib, BRAF and MEK inhibitors, respectively. She developed a sub-acute axonal motor neuropathy, with predominant cranial nerve involvement. She was successfully treated with methylprednisolone (1000 mg for 5 days). The latter, a man with a gastrointestinal stromal tumour (GIST), received therapy with Imatinib, tyrosine kinase inhibitor and precursor of the targeted therapy. He developed head drop, dysphagia and respiratory failure. AChR-Antibodies showed high-titre positivity. At first, he was treated with PE and pyridostigmine, but only a subsequent IVIg cycle (2g/kg) allowed extubation. In conclusion, we strengthen the relevance of neuromuscular complications in patients treated not only with the latest ICPi, but also with “older” and apparently better-known targeted therapies; in both cases consequences can be life-threatening, if not promptly managed.

EMERGENT STENTING AFTER IV RT-PA IN ACUTE ISCHEMIC STROKE: EFFICACY AND SAFETY OF LOADING DOSE OF ANTIPLATELETS

Laura Filippi, C. Finocchi, M. Balestrino, N. Mavilio, L. Castellan, M. Bandettini di Poggio

[1] Policlinic San Martino Hospital, department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI) - University of Genoa and Neurology Clinics – Genoa
[2] Unit of Neuroradiology - Policlinic San Martino Hospital – Genoa

Tandem occlusions (proximal intracranial occlusion and cervical carotid artery occlusion or stenosis>90%) lead to the 10-20% of all acute ischemic stroke (AIS). Intravenous rt-PA followed by interventional treatment with mechanical thrombectomy-in combination with acute stenting of underlying atherosclerotic stenosis or dissection-is increasingly used. The lack of optimal management strategies of implanted stents and of follow-up data on stent patency encouraged us to review the literature and to formulate an operative protocol for the management of emergent stenting in AIS.

Background It is well known that a loading dose of antiplatelet could reduce in-stent thrombosis (1), although this treatment is not recommended within 24 h after IV rt-PA (AHA and SPREAD guidelines). The aim of our work is to shed new light on the appropriate management in acute setting of stents implantation in AIS, thus defining a protocol in order to identify patients at high and low risk of bleeding.

Methods Consecutive AIS patients treated or not with IV rt-PA followed by acute stenting placement will be included. A loading dose of antiplatelets (Lysine Acetilsalicilate 500mg and clopidogrel 300 mg) will be administered to all patients immediately after stenting or 24 hours later, based on the hemorrhage after thrombolysis (HAT) score. This score is a validated easy-to-perform scale able to predict the risk of ICH and prognosis after treatment with IV rt-PA and it has been previously established that a score ‰ 2 is linked to a reasonable risk of ICH (2). The stent patency will be monitorated after 24 hours, 1 and 3 months by ecocolor-doppler or angioCT and occurrence of ICH by cerebral CT within 24-36 h after treatment. Functional outcome will be assessed at 90 days by the modied Rankin Scale (mRS).

Discussion This is a prospective multicenter protocol, coordinated by the San Martino Policlinic-University of Genoa. The study started in May 2019 and it is open to other HUB centers potentially interested. The aim of our study is to implement evidence on the safety and efficacy of a loading dose of antiplatelets after emergent stenting placement in patients with AIS treated with rt-PA.

References: Yun-Fei Han et al. Emergent loading dose of antiplatelets for stenting after IV rt-PA in acute ischemic stroke: a feasibility study. Int J Neurosci, April 2018
Lou M et al. HAT Score: a simple grading scale for predicting hemorrhage after thrombolysis. Neurology. 2008 Oct 28;71(18):1417-23.

MANEUVERING BETWEEN SCYLLA AND CHARYBDIS, MANAGEMENT OF ANTITHROMBOTIC THERAPY IN THROMBOCYTOPENIC PATIENTS WITH ISCHEMIC STROKE

Matteo Grazzini, C. Finocchi, M. Bandettini, M. Balestrino

Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI) - Policlinic Hospital San Martino - University of Genova – Genova

Background Paradoxically, thrombocytopenia often presents with AIS. These cases are difficult to treat, because of the opposite needs of combating thrombosis of stroke and preventing bleeding from thrombocytopenia.
Aims We intended to assess the incidence of association between AIS and thrombocytopenia in our patient cohort, in order to evaluate the management of antithrombotic therapy, their clinical outcome and its relationship with thrombocytopenia.
Materials and Methods We performed a retrospective analysis of all patients that came to our attention because of AIS associated with thrombocytopenia. Results We identified 28 patients admitted to our hospital from 2002 to 2018. Their platelet count ranged from 20,000 to 100,000/Î¼L, mean value 75,000/Î¼L (SD=29.89). Subtypes of stroke according to the TOAST classification were atherothrombotic (n=4), cardioembolic (n=13), other determined etiologies (n=5), unknown etiologies (n=6). Age was (mean±SD) 72±18; NIHSS was 9±7. Seven patients (25%) died during their hospital stay in the acute phase of the stroke. Causes of thrombocytopenia were: DIC n=3; HIT n=1; hematological malignancies n=7; antiphospholipid syndrome: n=3; undetermined etiologies: n=14.CHA2DS2-VASc score was (mean±SD) 5±1.02. In four cases IVT was performed, in such patients PLT count ranged between 80,000 and 100,000/ Î¼L. Mechanical thrombectomy was performed in three cases, one of them having severe thrombocytopenia (PLT=20,000/Î¼L). IVT was not performed in three eligible patients, because it was considered unsafe (platelets count ranging from 55,000 to 74,000/Î¼L). After AIS therapies prescribed for secondary prevention of stroke were antiplatelet therapy (n=7), DOAC (n=7), warfarin (n=7), enoxaparin at anticoagulant dosage (n=2), not prescribed yet (n=5, all in-hospital mortality cases). About half of patients who received DOACs the lower dose was prescribed. In at least one case, however, this was not fully justified, and one month later the patient experienced a minor ischemic stroke in spite of low platelet count (50,000/ Î¼L), after that the dose was increased.
Conclusion Despite that thrombocytopenia carries by itself a bleeding risk, our data show that its presentation with AIS is not rare. This finding is known in the literature. Yet, little is known about safety of thrombolytic and antithrombotic therapies in these patients, who are generally excluded from clinical trials. None of our patients received specific therapies for thrombocytopenia before stroke onset. In several cases, they did not receive thrombolytic therapies due to the fear of bleeding. However, our data suggest that i.v. thrombolysis may be safe for platelet values between 80,000 and 100,000/Î¼L, and that antiplatelet and anticoagulant treatments are tolerated in secondary prevention.

RELATIVE INCREMENTAL VALUE OF 18F-FDG-PET AND CSF BIOMARKERS IN MILD COGNITIVE IMPAIRMENT (MCI) SUSPECTED FOR ALZHEIMER'S DISEASE

Federico Massa[1], L. Farotti[2], P. Eusebi[3], E. Capello[1], M. Dottorini[4], C. Tranfaglia[4], M. Bauckneht[6], S. Morbelli[6], L. Parnetti[2], F. Nobili[7]

[1] Neurology Clinic - IRCCS Ospedale Policlinico San Martino - Genoa
[2] Center for Memory Disorders and Laboratory of Clinical Neurochemistry, Neurology Clinic - University of Perugia – Perugia
[3] Section of Neurology, Department of Medicine - University of Perugia – Perugia
[4] Nuclear Medicine Unit - "S. Maria della Misericordia" Hospital – Perugia
[6] Nuclear Medicine Unit - IRCCS Ospedale Policlinico San Martino – Genoa
[7] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health - University of Genoa – Genoa

Purpose: In Alzheimer's disease (AD) diagnosis, both cerebrospinal fluid (CSF) biomarkers and FDG-PET give sometimes inconclusive results. To evaluate the incremental diagnostic value ofFDG-PET over CSF biomarkers, and viceversa, in patients with Mild Cognitive Impairment (MCI) and suspected AD, in which the first biomarker resulted inconclusive.
Methods: A consecutive series of MCI patients was retrospectively selected from two Memory Clinics where, as per clinical routine, either the first biomarker choice is FDG-PET and CSF biomarkers are only used in patients with uninformative FDG-PET, or viceversa. We defined criteria of uncertainty in interpretation of FDG-PET and CSF biomarkers, according to current evidence. The final diagnosis was established according to clinical-neuropsychological follow-up of at least one year (mean 4.4).
Results: When CSF was used as second biomarker after FDG-PET, 14 out of 36 (39%) received informative results. Among these 14 patients, 11 (79%) were correctly classified with respect to final diagnosis, thus with a relative incremental value of CSF over FDG-PET of 30.6%. When FDG-PET was used as second biomarker, 26 out of 39 (67%) received informative results. Among these 26 patients, 15 (58%) were correctly classified by FDG-PET with respect to final diagnosis, thus with a relative incremental value over CSF of 38.5%.
Conclusions: Our real-world data confirm the added values of FDG-PET (or CSF) in a diagnostic pathway where CSF (or FDG-PET) was used as first biomarkers in suspected AD. These findings should be replicated in larger studies with prospective enrolment according to a Phase III design.

References: Frisoni GB, Boccardi M, Barkhof F, Blennow K, Cappa S, Chiotis K, et al. Strategic roadmap for an early diagnosis of Alzheimer's disease based on biomarkers. Lancet Neurol. 2017;16:661-76.
Herukka SK, Simonsen AH, Andreasen N, Baldeiras I, Bjerke M, Blennow K, et al. Recommendations for cerebrospinal fluid Alzheimer's disease biomarkers in the diagnostic evaluation of mild cognitive impairment. Alzheimer's Dement. 2017;13:285-95
Arbizu J, Festari C, Altomare D, Walker Z, Bouwman F, Rivolta J, et al. Clinical utility of FDG-PET for the clinical diagnosis in MCI. Eur J Nucl Med Mol Imaging. Springer Berlin Heidelberg; 2018;45:1497-508

18F-3,4-DIHYDROXYPHENYLALANINE POSITRON EMISSION TOMOGRAPHY FEATURES IN BRAIN TUMEFACTIVE DEMYELINATING LESIONS

Elvira Sbragia[1], C. Lapucci[1], S. Raffa[2], M. Bauckneht[2], S. Morbelli[2], F. Nobili[2], G. Mancardi[1], M. Inglese[1], L. Roccatagliata[3]

[1] Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DiNOGMI) - University of Genova and IRCCS AOU San Martino-IST - Genoa
[2] Nuclear Medicine Department - IRCCS AOU San Martino - Genoa
[3] Department of Health Sciences - University of Genova and IRCCS AOU San Martino-IST – Genoa

Background: Clinical and neuroradiological features of Tumefactive Demyelinating Lesions (TDLs) may mimic many space-occupying lesions (SOLs) [1]. It has been suggested that positron emission tomography (PET), particularly with labelled aminoacid tracers [2,3], could be useful in the differential diagnosis (d.d.) of TDLs, especially with primary brain tumors (PBTs); PET characteristics of high grade neoplasms usually allow easier discrimination, while d.d. might be more complex between TDLs and low grade gliomas (LGGs) or primary brain lymphomas. To date, there has been little attention on 18F-3,4-dihydroxyphenylalanine (18F-DOPA) to this aim.
Aims: To analyse retrospectively 18F-DOPA PET features in a case series including TDLs, LGGs and lymphomas.
Methods: We searched brain magnetic resonance imaging (MRI) and 18F-DOPA-PET performed between february 2018 and march 2019 in patients with SOLs whose d.d. included TDLs. MRIs were visually coregistered to 18-DOPA-PET images and maximum standardized uptake (SUV-max) values within lesions and their mutual ratios with striatum were calculated. Results: We identified 8 patients; in 3 patients, final diagnosis was TDLs; out of the 5 patients with PBTs, there were 4 LLGs, one with gliomatosis cerebri pattern, and one primary brain B-cell Lymphoma (PBBCL), all confirmed by hystology. Mean SUV-max was 2,02 for TDLs (standard deviation -s.d.- 0,48; range 1,31-2,42) and 4,48 (s.d. 0,86; range 3,19-5,53) for PBTs, with lowest value recorded in PBBCL (3,19). Mean ratios with striatum in TDLs were 0,7 (s.d. 0,17; range 0,6-0,9) and 1,5 (s.d. 0,44; range 0,9-2,1) for PBTs, with the lowest value recorded in PBBCL, overlapping with values of TDLs (0,9).
Conclusions: Lower values of SUV-max obtained from 18F-DOPA-PET studies could be useful in differencing TDLs from LLGs. A grey-zone between TDLs and lymphomas might exist; further data are needed to assess the value of 18F-DOPA PET in these cases.

References: 1. Algahtani H et al. Tumefactive demyelinating lesions: A comprehensive review. Mult Scler Relat Disord. 2017; 14: 72-79.
2. Kebir S et al. 18F'fluoroethyl''tyrosine positron emission tomography for the differential diagnosis of tumefactive multiple sclerosis versus glioma: A case report. Oncology Letters. 2016; 11: 2195-2198.
3. Barbagallo M et al. Value of 18F-FET PET in Patients With Suspected Tumefactive Demyelinating Disease-Preliminary Experience From a Retrospective Analysis. Clin Nucl Med. 2018; 43: 385-391.

POSTERIOR CIRCULATION EMBOLIC STROKE AFTER FOAM SCLEROTHERAPY FOR TREATMENT OF VARICOSE VEINS

Giulia Barbiera, A. Cagol, L. Bet, G. Meola

Department of Biomedical Sciences for Health, University of Milan - IRCCS Policlinico San Donato – Milan

Background and Aims Sclerotherapy of varicose veins is an ultrasound-guided minimally invasive procedure alternative to surgery. The introduction of irritant agents (liquid medium or foam preparations) produces endothelial damage and subsequent vein collapse. The complications of chemical sclerotherapy vary from local pain and inflammation to more serious conditions including microembolic events, such as pulmonary embolism and stroke.
Materials and Methods We describe the case of a 65-year-old woman, with a medical history of hypertension and varicose veins of the legs. A month prior to our observation the patient had started polidocanol-foam sclerotherapy of varicose veins, with a weekly scheme of treatment. Immediately after the fourth injection, the patient started to develop discomfort and vertigo. Four days later, she presented to the emergency room complaining of dizziness, left facio-brachial paresthesia and transient episodes of dysarthria and diplopia. At neurological evaluation the patient appeared markedly suffering, presented left facio-brachial hypoesthesia and bilateral dysmetria at the finger-to-nose test. A brain CT scan showed a focal hypodensity in the left cerebellar lobe, while CT-angiography displayed no intracranial vessels abnormalities. A brain MRI demonstrated multiple acute ischemic lesions involving bilaterally the cerebellum and the right thalamus. Conventional diagnostic procedures performed to detect stroke pathogenesis proved unremarkable. A patent foramen ovale (PFO) was detected at transthoracic and transesophageal echocardiography with bubble-study, with significant right-to-left shunt. Given the clinical and instrumental findings and the close temporal correlation with the sclerotherapy session, a diagnosis of multiembolic stroke by paradoxical embolism was made. A therapy with salicylic acid was started and percutaneous closure of PFO was proposed. At discharge patient's clinical status was normal, except for mild subjective imbalance during walking.
Discussion and Conclusion The most consistent risk factor for developing a stroke after sclerotherapy is the presence of a right-to-left cardiac shunt, especially a PFO. The pathogenic mechanism might be paradoxical clot embolism following vein thrombosis or paradoxical gas embolism. Gas embolism might cause direct occlusion of intracranial arteries or endothelial damage, resulting in a thrombo-inflammatory response. Stroke after sclerotherapy has been reported also in patients without right-to-left shunt, as a consequence of cerebral vasospasm. In fact, after sclerotherapy, increased blood levels of vasoconstrictor peptides (including endothelin-1) have been reported[2]. Both screening methods for detection of PFO and search for more bio-compatible sclerotizing agents should be object of future researches to reduce the risk of neurological complications after sclerotherapy.

References: Frullini A, Barsotti MC, Santoni T, Duranti E, Burchielli S, Di Stefano R., Significant endothelin release in patients treated with foam sclerotherapy, Dermatol Surg. 2012 May;38(5):741-7. pub 2012 Apr 27.

LATE-ONSET ANTI-VGKC AUTOIMMUNE ENCEPHALITIS: A CASE REPORT

Andrea Bellomo[1], L. Pantoni[2]

[1] Neurology – University of Milan – Milan
[2] University of Milan, Luigi Sacco Department of Biomedical and Clinical Sciences - University of Milan - Milan

Autoimmune encephalitis is an uncommon disease of the central nervous system that has gained increasing interest in the last decades. Neuroimaging, cerebrospinal fluid (CSF) examination and search of autoantibodies in serum and CSF differentiate autoimmune from viral encephalitis and others inflammatory CNS diseases. In accordance with laboratory investigation advances, it has become possible to recognize different types of autoantibodies against different types of cell-surface antigens (neuronal receptors, ion channels and cell-surface proteins), while intracellular antigens represent in most cases paraneoplastic encephalitis targets. Whereas in cases of cancer-related encephalitis the treatment consists in cancer removal, in autoimmune encephalitis treatment is based on early immunotherapy. One can occasionally suspect a specific type of autoantibody-mediated encephalitis based on clinical pattern; for example, antiVGKC antibodies encephalitis often cause seizures (typically faciobrachial dystonic seizures - FBDS), hyponatremia and myoclonus. We present a case of a 78-year-old woman who was admitted to our department for the subacute onset of cognitive impairment, hallucinations, and gait disturbances. Her recent clinical history was suggestive for episodes of altered consciousness associated with aspecific involuntary movements. Neurological evaluation showed some degree of cognitive decline and an inconstant mixed tremor. Serum examination was normal except for hyponatremia (130 mEq/L). EEG showed bilateral slow-wave activity with left hemisphere prevalence; MRI demonstrates diffuse, bilateral, cortico-subcortical T2 hyperintensity in the hippocampal areas, especially on the left side, extended to the temporo-mesial lobe without pathological restrictions on diffusivity. CSF examination was normal except for positivity of anti-VGKC antibodies (451,7 pmol/L, v.n < 100); in association, serum levels of anti-VGKC resulted elevated (12,1 pmol/L, v.n 0). Results of investigations confirmed the clinical suspect of anti-VGKC antibodies encephalitis. A paraneoplastic origin of disturbances was excluded. She was treated with two cycles of intravenous steroid (the first one with 750 mg/die for 3 days and the second one with 1 g/die for 3 days) and then with IvIg (25 g/die for 5 days); response to immunotherapy was good. The patient was discharged home without any gait disturbance, no further episodes of loss of consciousness or hallucinations were reported, while some degree of disorientation and tremor persisted.

IMPAIRED CORTICAL PLASTICITY IN FUNCTIONAL MOVEMENT DISORDERS: A TARGET FOR THERAPEUTIC INTERVENTION?

Francesca Bianchi[1], A. D'Arrigo[2], B. Demartini[3], O. Gambini[3], A. Priori[2], L. Campiglio[2]

[1] Neurology – University of Milan – Milan
[2] "Aldo Ravelli" for Experimental Brain Therapeutics Center, San Paolo Hospital - University of Milan – Milan
[3] San Paolo Hospital - University of Milan – Milan

Background Functional neurological movement disorders (FND) are heterogeneous neurological symptoms that cannot be explained by either lesions or dysfunctions of the central nervous system (CNS). Though FND was thought to be of psychological origin, recently imaging studies disclosed several possible abnormalities. In FND, physical and emotional triggers may result in neuroplastic changes in the CNS that can, in turn, perpetuate the symptoms after the triggering event. Repetitive paired associative stimulation (r-PAS) is a non-invasive brain stimulation protocol inducing prolonged changes of neuronal excitability expression of cortical plasticity.
Aims The primary aim of this study was to compare variations in r-PAS-induced cortical plasticity among FND and control patients, measuring TMS-evoked MEP amplitude induced by r-PAS. Furthermore, the study evaluated r-PAS effects on the neurological and emotional status of FND patients.
Materials and Methods Six FND patients aged 26-67 have been compared with healthy-control group. All subjects underwent a r-PAS protocol of 90 coupled stimuli (median nerve-contralateral motor cortex TMS) at 0,05 Hz at 25ms interstimulus interval: the MEP amplitude was evaluated immediately and 15' after r-PAS and compared with MEP measured at baseline. FND patients received a videotaped neurological examination prior, immediately after and two weeks after the r-PAS administration, and were assessed with psychological and neurological scales at the same time intervals.
Results Neurophysiologically, at baseline no significant differences in TMS motor threshold and in MEP amplitude were detected between the two groups. 15' after r-PAS, FND patients had MEP significantly smaller than healthy controls. Clinically, after r-PAS the patients Improved at Global Clinical Impression scale.
Discussion and Conclusion Our study shows an impaired r-PAS-dependent cortical plasticity in FND patients. Because cortical plasticity is related to the balance between Glutamatergic and GABA, an impairment in cortical plasticity could be related to down-regulation of glutamatergic receptors in FND patients, as suggested by magnetic resonance spectroscopy (MRS) findings. Also, r-PAS neurologically -but not psychologically- improved our patients. The uncoupling between psychological and neurological changes after r-PAS argues against a placebo effect but supports the hypothesis that r-PAS improves FND by specifically modulating motor cortical plasticity.

References: Stefan K et al. Induction of Plasticity in the human motor cortex by paired associative stimulation. Brain 123(3). 2000, pp. 572-584.
Suppa A. et al. The associative brain at work: Evidence from paired associative stimulation studies in humans. Clinical Neurophysiology 128. 2017, pp. 2140-2164
Gulyaeva N.V. Molecular Mechanisms of Neuroplasticity: An Expanding Universe. Biochemistry 82(3). 2017, pp. 237-242.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) IN A PATIENT TREATED WITH IMAB362, AN EXPERIMENTAL DRUG FOR GASTRIC CANCER

Alessandro Cagol, C. Dato, C. Starvaggi Cucuzza, F. Martinelli Boneschi, L. Bet, G. Meola

Neurology - IRCCS Policlinico San Donato - Milan – Milan

Background Posterior reversible encephalopathy syndrome (PRES) is a neurological disorder characterized by clinical and neuroimaging findings that are usually reversible. Classical clinical features include headache, visual disturbances, seizures and disorders of consciousness. Brain magnetic resonance imaging (MRI) reveals subcortical vasogenic edema, usually with a distinctive parieto-occipital pattern. Several conditions have been associated with PRES, including the assumption of chemotherapeutic drugs. IMAB362 (Zolbetuximab, Claudiximab) is a novel recombinant chimeric monoclonal antibody that binds to Claudin-18.2, a member of a family of proteins expressed at epithelial tight junctions [1]. IMAB362 is currently under investigation for the treatment of gastrointestinal adenocarcinomas.
Case report We describe the case of a 64 years-old woman, with a medical history notable for arterial hypertension. Two years prior to observation she had been diagnosed with gastric cancer. During follow-up, multiple hepatic metastases were discovered; two successive chemotherapy lines only led to a partial response. The patient was then enrolled in a clinical trial with intravenous IMAB362. Twenty days after the first infusion, the patient started complaining about interscapular pain and dyspnoea; she presented to the Emergency Room, where a CT scan revealed pulmonary embolism. During the first hours in the intensive care unit, the patient experienced a brief and sudden loss of consciousness; after about 15 minutes the patient was aware but severely disoriented, with expressive aphasia and cortical blindness. A brain CT scan showed diffuse brain edema; mild systolic hypertension was detected and subsequently treated. Over the following day, the patient presented two tonic-clonic seizures. A lumbar puncture showed only hyperproteinorrachia. Electroencephalography (EEG) showed diffused theta and delta rhythm. Treatment with levetiracetam was started, with seizure control. A brain MRI showed bilateral thalamic, cerebellar, brainstem and parieto-occipital subcortical white matter T2/FLAIR hyperintensity. Based on clinical presentation and neuroimaging findings, a diagnosis of PRES was made. In the following 48 hours, the speech disturbance resolved, as well as the cortical blindness and only mild disorientation persisted. A progressive improvement in neuroimaging and EEG was demonstrated. At discharge neurological status was unremarkable.
Discussion In early clinical trials, IMAB362 has demonstrated significant efficacy and safety profiles. To our knowledge, this is the first case of PRES associated with IMAB362 administration. Given that claudins are abundant in the tight junctions between the endothelial cells of the blood brain barrier, it may be speculated that IMAB362 could affect cerebral autoregulation and endothelial function.

References: Singh P, Toom S, Huang Y. Anti-claudin 18.2 antibody as new targeted therapy for advanced gastric cancer. J Hematol Oncol. 2017;10(1):105

ALS: A SYSTEMIC DISEASE?

Eleonora Colombo, V. Silani

[1] Neurology – University of Milan – Milan
[2] Auxologico - Unimi – Milan

Amyotrophic lateral sclerosis (ALS) has been considered for decades a disease characterized by the selective involvement of the motor neuron system. The most recent findings related to neuropathological evidence and genetic discoveries tend to suggest a continuum between ALS and other neurodegenerative diseases such as Frontotemporal Dementia (FTD), parkinsonisms and others. Clinical data collection supported by genetic findings acquired with a large series of DNA from over 1.500 ALS/FTD patients at the Istituto Auxologico Italiano, and result of ECAS, a rapid test for cognitive/behavioral changes in ALS have been combined to preliminary define the extramotor involvement of ALS patients. ALS has to be considered in almost 50% of cases a systemic disease with motor and cognitive/behavioral changes due to specific clinical features. Genetics is further supportive: C9ALS/FTD represent a distinct cohort of patients, often characterized by the cognitive involvement encompassing the pyramidal and extrapyramidal dysfunctions. Furthermore, ALS patients with TARDBP and FUS mutations have been reported to express cognitive/behavioral dysfunctions beside the ALS phenotype. SOD1 mutated ALS, on the contrary, still represents a model of pure motoneuronal involvement. ECAS has largely contributed to define the ALS patients with extrapyramidal involvement combined with the neuroradiological evidence of the cortical cognitive involvement, further suggestive for a more generalized spread of the disease. CSF and serum collection further can contribute to confirm the extramotoneuronal involvement, with the specific dipeptide expression in C9ALS patients. ALS must be considered today a unique referral for neurodegeneration: beside the motor system, evidence is accumulating for a broader expression of the disease, with a continuum that represent an unprecedented model for a disease process. Spreading according to the Braak stages also largely contributed to further define the diffusion of the pathogenic process, reaching the cortical and subcortical non-motor areas. The most correct interpretation of this multifaced disease is of today paramount relevance in designing the most appropriate therapeutical approach, aiming to correct the different aspect of the same disease.

MODULATION OF SELECTED MIRNAS IN ALS MODELS FOR THE DEVELOPMENT OF NOVEL THERAPEUTICS

Gianluca Costamagna[1], M. Rizzuti[1], G. Filosa[2], L. Calandriello[1], V. Melzi[1], N. Bresolin[1], G. Comi[1], M. Nizzardo[1], S. Corti[1]

[1] Department of Pathophysiology and Transplantation - University of Milan – Milan
[2] Department of biotechnology and bioscience - University of Milan Bicocca – Milan

Abstract: Motor Neurons (MNs) degeneration is the hallmark of Amyotrophic Lateral Sclerosis (ALS). Increasing evidence suggests that microRNAs (miRNAs) metabolism may play an important role in the disease pathogenesis. In this study, human iPSCs and control fibroblasts were differentiated into spinal MNs. A transcriptome analysis was performed, and deregulated miRNAs were detected. The MNs were subsequently transfected with specific miRNA mimic against selected candidates in vitro. Finally, we silenced an ALS-relevant miRNA downregulating a specific RNA-binding protein by injecting morpholino antisense oligonucleotides (MO) into SOD1G93A mice (MO-SOD1 mice). We showed that MO intracerebroventricular injection increases survival and muscle strength in MO-SOD1 mice as well as MNs life-span and fully innervated neuromuscular junctions compared with scramble-treated mice (scrSOD-controls). Our results demonstrate how exogenous regulation of miRNAs in vivo can modify genetic pathways involved in ALS in an effective manner contributing to the identification of novel therapeutics and biomarkers.

Background: Motor Neurons degeneration is the hallmark of Amyotrophic Lateral Sclerosis. Its underlying mechanisms remain elusive, even though a disruption of RNA metabolism involving micro RNAs seem to play a pivotal role in ALS-related genetic pathways and MNs survival. Aims: We aim at determining whether the modulation of disease-relevant miRNAs can halt MNs neurodegeneration in vitro and in an ALS mouse model (SODG93A). Methods: We generated iPSCs reprogramming ALS and controls fibroblasts, and we differentiated iPSCs into spinal MNs. We profiled the MNs miRNA transcriptome using the TaqMani Low Density Array. We transfected ALS IPS-derived MNs with specific miRNA mimic against selected candidates. Cell numbers and neurite outgrowth were quantified. Finally, we silenced an ALS-relevant miRNA downregulating the RNA-binding protein ELAVL4/HuD by injecting morpholino antisense oligonucleotides into SOD1G93A mice evaluating survival, MNs function and neuropathology.

Results: We obtained a transcriptomeof human ALS MNs and we found deregulated miRNAs implicated in MNs survival, synapsis and neurogenesis modulated by miRNA mimic in vitro. We demonstrated that MO intracerebroventricular injection increases survival and muscle strength in MO-SOD1 mice compared with scramble-treated mice. Considering MNs survival and neuromuscular junction (NMJ) denervation, we documented an increase in MNs life-span and in the number of fully innervated NMJs in MO-SOD1 mice. Finally, this improvement

was correlated with an up-regulation of the miRNA-target-HuD demonstrated by qPCR and western blot. Conclusion: The regulation of miRNAs in vivo can modify genetic pathways involved in neurodegenerative diseases such ALS in an effective manner contributing to the identification of novel therapeutics and biomarkers.

References: Rizzuti M, Filosa G, Melzi V, et al. MicroRNA expression analysis identifies a subset of downregulated miRNAs in ALS motor neuron progenitors. Sci Rep [online serial]. 2018;8:10105.

CLINICAL SPECTRUM OF SOD1-MUTATED ALS PATIENTS

Ignacio Juan Keller Sarmiento, C. Tiloca, F. Verde, S. Peverelli, C. Morelli, S. Messina, B. Poletti, L. Maderna, A. Ratti, V. Silani, N. Ticozzi

Department of Neurology and Laboratory of Neuroscience - IRCCS Istituto Auxologico Italiano – Milan

Background and aims: Although partial association between specific SOD1 mutations and ALS disease course has been observed, no clear genotype-phenotype correlation has been determined so far. Our purpose was to characterize our SOD1-mutated patients, to better delineate the clinical expression of each mutation.
Methods: We genotyped the five exons of SOD1 in 498 ALS patients. Concurrently, we collected patient data including age at onset, clinical and electrodiagnostic features and disease progression rate, calculated as the mean loss of ALSFRS points per month.
Results: We reported 10 SOD1 mutations in 19 cases. A novel V5M variant was also identified. The average age at onset was 52.2 years with no differences between the individual mutations, except for V5M, manifesting a notably late onset (87.5 years). The average loss of FRS points was 0.86/month. As expected based on existing literature, subjects carrying the A4V mutation had the worst outcome (mean loss of FRS 1.88 points/month); likewise, the patient with the V5M mutation, located in the adjacent codon, manifested a rapidly progressive disease (1.67 points/month loss). Conversely, the patient carrying the I113T mutation showed a remarkably long course of more than 20 years.
Conclusion: Our survey illustrated the wide clinical spectrum of SOD1-mutated ALS patients, elucidating the correlation between the specific genotype and the natural history of the disease. Moreover, we reported a novel SOD1 mutation, showing a particularly late-onset but fast-progressing disease; accordingly, we emphasized the cruciality of that site in exon 1, already known for another mutation with poor prognosis.

DOES THE SIDE OF ONSET OF MOTOR SYMPTOMS IN PARKINSONIAN PATIENTS HAVE AN IMPACT ON THE GLOBAL CLINICAL PHENOTYPE?

Giulia Lazzeri[1], G. Franco[1], F. Arienti[1], E. Monfrini[1], E. Frattini[1], I. Trezzi[1], L. Borellini[1], F. Cogiamanian[2], G. Ardolino[2], N. Bresolin[1], A. Di Fonzo[1]

[1] Neurology Unit, Department of Pathophysiology and Transplantation - Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan – Milan
[2] Neurophysiopatology Unit, Department of Pathophysiology and Transplantation - Foundation IRCCS Ca' Granda Ospedale Maggiore Policlinico, University of Milan – Milan

Background Not much is currently known about the possible impact of the side of onset of motor symptoms on the phenotypical expression of PD. Controversial evidence has been reported on its effect on cognitive aspects [1].
Aims The aim of the present study was is describe demographic and clinical characteristics of a cohort of 285 consecutive PD patients and to understand the phenotypic differences of right onset (RPD) and left onset PD (LPD).
Materials and methods In this retrospective study, 285 consecutive PD patients visited by a movement disorders specialist between 2013 and 2018 at Ospedale Maggiore Policlinico, Milan, were enrolled. From all available clinical records, their data were collected and grouped into 5 thematic areas: demographic characteristics and disease history, motor complications, cognitive or behavioral disturbances, non-motor symptoms (NMS), dopaminergic therapy. We analyzed the data of the total cohort, and afterwards of the two subgroups.
Results Our general population does not seem to differ from demographic characteristics of PD patients available in literature, with a slight predominance of male gender (57.2%) and a median age at disease onset of 62 years. In approximately 25% of patients motor symptoms were developed before 50 years. The presence of familial history is slightly higher than previous reports: 38.6% of patients have at least one case of PD among their relatives, and in 63.6% of familial cases a first degree relative is affected. Regarding the comparison between the RPD and LPD, demographic and disease history aspects do not suggest significant differences, except for longer disease duration in LPD (median: 8 years vs 6 years, p 0.029). As for cognitive, behavioral and NMS, all seem to be more frequent in LPD, but only ICD reached statistical significance (30.7% vs 16.2%, p 0.007). Similarly, dopaminergic drugs side effects were significantly more common in LPD (motor fluctuations: 63.7% vs 48%, p 0.013; dyskinesia: 52.5% vs 39.8%, p 0.045).
Discussion and conclusion The higher frequency of many phenotypic aspects of LPD patients may be due to a physioanatomic reason, related to the asymmetry of dopaminergic circuits in the CNS involved in the two subgroups of patients. Nevertheless, a significant impact of the longer disease duration and the higher dopaminergic drugs dosage in this subgroup cannot be excluded. It is our aim to investigate this finding by means of a prospective study.

References: R. Erro, G. Santangelo, M. Picillo, C. Vitale, M. Amboni, K. Longo, F. Giordano, M. Moccia, P. Barone, and M. T. Pellecchia, "Side of onset does not influence cognition in newly diagnosed untreated Parkinson's disease patients" Parkinsonism Relat. Disord., Feb. 2013, vol. 19, no. 2, pp. 256-9.

MULTIPLEX LIGATION-DEPENDENT PROBE AMPLIFICATION IN UNDIAGNOSED AUTOSOMAL RECESSIVE LIMB GIRDLE MUSCULAR DYSTROPHIES

Eleonora Mauri, F. Magri, D. Ronchi, S. Corti, N. Bresolin, G. Comi

Neurology - Centro Dino Ferrari - IRCCS Ca Granda OMP – Milan

Abstract Background: Limb Girdle Muscular Dystrophies (LGMD) type 2A and 2B are genetic disorders associated with biallelic mutations in CAPN3 and DYSF genes. Sequencing of CAPN3 and DYSF is laborious and time-consuming due to the large size of coding sequence and the absence of mutational hot spots. Although Next-Generation Sequencing (NGS) has improved the diagnostic rate, the molecular diagnosis in few LGMD2A/2B patients remains elusive.
Aim: to resolve new diagnosis in autosomal recessive Limb Girdle Muscular Dystrophies when a first mutation has been identified or in case of protein absence at Western blot analysis.
Materials and Methods: Multiplex ligation-dependent probe amplification (MLPA) allows the detection of deletions/duplications of one or more exons within a single reaction. We applied this method to a cohort of LGMD patients displaying a clinical suspect of LGMD2A (n=18) or LGMD2B (n=13). Western blot analysis confirmed the reduction of calpain-3 and dysferlin protein levels. Conventional or Next-generation sequencing resulted in one or no candidate/causative mutations.
Results: MLPA improved the molecular diagnosis in 5 of 26 patients (19%). MLPA detected: i) an heterozygous CAPN3 deletion including exons 1-6 in a LGMD2A patient; ii) heterozygous DYSF deletion of exons 25-27 in two patients; ii) homozygous DYSF deletion of exon 55 in two subjects. Segregation was confirmed in available samples. No duplication was found.
Discussion and Conclusion: MLPA analysis has been demonstrated to be useful in selected cases. MLPA allowed a firm diagnosis in 31% of undiagnosed LGMD2B patients. It should not be used as a screening technique because it is tailored for the suspected candidate gene. It is strongly suggested in cases with only one mutation identified and/or in case of protein absence at Western blot analysis. In the latter scenario, MLPA could precede gene sequencing.

References: Shin HY, Jang H, Han JH et al., Targeted next generation sequencing for the genetic diagnosis of dysferlinopathy. Neuromuscular disorder, 2015, 25:502-510
Krahn M, Borges A, Navarro C et al., Identification of Different Genomic Deletions and One Duplication in the Dysferlin Gene Using Multiplex Ligation-Dependent Probe Amplification and Genomic Quantitative PCR. Genetic testing and molecular biomarker, 2009. 13
Bartoli M, Desvignes JP, Levy N, Krahn M. Exome sequencing as a second-tier diagnostic approach for clinically suspected dysferlinopathy patients. Muscle and nerve, 2014, Dec 1007-1010

NEUROFASCIN IS A NOVEL GENE CAUSING HEREDITARY ATAXIA

Edoardo Monfrini

Neurology – Milan

Background: Neurofascin, encoded by NFASC, is a transmembrane protein that plays an essential role in nervous system development and node of Ranvier function. Anti-Neurofascin autoantibodies cause a specific type of chronic inflammatory demyelinating polyneuropathy (CIDP) often characterized by cerebellar ataxia and tremor. Recently, homozygous NFASC mutations were associated with a neurodevelopmental disorder in two families.
Aims: To find the genetic cause of cerebellar ataxia with neuropathy in two siblings from a consangineous Italian family.
Materials And Methods: A combined approach of linkage analysis and whole-exome sequencing was performed. Functional studies were conducted on neurons from induced pluripotent stem cells (iPSCs) generated from the patients.
Results: Genetic analysis revealed a homozygous p.V1122E mutation in NFASC. This mutation, affecting a highly conserved hydrophobic transmembrane domain residue, led to significant loss of Neurofascin protein in the iPSC-derived neurons of affected siblings.
Discussion And Conclusion: The identification of NFASC mutations paves the way for genetic research in the developing field of nodopathies, an emerging pathological entity involving the nodes of Ranvier, which are associated for the first time with a hereditary ataxia syndrome with neuropathy.

CLINICAL CASE OF A PATIENT AFFECTED BY FAMILIAL MEDITERRANEAN FEVER WHO DEVELOPED A FORM OF RELAPSING-REMITTING MULTIPLE SCLEROSIS. WHICH IS THE BEST THERAPY?

Mattia Pozzato, A. Cagol, C. Starvaggi Cucuzza, L. Bet, F. Martinelli Boneschi, G. Meola

Department of Neurology and Multiple Sclerosis Research Unit, IRCC Policlinico San Donato Hospital - University of Milan – Milan

Background and Aims Familial Mediterranean Fever (FMF) is an inherited disease characterized by recurrent fever and serositis symptoms. It is associated with a mutation in the MEditerranean FeVer (MEFV) gene; most of mutations occur in exon 10 (e.g., M680I, M694V, M694I and V726A) in homozygote or heterozygote state. Multiple Sclerosis (MS) is an inflammatory disease that mainly involves the white matter of the central nervous system that can lead to physical or cognitive disability. Previous works already described the association between FMF and MS [1,2], but little is known, and follow-up is absent regarding which is the best therapy for these patients.

Materials and methods We describe the case of a 53-year-old man with a history of FMF since 2006. The patient has a positive family history (brother and son), and he carries the M694V mutation in heterozygous state. The onset of the disease was characterized by attacks of abdominal pain, emesis and worsening asthenia since the age of 4. The patient is currently on colchicine 1.5 mg/day. Patient has come to our attention because of the acute appearance of itch and tingling paresthesia involving the right trunk and right upper limb on April 2019; moreover, patient reported acute urinary urgency. He performed a brain and spinal cord MRI, which showed the presence of multiple T2-hyperintense lesions periventricular, at right internal capsule, corpus callosum, right white diencephalic substance, pons and right cerebellum, and a gd-enhancing lesion in the cervical spinal cord at C2-C3 level. CSF analysis revealed oligoclonal band positivity, and serological screening for autoimmunity was negative. Neurological examination showed sensory symptoms, severe bilateral hypopallestesia at lower limbs and mild right upper and lower limb weakness (EDSS: 3.5). The patient was treated with high-dose steroid treatment with a good recovery. Considering his JCV-positivity at high titer, we are now choosing the best treatment.

Discussion and conclusions The association between FMF and MS has already been described in previous works, which reported the use of natalizumab and interferon-beta (IFN-beta) in these rare patients with unclear clinical response. We plan to discuss also other potential therapeutical options.

References: Ceylan G., et al. Co-existence of familial Mediterranean fever and multiple sclerosis in two patients. Acta Reumatol Port, 2004.
Yahalom G., et al. Familial Mediterranean fever (FMF) and multiple sclerosis: an association study in one of the world's largest FMF cohorts. European Journal of Neurology, 2011.

NEURO-BEHÇET: THE CLINICAL EXPERIENCE OF THE LUIGI SACCO HOSPITAL NEUROLOGICAL UNIT

Giacomo Querzola[1], F. Mele[1], S. Rosa[1], L. Pantoni[2]

[1] Neurology Unit "Luigi Sacco Hospital" Milan - University of Milan – Milan
[2] Department of Biomedical and Clinical Sciences, "Luigi Sacco Hospital" - University of Milan – Milan

Behçet's Disease (BD) is an uncommon inflammatory disease of the central nervous system (CNS) and is classified in two forms: parenchymal and non-parenchymal, based upon the pattern of CNS involvement. Neuro-BD (NBD) usually accompanies the systemic manifestation of the disorder and can rarely precede them. Recent proposals also suggest that NBD can be classified into an acute type and a chronic progressive type, depending on the differential clinical courses. We report a series of three cases of NBD. The first one was a 30-year-old woman with a history of optic neuritis, initially diagnosed with multiple sclerosis with a poor response to disease-modifying treatments and who subsequently developed recurrent oral and genital ulcerations, polyarthralgias, and erythema nodosum and was then diagnosed with NBD. The second patient was a 28-year-old man with a previous diagnosis of 'possible BD', who developed an acute right hemiparesis, with evidence of a multiple domain cognitive dysfunction and of an extensive cerebral lesion on MRI involving pons, mesencephalon and diencephalon, with a patchy contrast enhancement and with mass effect, compatible with the diagnosis of NBD. The third patient was a 47-year-old man with a history of uveitis and iridocyclitis in his left eye, determining monocular blindness and who developed fluctuating cognitive impairment and apathy. Neuropsychological assessment showed a multiple domain cognitive dysfunction. MRI evidenced multiple lesions with contrast enhancement in the basal ganglia; digital subtraction angiography evidenced asymptomatic thrombosis of left cavernous sinus. HLA-B51 aplotype was positive while auto-antibodies and infective screenings were negative. The patient was diagnosed with NBD according to BD current diagnostic criteria. Several reports showed a high prevalence of cognitive impairment in patients with BD with or without overt neurological symptoms. The domains that have been most often associated with the disease are attention, working memory, and executive functions. The neuropsychological profile of our patients revealed some of these abnormalities but also an extended spectrum of cognitive dysfunction. Our small case series underlines the heterogeneous clinical and radiological picture of NBD.

References: International Study Group for Behçet's Disease. Criteria for diagnosis of Behçet's disease. Lancet 1990; 335:1078-80.
Akman-Demir G, Serdaroglu P, Tasci B; The neuro- Behçet study group: clinical patterns of neurological involvement in Behçet's disease: evaluation of 200 patients. Brain (1999); 122:2171-82
S Hirohata, H Kikuchi, T Sawada, H Nagafuchi, M Kuwana, M Takeno, Y Ishigatsubo; Retrospective analysis of long-term outcome of chronic progressive neurological manifestations in Behçet's disease. Journal of the Neurological Sciences (2015); 349:143-8. M J Cascio, Kuang-Yu Jen;
Cocaine/levamisole-associated autoimmune syndrome: a disease of neutrophil-mediated autoimmunity. Current Opinion in Hematology. 25(1):29-36, JAN 2018

NON-ATAXIC ACUTE POLYRADICULONEURITIS ASSOCIATED TO SERUM ANTIGD1B ANTIBODIES AND IGM LAMBDA MONOCLONAL COMPONENT: A CASE REPORT

Chiara Starvaggi Cucuzza, A. Cagol, M. Cavalli, L. Bet, F. Martinelli Boneschi, G. Meola

Department of Medical Surgical Physiopathology and Transplantation - University of Milan – Milan

Background Guillain-Barrè syndrome and related disorders are acute polyradiculoneuritis with several different clinical presentations depending on the pattern of peripheral nerve involvement. Anti-ganglioside antibodies are diffusely described in these syndromes with possible pathogenetic mechanism and clinical-serological association relying on their neuronal expression topography.
Case presentation A 44-year-old man presented to our emergency department with a 2-day history of fever and flu-like symptoms associated with rapidly worsening visual disturbance, up to a frank diplopia in primary position and right horizontal gaze. His history was notable only for migraine, known since his youth and treated with ergot derivatives. He was exposed to his febrile school-age son in the previous week. The neurological examination showed right sixth cranial nerve palsy, left lid ptosis, minimal drift of the right limbs at antigravity strength tests and slight left deviation at Romberg test. Deep tendon reflexes were diffusely reduced and absent at Achilles tendon level. Routine blood tests and a brain CT scan were unremarkable. Given the clinical picture, the patient underwent cerebrospinal fluid examination, which was normal. During the observation the patient developed also perioral and distal limb paresthesia, with a 'stocking and glove' distribution, and uvula deviation as for a right ninth cranial nerve palsy. A brain MRI with gadolinium resulted negative for parenchymal or meningeal alteration. Considering the evolution of the clinical picture and the absence of pathological findings at neuroimaging tests, acute polyradiculoneuritis was suspected and high dose intravenous immunogobulin started. On the third day after admission the patient underwent nerve conduction studies and electromyography which resulted aspecific; blood tests showed a monoclonal component of IgM lambda type and the search for antiganglioside antibodies detected only anti-GD1b IgM. Infectious and other autoimmune tests were negative. A diagnosis of autoimmune polyradiculoneuritis was thus formulated. On the following days the patient progressively improved, with complete regression of cranial deficits and paresthesias, and only diffuse hyporeflexia persisted at discharge.
Discussion and conclusion Anti-GD1b antibodies are classically described in association with ataxia both in the animal model and in human acute polyradiculoneuritis. Moreover, the association of monoclonal IgM component and anti-GD1b antibodies is described as part of CANOMAD syndrome, a rare chronic sensory neuropathy leading to progressive disabling sensory ataxia with concurrent cranial neuropathies.
This patient could represent an atypical case of non-ataxic anti-GD1b-related autoimmune polyradiculoneuritis and the presence of IgM monoclonal component recommend a close follow-up in order to rule out a chronic evolution.

References: Kaida K et al., GD1b-specific antibody induces ataxia in Guillain-Barrè syndrome. Neurology 2008, 71 (3) 196-201
Willison HJ, Yuki N (2002) Peripheral neuropathies and anti-glycolipid antibodies. Brain 2002, 125:2591-2625
Garcia-Santibanez R. et al., CANOMAD and other chronic ataxic neuropathies with disialosyl antibodies (CANDA), J Neurol 2018, 265: 1402

AN ATYPICAL CASE OF REVERSIBLE HYPERTENSIVE ENCEPHALOPATHY

Gloria Valcamonica, S. Lanfranconi, I. Ghione, P. Basilico, I. Trezzi, N. Bresolin, S. Bonato

Stroke Unit-Neurology Department - IRCCS Foundation Ca' Granda - Ospedale Maggiore Policlinico, Dino Ferrari Centre, Department of Pathophysiology and Transplantation (DEPT), University of Milan – Milan

Background and Aims: Hypertensive encephalopathy is characterized by the presence of brain edema along with neurological signs caused by severe hypertension. Usually brain MRI shows a posterior reversible encephalopathy syndrome (PRES) caused by dysfunction of cerebrovascular autoregulation and endothelial damage. We present a case of a patient with malignant hypertension and an atypical pattern of brain damage, not compatible with PRES or other form of hypertensive encephalopathy.
Methods: A 54-year-old man came to the Emergency Department for a subacute onset of confusion, acute renal failure and severe hypertension. At clinical evaluation the patient was disoriented, drowsy, confused, and poorly aware of his symptoms. Brain MRI scans disclosed widespread white matter abnormalities involving supratentorial white matter, brainstem and cerebellar hemispheres. The diffuse damage was atypical for PRES, so we considered numerous differential diagnosis including infective encephalitis, leucodystrophy, mitochondrial disease and immune-mediated damage. We performed blood tests, autoimmune screening, eye examination and lumbar puncture with negative results.
Results: The patient was treated only with aggressive antihypertensive therapy with a partial regression of symptoms. Serial brain MRI showed a progressive, but not complete, improvement of leukoencephalopathy, especially of the infratentorial damage. The clinical course allowed us to exclude other type of disease such as leukodistrophy and Binswanger disease.
Conclusions: This is an atypical case of reversible hypertensive encephalopathy, since usually the damage has a bilateral parieto-occipital distribution. Cases with such extensive radiological involvement both supra and infratentorial caused by malignant hypertension have been rarely described in literature.

SHABU ABUSE AND ISCHEMIC STROKE IN AN ASIAN ADULT

Davide Villa, G. Valcamonica, I. Ghione, S. Lanfranconi, D. Gagliardi, N. Bresolin, S. Bonato

Stroke Unit-Neurology Departement IRCCS Foundation Ca' Granda Ospedale Maggiore Policlinico, Dino Ferrari Centre, Departement of Pathophysiology and Transplantation (DEPT), - University of Milan – Milan

Background: Methamphetamine abuse is an increasingly recognized risk factor for stroke, causing up to 6% of ischemic strokes in young people1. "Shabu", the purest form, is widespread in Southeast Asian communities. Shabu is frequently assumed by inhalation and it is tipically associated with ischemic stroke1. We are reporting a case of ischemic stroke in a Shabu abuser.
Methods: A 55-year-old Asian active Shabu abuser male presented with a 24-hours history of headache and left limbs weakness. The patient suffered from hypertension, diabetes and dyslipidemia. Neurologic evaluation revealed left facial palsy, left hemiparesis with sensory loss. Brain Magnetic Resonance Imaging (MRI) showed recent ischemic lesions located in the frontal right deep white matter and corpus callosum. Multiple focal vessel wall thickening and narrowings affecting cervical and intracranial vessels and subocclusive stenosis of the right anterior cerebral artery were disclosed by MR Angiography (MRA) and confirmed by cerebral angiography. To rule out central nervous system (CNS) or systemic vasculitis, autoimmune screening, lumbar puncture and total body positron emission tomography (PET) were performed with negative results. Intravenous metilprednisolone was administered without clinical and radiological improvements.
Conclusions: Amphetamine-related cerebral vasculopathy (ARCV) is associated to higher risk of strokes. Ischemic strokes may result from accelerated atherosclerosis, often associated with cardiovascular risk factors, rather than necrotizing arteritis2. Even if radiological findings are suggestive for CNS vasculitis, there is no evidence of inflammation or necrosis in histological samples. In support of this hypothesis, our patient did not recover after steroids treatment. Accelerated atherosclerosis represents the most likely pathogenic mechanism underlying ARCV3.

References: [1] Julia M Lappin, Shane Darke, Michael Farrell, Stroke and methamphetamine use in young adults: a review J Neurol Neurosurg Psychiatry 2017;88:1079-1091
[2] David S. Younger: Vasculitis of the nervous system, Current Opinion in Neurology 2004, 17:317-336
[3] Emily L. Ho, S. Andrew Josephson, Han S. Lee, Wade S. Smith: Cerebrovascular Complications of Methamphetamine Abuse Neurocrit Care (2009) 10:295-305

SPINAL CORD INVOLVEMENT IN MULTIPLE SCLEROSIS IS HIGHLY PREDICTIVE OF DISABILITY AND DISEASE PHENOTYPE

Raffaello Bonacchi, M. Rocca, E. Pagani, A. Meani, L. Cacciaguerra, P. Preziosa, E. De Meo, M. Filippi

Neuroimaging Research Unit & Department of Neurology - San Raffaele Scientific Institute – Milan

Background. Spinal cord (SC) syndromes and MRI-visible lesions are central in neurologist's approach to MS patients. Translational knowledge about MRI SC involvement is still incomplete, likely owing to the inherent technical challenges associated with imaging a small, mobile structure.
Aims. We aimed at better elucidating the role of SC involvement in explaining the severity of clinical disability and the heterogeneity of disease clinical phenotypes in MS, also by comparing it to brain involvement.
Materials and Methods. Fifty-seven relapsing-remitting (RR) MS, 54 progressive MS (PMS) patients and 32 healthy controls underwent 3T MRI acquisition, including: (1) brain 3D T1, 3D T2-FLAIR and 3D T2; (2) cervical SC 3D T1, 3D T2, diffusion weighted imaging and sagittal short-tau inversion recovery; and (3) axial phase-sensitive inversion recovery at C2-C3 vertebral level. Expanded disability status scale (EDSS) and clinical phenotype were recorded. The associations between MRI and clinical variables were explored by age-, sex- and phenotype-adjusted linear models. Differences between phenotypes were tested by specific interaction terms.
Results. In MS patients, EDSS was associated with SC regional and whole-cord (WC) T2-lesion load (LL), SC fractional anisotropy (FA) and mean diffusivity (MD), brain T2-LL and brain atrophy measures. Significant differences of associations with EDSS between RRMS and PMS patients were identified for: SC lateral column, grey matter (GM) and WC T2-LL; SC GM atrophy. Multivariate analysis identified normalized lateral column T2-LL (standardized $\hat{I}^2$ (B)=0.56; p
Discussion and Conclusion. Cervical SC MRI involvement has a central role in explaining disability in all MS patients and across phenotypes. Different MRI measures contribute to explain disability accumulation in RRMS and PMS: normalized SC T2-LL and brain volume in RRMS, SC FA and SC atrophy measures in PMS. Cervical SC MRI involvement is an accurate predictor of MS phenotype.

SPINAL CORD ATROPHY IN NEUROMYELITIS OPTICA IS SPATIALLY RELATED TO CORD LESIONS AND DISABILITY

Laura Cacciaguerra, P. Valsasina, V. Martinelli, M. Rocca, M. Filippi

Neuroimaging Research Unit, Department of Neurology, Institute of Experimental Neurology, Division of Neuroscience, IRCCS San Raffaele Scientific Institute - Vita-Salute San Raffaele University – Milan

Background. Spinal cord T1-hypointense lesions and atrophy occur in multiple sclerosis, but less in known about neuromyelitis optica (NMO).
Aims. Aim of this study was to characterize the spatial distribution of spinal cord atrophy in NMO patients, its relation with T1-hypointense lesions and their correlation with clinical disability.
Methods. Cord 3D T1-weighted MRI scans were acquired at two European centers from 52 aquaporine4-IgG seropositive NMO patients and 28 age-matched healthy controls (HC). After identification of cord T1-hypointense lesions, binary lesion masks were produced. The active surface method was applied to calculate cross-sectional area of the cervical and upper thoracic cord (until T3). A voxel-wise assessment of T1-hypointense lesions and cord atrophy distribution and their correlation with clinical and brain MRI variables was performed using statistical parametric mapping.
Results. Thirty-eight/52 (73.1%) NMO patients had T1-hypointense cord lesions. Lesion probability maps showed a predominant involvement of the upper cervical cord (C2-C4) and upper thoracic cord (T1-T3), with a prevalent distribution in the gray compared to the white matter. In NMO patients, cord atrophy co-localized with focal cord lesions. Anterior cord atrophy correlated with Expanded Disability Status Scale (EDSS) pyramidal subscore (r ranging from -0.53 to -0.40, $p<0.001$), whereas lateral cord atrophy correlated with EDSS sensitive subscore (r ranging from -0.48 to -0.46, $p<0.001$). NMO patients without spinal cord lesions had no cord atrophy compared to HC.
Discussion and Conclusions. NMO patients showed focal areas of spinal cord atrophy, corresponding to regions involved by focal lesions. Such an evidence suggests the existence of a focal, inflammatory-driven mechanism of damage rather than a primary and diffuse neurodegenerative process in this disease.

DIAGNOSING AUTOIMMUNE ENCEPHALITIS IN CLINICAL PRACTICE: APPLICATION AND ANALYSIS OF DIAGNOSTIC ALGORITHM IN A SINGLE-CENTER COHORT

Antonino Giordano, R. Fazio, S. Gelibeter, G. Magnani, M. Volonté, V. Martinelli, M. Filippi

Department of Neurology - San Raffaele Scientific Hospital – Milan

Background and aims: A syndrome-based approach to diagnose autoimmune encephalitis (AE) was recently proposed (Graus, 2016). Little is known in literature about its application and no published study to date has analyzed in detail potential reasons for lack of criteria fulfillment in suspected AE. Our aims are to test feasibility of such criteria in clinical practice and to analyze the most relevant factors in criteria fulfillment.
Methods: We retrospectively applied such criteria to our cohort of AE patients (n=33; 19 autoantibody-positive in serum and/or CSF), following step-by-step the diagnostic process to final diagnosis.
Results: All the patients fulfilled criteria for possible AE. Final diagnoses were attributed as follows. Eighteen patients (55%) matched criteria for definite autoimmune limbic encephalitis (dALE); of these, 15/18 were autoantibody-positive and 3/18 were negative. Three patients fulfilled criteria for probable anti-NMDA-R AE (pNMDA). After recognition of the autoantibody, definite anti-NMDA-R encephalitis (dNMDA) was diagnosed in 4 patients, but surprisingly none of these had fulfilled criteria for pNMDA. Among 11 patients who did not meet criteria for dALE or dNMDA, only one matched criteria for autoantibody-negative but probable autoimmune encephalitis (prAE-), while the others remained classified as pAE. Detailed criteria fulfillment analysis showed that CSF analysis contributed less often to reach final diagnosis, while EEG and MRI had a more relevant role.
Conclusion: Different issues have emerged, which suggest the need for a potential criteria revision. CSF showed limited value in diagnosing these patients. Criteria for pNMDA encephalitis showed low sensitivity in our cohort. Criteria for prAE- may be too much restrictive.

References: Graus F et al. A clinical approach to diagnosis of autoimmune encephalitis. Lancet Neurol, 2016

LONGITUDINAL EVOLUTION OF WHITE MATTER DAMAGE IN PARKINSON'S DISEASE

Pietro Giuseppe Scamarcia[1], F. Agosta[1], E. Spinelli[1], T. Stojkoviç[2], I. Stankovic[2], V. Markovic[2], I. Petroviç[2], E. Stefanova[2], V. Kostic[2], M. Filippi[1]

[1] Neuroimaging Research Unit, and Department of Neurology, Institute of Experimental Neurology, Division of Neuroscience - San Raffaele Scientific Institute, Vita-Salute San Raffaele University – Milan
[2] Clinic of Neurology, Faculty of Medicine - University of Belgrade - Belgrade, Serbia

Background. Although Parkinson's Disease (PD) is mainly associated with neurodegeneration of subcortical grey matter [1], WM involvement has been suggested to have a role in disease progression [2]. Currently, there are no established magnetic resonance imaging (MRI) biomarkers to monitor or predict disease evolution [3].
Aims. The aim of our study was to investigate the longitudinal evolution of cerebral white matter (WM) micro- and macrostructural damage and its relationship with motor and non-motor symptoms in PD.
Materials and methods. 152 patients with PD underwent clinical assessment, cognitive evaluation and MRI scan on a 3.0 Tesla scanner (including T2-weighted and diffusion tensor [DT] MRI sequences) once a year over a follow-up time of 36 months. White matter lesions (WML) were manually identified on T2-weighted scans and the total WML volume was calculated for each subject. Applying tract-based spatial statistics (TBSS), mean fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (axD) and radial diffusivity (radD) values of the total WM skeleton were extracted. Longitudinal regression models and Pearson correlation analyses between MRI and clinical/cognitive data were performed, adjusting for baseline motor impairment measured using the Unified Parkinson's Disease Rating Scale part III (UPDRS-III).
Results. Variables showing significant progression over follow-up included UPDRS-III score ($p<0.001$), WML volume ($p<0.001$), MD ($p=0.005$) and axD ($p<0.001$) global values. Longitudinal trajectories of MD, axD, and radD values significantly correlated with UPDRS-III (r ranging 0.24/0.37, p ranging 0.01/0.04) and Addenbrooke Cognitive Examination total score (r ranging -0.27/-0.29, p ranging 0.01/0.02). WML volume did not correlate with longitudinal alterations of motor and cognitive clinical variables.
Discussion and conclusion. Although PD is mainly associated with neurodegeneration of subcortical grey matter, WM involvement has been suggested to have a role in disease progression. Our study showed that longitudinal evolution of WM microstructural damage is associated with both motor and global cognitive deterioration in PD, whereas the observed increase over time of WM macroscopic alterations is probably not related with neurodegenerative mechanisms. Our results suggest that longitudinal evolution of WM microstructural damage measured by DT MRI might provide a sensitive biomarker of disease progression in PD.

References: O'Keeffe GW, Sullivan AM. Evidence for dopaminergic axonal degeneration as an early pathological process in Parkinson's disease. Parkinsonism Relat Disord. 2018 Nov; 56:9-15.
Bohnen NI, Albin RL. White matter lesions in Parkinson disease. Nat Rev Neurol. 2011 Apr;7(4):229-36.
Saeed U, Compagnone J, Aviv RI, Strafella AP, Black SE, Lang AE, Masellis M. Imaging biomarkers in Parkinson's disease and Parkinsonian syndromes: current and emerging concepts. Transl Neurodegener. 2017 Mar 28; 6:8.

TOWARDS DIGITAL NEUROEPIDEMIOLOGY. ASSESSING SEASONAL DYNAMICS OF GUILLAIN-BARRE' SYNDROME WITH GOOGLE TRENDS DATA

Marco Vabanesi, A. Giordano, G. Dalla Costa, F. Cerri, G. Comi, V. Martinelli, R. Fazio, M. Filippi

Department of Neurology - University Hospital San Raffaele – Milan

Background. Overall annual incidence of Guillain-Barre' syndrome (GBS) in the world is between 1 and 2 cases for 100,000 people. The incidence of GBS seems to show a seasonal trend, but there is contrasting evidence about the season peaks and their relationship with different climates. Google Trends publicly provides an extensive range of web search volume data series for specified search queries, categorized by geographical regions.
Aims. To analyse seasonal variations in GBS web search volume in the USA, overall and in geographic sub-regions, assessing the relationship with temperature variations and comparing with data from traditional epidemiology.
Materials and methods. Retrospective Google Trends web search for item "Guillain-Barre' syndrome" in the USA (from Jan-2008 to Dec-2017), analysing the monthly average over ten years studied. Sub-region analysis was performed grouping the data series from the 10 most popolous US States, weighted by population, into 5 regions; monthly average temperatures were calculated from monthly averages over a 10-year period. Analyses were performed with generalized-estimating equation models (GEE) and post-hoc Wald tests.
Results. Monthly search volume for GBS displayed the greatest positive peak for October (p=0.002), clustering with September and November. Region-wide analysis confirmed this pattern and showed secondary spring (Feb/Apr) subpeaks in Pacific (p=0.04) and Midwest (p=0.016). Association of GBS search volume with month-to-month average temperature variations showed J-shaped relationship, with the highest incidence peak occurring in months with greatest temperature falls, and subpeak in months with sharpest temperature rises.
Discussion and Conclusion. This study represents the first approach in investigating digital epidemiology of GBS and establishing possible links with traditional epidemiology. Cold season GBS peaks have been observed by some traditional studies. Pathogenic relationship with infectious antecedents (e.g., upper respiratory tract infections in cold season, C. jejuni gastroenteritis in warm season) is compatible with our finding of GBS peaks occurring in the months with greatest temperature change.

References: Giordano A, Vabanesi M, Dalla Costa G et al. Assessing seasonal dynamics of Guillain-Barre' syndrome with search engine query data. Neurol Sci (2019) 40:1015-1018

CONTACTIN-1-MEDIATED CHRONIC INFLAMMATORY DEMEYELINATING POLINEUROPATHY TREATED WITH RITUXIMAB: A CASE REPORT

Claudia Cutelle'[1], C. Balducci[1], V. Francioni[1], A. Stabile[1], L. Marzorati[1], M. Frigo[1], L. Brighina[1], D. Vallauri[1], G. Padovano[1], E. Nobile-Orazio[2], C. Giannotta[2], I. Appollonio[1], C. Ferrarese[1], G. Cavaletti[1]

[1] Department of Neurology, S. Gerardo Hospital - University of Milano-Bicocca – Monza
[2] Neuromuscular and Neuroimmunology Service, Department of Medical Biotechnology and Translational Medicine, Humanitas Clinical and Research Institute - Milan University - Rozzano, Milan

Background: Chronic inflammatory demyelinating polyneuropathy (CIDP) is not a defined disease entity but rather a spectrum of related chronic neuromuscular disorders with high variability in clinical phenotype and therapeutic response, including about 20% of patients refractory to conventional therapies.
Case report: A 54 years-old woman come to our clinic for a 6 weeks history of backache, gloves-socks dysesthesia, progressive postural instability and severe lower limbs weakness. Neurological examination revealed symmetrical muscular weakness and hypoesthesia especially at distal limbs, diffuse areflexia and pareto-ataxic gait. A nerve conduction study evidenced decrease of motor and sensitive nerve conduction velocity, prolonged distal latencies and F-wave latencies. Analysis of the cerebrospinal fluid showed albumin-cytological dissociation. Plasma exchange (PE) followed by intravenous immunoglobulins (IVIG) were administrated with initial clinical improvement; the patient was discharged with diagnosis of Guillain-Barré syndrome and admitted to rehabilitation clinic. Three weeks after the last infusion of IVIG (12 weeks from onset) she deteriorated her clinical status with severe ataxia and muscular weakness, losing the ability to walk. Electrophysiological study documented worsening of all the nerve conduction parameters including amplitude, appearance of active denervation and initial reinnervation findings. Magnetic resonance imaging showed hypertrophy and intense gadolinium enhancement of the cauda equina and milder enhancement of several cervico-dorsal nerve roots. A targeted autoimmune panel identified serum auto-antibodies directed to Contactin-1 and the diagnosis was modified to CIDP. New cycles of IVIG, PE, and high dose methylprednisolone were performed without any benefit. Rituximab was finally administrated without complications and with considerable clinical improvement. Discussion: We described the case of a Contactin-1-mediated CIDP with GBS-like subacute onset and severe remitting-relapsing course poorly responsive to traditional treatments but highly responsive to B cell depleting therapy. IgG4 auto-antibodies against paradonal proteins like Contactin-1 are detected in less than 10% of CIDP and are specific for a defined clinical phenotype, named "autoimmune paranodopathy" from some authors, characterized by an aggressive onset of weakness, a very high ratio of ataxia, early axonal involvement and refractoriness to IVIG. In literature Rituximab administration is documented only in a few

CIDP cases with Contactin-1-autoantibodies and it is associated to a favourable outcome as in other IgG4 related-disorders. Auto-antibodies determination in CIDP patients could be useful to delineate the correct diagnostic and prognostic framework, driving the clinicians to more individualised treatment regimes.

References: Roggenbuck JJ, Boucraut J, Delmont E, Conrad K, Roggenbuck D. Diagnostic insights into chronic-inflammatory demyelinating polyneuropathies. Ann Transl Med. 2018. 6(17):337.
Doppler K, Appeltshauser L, Wilhelmi K, Villmann C, Dib-Hajj SD, Waxman SG, MÃ¤urer M, Weishaupt A, Sommer C. Destruction of paranodal architecture in inflammatory neuropathy with anti-contactin-1 autoantibodies. J Neurol Neurosurg Psychiatry. 2015. 86(7):720-8.
Querol L, Rojas-GarcÃ-a R, Diaz-Manera J, Barcena J, Pardo J, Ortega-Moreno A, Sedano MJ, SerÃ³-Ballesteros L, Carvajal A, Ortiz N, Gallardo E, Illa I. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. Neurol Neuroimmunol Neuroinflamm. 2015. 2(5):e149.

BILATERAL FACIAL NERVE PALSY UNVEILING "THE GREAT IMITATOR"

Fiammetta Pirro, I. Appollonio, C. Ferrarese

Department of Neurology, S. Gerardo Hospital - University of Milano-Bicocca – Monza

Background: Bilateral facial nerve palsy can be due to several conditions: systemic, infectious, autoimmune, neoplastic, toxic, genetic and other. Reaching the correct diagnosis may therefore be challenging and require several diagnostic examinations.
Clinical case: A 46-year old woman with immune thrombocytopenia and common variable immunodeficiency presented to San Gerardo Hospital with peripheral left VII cranial nerve palsy at the end of October. Brain CT scan and ENT visit were both negative and she was therefore discharged under time-limited oral steroid treatment. One month later, she returned with a right VII cranial nerve palsy, associated with diffuse non-pruriginous erythematous papules. Neurological examination showed bilateral facial nerve palsy (right>left). She was therefore admitted to the Neurology ward. A brain MRI showed bilateral facial nerve enhancement. A first lumbar puncture was non-diagnostic. Blood examinations were performed, including autoimmune and infectious screening. A positivity to treponema pallidum antibodies with RPR negativity was found. Lumbar puncture was repeated and treponema pallidum antibodies were also found in the spinal fluid, allowing a diagnosis of central nervous system syphilis even though the patient had not presented with characteristic symptoms. The patient was treated with penicillin and amoxicillin with improvement of neurological symptoms.
Discussion: This case shows how sometimes several factors (such as an altered immune system) can determine an atypical presentation of a known disease. In fact, in this case, syphilis did not follow the normal stages of the infection, complicating the diagnosis. Syphilis is a reemerging disease therefore it is important to keep it in mind when considering differential diagnoses.

THE IMPORTANCE OF FAILURE: WHAT TRIALS' MISFORTUNE COULD TEACH US

Benedetta Storti

Department of Neurology, S. Gerardo Hospital - University of Milano-Bicocca – Monza

Introduction In Italy almost six hundred thousand people suffer from Alzheimerâ€™s disease (AD) and about three million people are involved, directly or not, in taking care of patients. As the size and proportion of the Italian population aged 65 and older continues to increase, the number of people affected will grow rapidly in the coming years. The cost of health care and long-term care for individuals with AD is substantial and is one of the costliest conditions to society. A huge effort have been made in the last ten years in terms of experimental methods and clinical trials and in the next few years many phase 2-3 trials which utilize disease modifying drugs will reach their conclusion. Unfortunately, despite the massive investments in AD drugs, there have been more failures than successes.

The reasons The obvious question to ask is: why so many setbacks? Actually, there could be many good reasons that have to be considered. Firstly, AD is thought to begin twenty years or more before symptoms arise. According to this, it has been postulated that treatment of patients should start earlier during the disease's course. Therefore, several trials are going to enrol patients with mild cognitive impairment (MCI) or even cognitive unimpaired (CU) people 'at-risk of developing AD'. Inevitably, scientists came across the necessity of the right biomarkers for fair identification of AD at its very earliest stages. This demanding research is still open, but there have been promising discoveries in the field. The identification of more precise diagnostic criteria will ensure appropriate enrolment in clinical trials and accelerate the development of new therapies. Finally, the biggest unanswered question: are the therapeutic targets chosen so far incorrect? The fact is that, while abundant data implicate brain amyloid deposition in the primary pathogenesis of AD, we do not own an unquestionable assumption about AD development. Nowadays, the most prevalent theory is still that of 'amyloid cascade hypothesis', however the failure of drugs acting against amyloid plaques have brought this idea into question.

Future directions As long as we continue to study, experiment and experience, we will advance our knowledge and get closer to the solution of the AD problem, bearing in mind that you only fail when you stop trying. This presentation summarizes the reasons why drugs have failed and offers possible explanations about this misfortune.

TREATMENT OF ESTABLISHED STATUS EPILEPTICUS: DATA FROM AN OBSERVATIONAL STUDY OF THE ADULT STATUS EPILEPTICUS POPULATION OF MODENA

Niccolò Orlandi, G. Giovannini, A. Vaudano, J. Rossi, M. Cioclu, S. Meletti

Department of Biomedical, Metabolic and Neural Science - Neurology Unit, OCB Hospital, AOU Modena – Modena

Abstract Background: Status Epilepticus (SE) is a neurological emergency and life-threatening event, with an important mortality and morbidity rate. Despite an increasing knowledge on the biological and molecular processes taking place during SE, its treatment still represents a very important issue in the field of neurology
Aims: To evaluate and compare the AEDs administered in Established Status Epilepticus (ESE) treatment in our clinical practice.
Methods: We reviewed all consecutive SE episodes observed at the OCB hospital, Modena, from September 1st 2013 to March 30th 2019. Demographic, clinical features, and anti-epileptic treatment responses were collected and analyzed, focusing on ESE episodes and on the second lines agents used. We considered as effective the last AED administered prior the resolution of SE. Head to head comparisons were performed, as well as between traditional and newer AEDs. Modified Rankin Scale (mRS) was used to evaluate functional outcomes at the hospital discharge and at 30 days from SE onset. Categorical variables were compared using Pearson Ï‡2 test or the Fisher exact test. The statistical significance cutoff was set at 0.05.
Results: 311 episodes of Established Status Epilepticus were observed. In the majority of episodes an acute symptomatic etiology was found (159/311; 51%) and cerebrovascular diseases were the most frequent ones (87/311; 28%). VPA and LEV were the most used AEDs in our clinical practice. When compared to each other, VPA resulted with an higher efficacy rate than LEV (p=0.002), with the latter showing a lower incidence of adverse events (p=0.004). LCM showed a better efficacy rate when compared to LEV (p=0.009) without differences in terms of safety (p=0.09). We observed an higher number of adverse events when PHT was compared to LEV (p=0.02). Traditional AEDs (PHT, PB and VPA) were used as last drug in a significantly higher number of episodes than newer ones (LEV and LCM) (p=0.04), but with more adverse events (p=0.005). In-hospital mortality was 17% and 30-days mortality increased to 21%. In 47% of cases a return to baseline condition at 30 days was observed.
Conclusions: in this prospective monocentric study traditional AEDs showed higher rate of SE resolution than newer agents. Considering VPA and LEV, the most frequently used AEDs, the first showed an higher resolution rate, but a worse safety profile. No significantly differences were found in head-to-head comparison between PHT, VPA and LCM, whereas LEV showed a better safety profile when compared to PHT. In future high class-randomized clinical trials are needed in order to obtain clear evidence for leading clinical practice.

SPASMODIC DYSPHONIA AS A PRESENTING SYMPTOM OF SPINOCEREBELLAR ATAXIA TYPE 12

Jessica Rossi[1], F. Cavallieri[2], G. Giovannini[1], C. Budriesi[1], A. Gessani[1], M. Carecchio[3], D. Di Bella[3], E. Sarto[3], J. Mandrioli[1], S. Contardi[1], S. Meletti[1]

[1] Department of Neural Sciences - University of Modena and Reggio Emilia - Modena
[2] Neuromotor & Rehabilitation Department - USL-IRCCS of Reggio Emilia - Reggio Emilia Unit of Neurology - AOU Modena – Modena
[3] Medical Genetics and Neurogenetics Unit - IRCCS Foundation, Carlo Besta Neurological Institute – Milan

Background: Autosomal dominant spinocerebellar ataxia (SCA) type 12 is due to a CAG expansion (>51 CAG) in the 5' region of the PPP2R2B gene mostly described in the Indian population. Two cases of SCA12 have been reported from two families coming from Ferrara area, in North-East of Italy. Only in SCA12 action tremor of the upper limbs is the most common sign at onset. Subsequently, mild cerebellar dysfunction, hyperreflexia, parkinsonian features, dystonia, psychiatric symptoms and dementia can appear. Spasmodic dysphonia has been observed only in one case of SCA12 and it has never been reported at disease onset.
Materials and Methods: A 61-year-old woman born in Ferrara province developed at the age of 50 alteration of voice, followed by head dystonic tremor. Few years later she developed gait instability and ataxia. Later on, cognitive deterioration and depression appeared. Her paternal aunt died from an unspecified neurodegenerative disorder and two first-degree cousins developed a similar condition in their fifties. The proband's neurological examination showed dystonic postural and intentional tremor, mild left dysmetria and diffuse hyperreflexia. Stance and gait were characterized by instability, wide based and impossibility to perform tandem gait. A brain-MRI revealed generalized cortical cerebral atrophy particularly evident in the anterior-posterior diameter of the midbrain. Speech evaluation based on analysis of sustained phonation, diadochokinesis, spontaneous speech and reading through perceptual and acoustic analysis using PRAATA was performed. The patient could not produce sustained phonemic vowel-like sounds or to voluntary change voice fundamental frequency. Perceptual analysis showed frequent voice breaks, strained and dysfluent effortful speech production consistent with spasmodic adductor dysphonia.
Results: Given the family history, the provenience of the patient and the peculiar finding of spasmodic dysphonia, CAG repeat length in the PPP2R2B gene was tested. The analysis revealed heterozygosity for an expanded allele with 61 CAG repeats confirming the diagnosis of SCA12. Treatment with Trihexyphenidyl (4mg/day) determined partial amelioration of tremor and dysphonia.
Discussion and conclusion: As other SCAs, SCA12 is characterized by a heterogeneous phenotypic variability and ataxia or tremor can appear long after disease onset. In many cases other signs, like dystonia, can be predominant even at onset making the diagnosis challen-

ging. Dystonia can affect upper limbs, neck, face, but also the larynx. In the present case the presence of spasmodic dysphonia combined with the neurological examination and an autosomal dominant family history for neurodegenerative disorders led to the suspicion of SCA12, a condition needing a multidisciplinary team.

References: Alessandro Brussino, Claudio Graziano, Dario Giobbe, Marina Ferrone, Elisa Dragone, Carlo Arduino, Raffaele Lodi, Caterina Tonon, Anna Gabellini, Rita Rinaldi, Sara Miccoli, Enrico Grosso, Maria Cristina Bellati, Laura Orsi, Nicola Migone, and Alfredo Brusco. Spinocerebellar ataxia type 12 identified in two italian families may mimic sporadic ataxia. Movement Disorders, 25(9):1269-1291, 2010.
Christos Ganos, Tabish A. Saifee, Panagiotis Kassavetis, Roberto Erro, Amit Batla, Carla Cordivari, Kailash P. Bhatia. Dystonic tremor and spasmodic dysphonia in spinocerebellar ataxia type 12. Movement Disorders, pages 79-81, 2014.
Lorraine V. Kalia, Cheryl Rockman-Greenberg, Andrew Borys, Anthony E. Lang. Tremor in spinocerebellar ataxia type 12. Movement Disorders, pages 76-78, 2014.

NEUROFILAMENTS IN NEURODEGENERATIVE DISEASES: THE "PASS-PARTOUT" BIOMARKERS

Elisabetta Zucchi[1], S. Meletti[2], J. Mandrioli[1]

[1] Neurology Unit - S. Agostino Estense Hospital, Department of Neuroscience, A.O.U. Modena - Modena
[2] Department of Biomedical, Matabolic, and Neural Sciences - University of Modena and Reggio Emilia - Modena

Neurodegenerative diseases are marked by key histopathological signatures were aggregates of different proteins are variably found across central nervous system regions. In this setting a great effort has been made to measure in vivo tau, beta-amyloid, alpha-synuclein and TDP-43, with variable outcome in terms of correlations with clinical diagnosis, prognosis or response to drugs. The last decade has witnessed the rising of an outstandingly simple and brilliant idea for the assessment of neurodegeneration: the quantification of highly specific neuronal proteins, i.e., neurofilaments (NFs). Neurofilaments are scaffolding proteins constituting the axonal and, in least quantities, dendritic cytoskeleton, with mainly structural functions. Independently from the causal event leading to degeneration and thus axonal loss, neurofilaments are released in the extracellular fluid, and next CSF and peripheral blood, according to the extent of the damage. Due to the advancement of highly-sensitive automated technologies capable to precisely quantify neurofilaments in vivo, it is now possible to detect them not only in CSF but also in serum. This allows to collect the biospecimen of interest more easily without invasive maneuvers, and potentially to re-assess NFs levels across longitudinal sampling. The sensitivity of current detection methods has empowered to gather data around physiological release of neurofilaments in healthy individuals, obtaining normative data about their rising levels during aging. Moreover, small changes in their concentrations can be traced, boosting comparisons on longitudinal scales [1]. We propose to review how neurofilaments are going to impact research in amyotrophic lateral sclerosis (ALS), dementias (frontotemporal dementia and Alzheimer disease), atypical parkinsonisms, Huntington disease and Creutzfeldt-Jacob disease. Besides aiding in the diagnosis already at the early stages of some of these neurological diseases, when clinical criteria cannot be satisfied, neurofilaments provide a prognostic insight of the nature of the suspected disease. This information may help to plan timely interventions and, on a larger scale, will foster clinical trials helping to stratify patients in homogenous groups. Moreover, their determination may support the assessment of response to putative therapies [2]. This hot topic presentation aims at discussing limits and applications of these powerful biomarkers, with a particular focus on their potentialities for the daily neurological clinical practice.

References: Gaetani L, Blennow K, Calabresi P, Di Filippo M, Parnetti L, Zetterberg H. Neurofilament light chain as a biomarker in neurological disorders. J Neurol Neurosurg Psychiatry. 2019. pii: jnnp-2018-320106.
Khalil M, Teunissen CE, Otto M, Piehl F, Sormani MP, Gattringer T, Barro C, Kappos L, Comabella M, Fazekas F, Petzold A, Blennow K, Zetterberg H, Kuhle J. Neurofilaments as biomarkers in neurological disorders. Nat Rev Neurol. 2018. 14: 577-589

FACIOBRACHIAL DYSTONIC SEIZURES IN ANTI-LGI1 ENCEPHALITIS: A CASE REPORT

Matilde Lazzari, G. Strigaro, C. Varrasi, R. Cantello

Clinical Neurology, Department of Translational Medicine - University of Piemonte Orientale – Novara

Background and Aims Anti leucine-rich glioma-inactivated protein 1 (LGI1) encephalitis is a rare autoimmune encephalitis associated with antibodies against ADAM22 and ADAM23 receptors' ligand protein [1]. The main features are cognitive impairment, hyponatremia and faciobrachial dystonic seizures [2]. Diagnosis may be insidious, due to the frequent aspecific neuroradiological and electrophysiological findings.
Case Report - Material and Methods – Results - We report a case of a 70-year-old man admitted to our Neurological Clinic for progressive mental confusion and memory loss. His past medical history was unremarkable. CT-scan and EEG were normal. After three days recurrent brief and stereotyped episodes with involuntary right face and arm jerking appeared with no consciousness impairment. No ictal electric activity on video-EEG was found. Low dose of Carbamazepine was started. Blood tests revealed a mild hyponatremia. Full-body PET scan was negative. Anti-LGI1 antibodies on both serum and CSF were found and a course of intravenous corticosteroid was started, with a complete clinical remission. The patient was discharge with outpatient follow up visits. Two courses of intravenous immunoglobulin were administered. A second full-body PET scan was still negative. To date, we documented one clinical relapse successfully treated with an additional corticosteroid course.
Discussion and Conclusion We suggest that an accurate clinical history and examination, despite negative neuroradiological and electrophysiological tests, was a powerful tool for a correct initial diagnosis and triggered a prompt administration of a successful immunomodulatory therapy.

References: Lai M. et al. Investigation of LGI1 as the antigen in limbic encephalitis previously attributed to potassium channels: a case series. Lancet Neurol. 2010;9(8):776. Epub 2010 Jun 28.
Sen A. et al. Pathognomonic seizures in limbic encephalitis associated with anti-LGI1 antibodies. Lancet. 2014 Jun;383(9933):2018

OCCULT BREAST TUMOR MIMICS MILLER-FISHER SYNDROME

Clara Lunardon, C. Varrasi, I. Campini, R. Cantello

Department of Translational Medicine, Section of Neurology - University of Piemonte Orientale – Novara

Background and Aims: breast cancer can have a defying course, presenting to clinical attention at an advanced disease stage. Our report describes an atypical presentation of occult breast cancer, with uncommon (orbital) metastasis sites and a paraneoplastic neuropathy, altogether mimicking a Miller-Fisher syndrome.
Materials and Methods, Results: a 55-year-old woman presented to the Emergency Department with bilateral ophthalmoplegia and a left ptosis. A CT brain scan detected a right orbital mass. Biopsy was performed, with a diagnosis of lipoma. A few days later, progressive leg weakness appeared. The patient was transferred to the Neurology Unit, in the suspect of a Miller-Fisher syndrome. Lumbar puncture showed a slight protein increase. Nerve conduction studies (NCS) suggested an acute motor neuropathy. Therefore, a course of intravenous steroid and immunoglobulins was administered with limited benefit. AntiGQ1B and onconeural antibodies were negative. A Brain MRI scan showed multiple lesions involving, among others, the bilateral ocular muscles. A PET scan detected multiple disseminated body metastases. Histology of an inguinal lymph node was positive for metastatic breast cancer with estrogen receptors. A diagnosis of metastatic breast cancer (including the orbits) was then made.
Discussion and Conclusion: in the case of ours, occult breast cancer mimicked a Miller-Fisher syndrome, because of the acute ophthalmoplegia, paraparesis and albumino-cytological dissociation, in a patient with no history of neoplastic disease. However the oculomotor defect was due to orbital metastases, a quite uncommon finding in breast cancer (1). In turn, progressive paraparesis was related to an axonal neuropathy as detected by electrophysiological studies. The neuropathy may be interpreted as paraneoplastic in nature, although common onconeural antibodies were negative. The first orbital mass histology was a false negative result, due to a superficial resection, which delayed the final diagnosis. The correct diagnosis of a solid tumor may be difficult in patients with occult cancer and an acute/subacute neurologic presentation. The clinical picture may be puzzling and requires extra-attention.

References: Amer NM, Bashir G, Ogedegbe A, Saeed I. Metastatic breast cancer: an unusual cause of diplopia. J Cancer Metastasis Treat 2016;2:123-6.

DYSTONIC POSTURES IN FRAGILE X ASSOCIATED TREMOR/ATAXIA SYNDROME

Anna Vera Milner, L. Magistrelli, C. Comi, R. Cantello

Department of Translational Medicine, Section of Neurology - University of Piemonte Orientale – Novara

Background and aim: Fragile X Associated Tremor/Ataxia Syndrome (FXTAS) is a neurodegenerative disease caused by an expansion of the trinucleotide CGG (50 to 200 repeats) in the Fragile X Mental Retardation gene (FMR1). Initially, it was described as a late-onset cerebellar ataxia associated with action tremor. Yet, patients can also suffer from cognitive defects, parkinsonism, peripheral neuropathy and autonomic dysfunction. MRI usually reveals brain atrophy and high signal lesions in the middle cerebellar peduncle in T2/FLAIR sequences. Here we report a 70-year-old male suffering from FXTAS, who presented with typical late-onset ataxia, which was however associated with dystonic postures, a feature not described previously.
Case report: the patient complained of frequent unexplained falls in the last 6 months and short-term memory impairment in the last 2 years. He suffered from chronic hepatitis C virus infection and his family history was unremarkable. His neurological examination revealed a wide-based gait, imbalance, camptocormia with a mild anterocollis and a dystonic posture of the hands. Moreover, he presented dysmetria, striatal toe and slow pursuit movements. There was no dysautonomia. Neuropsychological tests revealed mild mnesic difficulties. Serum and CSF examination were normal. Other potential causes, such as vitamin E deficiency, celiac and Wilson disease, paraneoplastic and autoimmune syndromes were ruled out. Nerve conduction was normal too. Brain MRI showed cortical and subcortical atrophy and hyperintensity of the medium cerebellar peduncles in T2/FLAIR sequences. Because of the clinical and MRI features, a genetic test for FXTAS was performed, with a positive result (99 repeats).
Discussion and conclusion: FXTAS was described almost 20 years ago. Later, its clinical spectrum has been expanded. Affected women have been reported, too. However, the current diagnostic criteria are still based on the classical clinical picture. Thus, FXTAS can be often under-recognized or misdiagnosed. We propose two take-home messages. First, clinicians should keep in mind this rare cause of adult onset ataxia. Secondly, a dystonic posture of the upper limb (not previously described) may be a remarkable feature in the clinical spectrum of FXTAS.

References: Dávila-Ortiz de Montellano D.J et al.; Low Diagnostic Accuracy of Fragile X Tremor/Ataxia Syndrome Diagnostic Criteria in Late Onset Ataxia; Movement Disorders, 2019, 34: 582-583
Grigsby J.; The Fragile X Mental Retardation 1 Gene (FMR1): Historical Perspective, Phenotypes, Mechanism, Pathology, and Epidemiology; Clinical Neuropsychology, 2016, 30: 815-833
Hall D.A. et al.; Emerging Topics in FXTAS; Journal of Neurodevelopmental Disorders, 2014, 5: 31-41

ACUTE CONFUSIONAL MIGRAINE: A CASE REPORT AND LITERATURE REVIEW

Claudia Montabone, E. Virgilio, L. Bolamperti, D. Mittino, R. Cantello

Department of Translational Medicine - University of Oriental Piedmont – Novara

Background/Aims: acute confusional migraine is a rare migraine variant that manifests with sudden confusion, agitation, speech difficulties and memory impairment followed or accompanied by headache. It usually affects children, but in 17% of cases adults are involved. It accounts for 3-10% of migraine variants; about 120 cases are reported in literature. It usually has a benign course with complete resolution of symptoms after 24 hours (except for partial amnesia) and very low recurrence risk.
Materials/Methods: a 44-year-old woman presented to Emergency Department complaining of throbbing headache started on awakening, localized to forehead and vertex (same features of her previous migraine attacks), immediately followed by word-finding difficulties and confusional state. Neurological examination was normal, except for spatial-temporal disorientation and psychomotor agitation. She denied head trauma, epileptic disorders or intercurrent infectious diseases, nor signs of meningeal irritation could be found. She reported 2-3 attacks of migraine with visual aura per month, started about 10 years before, two episodes of aphasic aura and one episode of paraesthetic aura.
Results: blood examinations (including blood gas test) excluded metabolic abnormalities and drug intoxication. Brain Computerized Tomography with angiography excluded cerebrovascular diseases, particularly cerebral sinus venous thrombosis. Electroencephalogram (EEG) evidenced diffuse slow abnormalities, predominantly over anterior regions; antiepileptic drug was started. A lumbar puncture was performed; glucose, protein levels and cellularity were normal, viral and bacterial antigens were undetectable. The patient was admitted to neurology ward, the following day clinical improvement was observed with headache and confusional state resolution. EEG repeated on day 2 and 4 showed progressive decrease and subsequent disappearance of epileptiform abnormalities; antiepileptic drug was interrupted. A magnetic resonance (performed on day 5) showed small frontal white matter hyperintensities (a common finding in migraineurs), intracranial vessels were normal. Blood screening for autoimmune diseases evidenced mild positivity for lupus anticoagulant, not confirmed 12 weeks later. The patient was dismissed at one week from the beginning of symptoms, her neurological exam was normal. Flunarizine as migraine prophylaxis was started. Three months later, she didn't complain any neurological symptom, she reported three attacks of migraine with visual aura.
Conclusion/Discussion: acute confusional migraine needs to be considered in differential diagnosis of sudden confusional state; actually is a diagnosis of exclusion. Absence of brainstem symptoms, transient presence of frontal intermittent rhythmic delta activity on EEG with negative findings at neuroimaging, past history of migraine and short duration of symptoms are the main features of this clinical entity.

References: Schipper S, Riederer F, Sándor PS, Gantenbein AR. Acute confusional migraine: our knowledge to date. Expert Rev Neurother. 2012 Mar;12(3):307-14
Verma R, Sahu R, Jaiswal A, Kumar N. Acute confusional migraine: a variant not to be missed. BMJ Case Rep. 2013 Aug 2;2013
Pietrini V, Terzano MG, D'Andrea G, et al. Acute confusional migraine: clinical and electroencephalographic aspects. Cephalalgia 1987;2013:29-37

FUNCTIONAL TESTS IN MYOTONIC DYSTROPHY TYPE 1: A THREE-YEAR LONGITUDINAL STUDY

Virginia Bozzoni, L. Bello, S. Tripodi, L. Caumo, G. Sorarù, E. Pegoraro

Neuromuscolar Unit, Department of Neuroscience - University of Padua – Padua

Background. Myotonic Dystrophy Type 1 (DM1) is an autosomal dominant multisystem disease caused by an unstable CTG repeat expansion in the 3â€™ UTR of the DMPK gene. DM1 is clinically heterogeneous. Outcome measures in DM1 should be explored to capture patients clinical status, to describe the natural history and to facilitate clinical trial design. Functional tests - including Six-minute walk test (6MWT), 10-meter run and time up and go (TUG) - could represent a reliable method to quantify disease progression. Longitudinal studies in DM1 patients using functional tests, manual muscle testing (MRC scale) and CTG expansion data are scarce. Here we present an observational 3-year longitudinal study to assess the role of functional tests as clinical progression biomarker in DM1.
Materials and methods. Between 2015 and 2018 we longitudinally evaluated 57 DM1 patients according to a neuromuscular assessment protocol including MRC score from 20 muscle, MIRS scale and functional tests - 6MWT, 10-meter run, TUG. Data were analyzed including as covariate CTG expansion size.
Results. Of the 57 DM1 patients included in the study protocol, longitudinal data were available for 49. 6MWT showed a statistically significant decrease at 3 years (-47.5m, SD +/- 87.8, p=0.031), while no significant variations were detected on the 10 meter-run and TUG tests. Muscle strength showed a progressive significant decrement on the average MRC values during the 3-year follow-up (-0.33, SD +/- 0.23, p=0.001).
Conclusion. Our data confirm the well-known slowly progressive course of DM1 and support the use of 6MWT for clinical follow-up.

LONGITUDINAL FUNCTIONAL CHANGES IN A COHORT OF ADULT NUSINERSEN-TREATED SPINAL MUSCULAR ATROPHY PATIENTS AT THE PADOVA NEUROMUSCULAR CENTER

Luca Caumo[1], V. Bozzoni[1], L. Bello[1], C. Semplicini[1], G. Cester[2], J. Gabrieli[2], F. Causin[2], G. Soraru'[1], E. Pegoraro[1]

[1] Department of Neurosciences - DNS - University of Padua – Padua
[2] Neuroradiology Unit - Padova University Hospital – Padova

Objective: To evaluate longitudinal functional changes in clinical outcome measures in a cohort of nusinersen-treated spinal muscular atrophy (SMA) type II and III patients in a single center.
Materials And Methods: Thirty-three ambulant and non-ambulant SMA patients (4 type II and 29 type III), aged 15-68 years, were treated with nusinersen, an antisense oligonucleotide modulating pre-mRNA splicing of the survival motor neuron 2 gene (SMN2). Patients underwent intrathecal administration of 12 mg of nusinersen on days 1 (L1), 14 (L2), 28 (L3), 63 (L4) (loading doses) and approximatively every 4 months thereafter (maintenance doses) (M1, etc). The patients were clinically evaluated at L1, L4 and thereafter every 4 months using Hammersmith Functional Motor Scale-Expanded (HFMSE), Six-Minute Walk Test (6MWT), manual muscle strength evaluation according to Muscle Research Council (MRC) scale, Timed-Function Tests (TFTs) and Revised Upper Limb Module (RULM). RESULTS: Almost all patients reported subjective benefit from the treatment. HFSME (L1-L4 p=0.00002; L1-M1 p=0.001, L1-M2 p=0.029) and MRC (L1-L4 p=0.013; L1-M1 p=0.002, L1-M2 p=0.007) improved significantly. RULM and time to climb 4 stairs were not significant but a positive trend was observed. The 6MWT was significant at L1-L4 (p=0.036) and trended but did not reach significance thereafter.
Conclusions: SMA type II and type III patients treated with nusinersen showed subjective and statistically significant improvement in some meaningful outcome measures.

SELECTIVE CEREBELLAR ATROPHY ASSOCIATES WITH DEPRESSION AND FATIGUE IN THE EARLY PHASES OF RELAPSING REMITTING MULTIPLE SCLEROSIS

Andrea Lazzarotto[1], M. Margoni[1], S. Franciotta[1], S. Zywicki[1], A. Miscioscia[1], A. Riccardi[1], D. Poggiali[1], M. Anglani[2], A. Favaretto[1], P. Gallo[1]

1 Department of Neuroscience - University of Padua – Padova
2 Neuroradiology Unit - University of Padua – Padova

Background. Cerebellar dysfunctions have been associated to depressive disorders and cognitive impairments in neurodegenerative diseases.
Objective. To analyze the possible correlations between cerebellar volumes and fatigue, depression and cognitive impairment in the early phases of relapse-onset multiple sclerosis (RMS). Methods. Sixty-one RMS and 14 healthy controls (HC) were enrolled in the study. All patients underwent Expanded Disability Status Scale (EDSS), Brief Repeatable Battery of Neuropsychological Tests (BRB-NT), Delis-Kaplan Executive Function System Sorting Test (D-KEFS ST), Beck Depression Inventory II (BDI-II), Fatigue Severity Scale (FSS) and the MS Neuropsychological Questionnaire (MSNQ). Cerebellar volumes were automatically obtained using the Spatially Unbiased Infratentorial Toolbox. The relationships between the MRI variables of cerebellar and supratentorial damage and motor, cognitive, fatigue and depression scores were assessed by multiple linear regression analysis.
Results: No difference was found in cerebellar volumes between RMS and HC. Depressed RMS (dRMS) had significantly lower cerebellar volumes (Vermis Crus I) compared with not depressed RMS (ndRMS) (p=0.009), Moreover, dRMS suffering from fatigue had a significantly lower Vermis Crus I volume compared to ndRMS without fatigue (p=0.01). Regression analysis showed that cerebellar lobules V atrophy was an independent predictor of FSS (p=0.034) and Crus I and VIIb atrophy was an independent predictor of BDI-II scores (p=0.026 and p=0.04).
Conclusions: Atrophy of specific cerebellar lobules explains different aspects of disability in RMS. Our study shows that cerebellar pathology is one of the determinants of fatigue and depression in early stages of RMS and further point out to cerebellar pathology as a major determinant of disability.

DRUG-INDUCED NEGATIVE MYOCLONUS: A CASE REPORT

Lisa Lerjefors, M. Mainardi, A. Antonini, M. Carecchio

Department of Neurosciences - University of Padua – Padua

Background: Myoclonus is a shock-like jerk due to brief bursts of muscular activity. Negative myoclonus is caused by a brief cessation of muscular activity. Iatrogenic myoclonus can be caused by several drugs, mainly opiates, antidepressants, antipsychotics and antibiotics.
Aims: To report on a case of drug-induced negative myoclonus in a patient with a complex oral therapy
Materials and Methods: An 83-year-old female was admitted to the neurology ward after subacute onset of generalized involuntary jerks. The patient had abnormal cognition, trigeminal neuralgia and chronic tension-type headache, and was on several analgesic drugs. At clinical examination she was disoriented and aggressive and presented generalized negative myoclonus involving the limbs and trunk, making walking and standing impossible. There were no metabolic abnormalities on blood tests including liver function and plasma ammonium. An EEG/EMG study showed slowness of the background activity and confirmed the presence of negative myoclonus without EEG cortical correlates. Brain MRI was unremarkable. After the admission the patient had a focal epileptic motor seizure (head jerks, clenched jaw and loss of consciousness followed by drowsiness). CSF analysis was normal.
Results: In absence of metabolic and cerebral structural abnormalities, a diagnosis of toxic iatrogenic encephalopathy with negative myoclonus was made. Tramadol and pregabalin were progressively tapered and withdrawn. Ten days later no myoclonic jerks were detectable on examination and patient was discharged.
Discussion and Conclusions: Drug-induced movement disorders are frequent in clinical practice and can mimic several neurodegenerative disorders such as prion diseases, atypical parkinsonism, and paraneoplastic syndromes when presenting with subacute onset. Generalized negative myoclonus is rarely encountered as a side effect of pain killers and must be promptly diagnosed to avoid diagnostic delays.

References: Kojovic M, Cordivari C, Bhatia K. Myoclonic disorders: a practical approach for diagnosis and treatment. Ther Adv Neurol Disord. 4(1): 47-62, 2011.
Janssen S, Bloem BR, van de Warrenburg Bart P. The clinical heterogeneity of drug-induced myoclonus: an illustrated review. J Neurol. 264: 1559-1566, 2017.

A CASE OF RELAPSING HYPERSOMNIA: WHEN HYDROGEN BREATH TEST FOR SMALL INTESTINAL BACTERIAL OVERGROWTH CAN BE USEFUL FOR MANAGEMENT OF KLEINE-LEVIN SYNDROME

Giorgia Bernabé, A. Melpignano, I. Trippi, R. Ciliento, C. Mutti, L. Parrino

Neurology - University of Parma – Parma

A 13 year-old boy started to present recurrent episodes, lasting from 3 to 12 days, characterized by prolonged sleep time, megaphagia, derealization, mood depression, rudeness and hypersexual behavior. Episodes occurred after infectious diseases (eg, flu syndrome), moderate alcohol assumption or sleep deprivation and were often heralded by terrifying visual hallucinations. Physical examination, blood tests, lumbar puncture, EEG, brain CT scan and MRI were normal. Structured interview, prolonged PSG investigation and actigraphic monitoring findings were consistent with a diagnosis of Klein-Levin syndrome (KLS) [1]. A PET/CT with 18F-fluorodeoxyglucose (FDG-PET) during active symptoms showed diffuse hypometabolism in left frontal and occipital lobes, parahippocampal gyrus, cingulate gyri, caudate nucleus, temporal lobes, parietal lobes, right medial frontal gyrus. One month after symptoms remission PET revealed persistence of cerebral hypometabolism although significantly reduced in cingulate gyri, temporal lobes, left frontal lobe, left parietal lobe and right parahippocampal gyrus. FDG-PET in KLS has been explored in number of studies [2]. In our case, FDG-PET revealed diffuse reduction of CMRglc during active period. These PET findings are compatible with the symptoms reported by the patient, especially irritable behavior and hyperphagia (orbito-frontal cortex); emotional cues processing (ventral anterior cingulate, dorsal anterior cingulate), depression (anterior cingulate cortex), hallucinations (occipital lobe), cognitive impairment and hypersexuality (parieto-temporal cortex). Hypometabolism was significantly decreased in the remission period but not completely withdrawn. To better understand the pathophysiology of KLS and considering the link between infective episodes and KLS relapse, a gastro-intestinal evaluation revealed a positive hydrogen breath test related to small intestinal bacterial overgrowth (SIBO). The patient has been symptom-free and behaviorally normal for months, paralleled by a negative breath test for SIBO. The last three relapses were associated with the reappearance of a positive breath test for SIBO supporting strong connection between intestinal environment and central nervous system [3]. Although limited to a single case, the breath test for SIBO could be a routine diagnostic procedure whenever KLS is suspected. Furthermore, our findings suggest a link between gastrointestinal microbiota and brain function, perhaps through metabolic or immune-mediated mechanisms.

References: Kleine-Levin syndrome. Arnulf I. Sleep Med Clin 2015 Jun;10(2):151e61. https://doi.org/10.1016/j.jsmc.2015.02.001 [Review].
Neuroimaging in the Kleine-Levin Syndrome. Engström M et al, Current Neurology and Neuroscience Reports (2018) 18: 58 https://doi.org/10.1007/s11910-018-0866-y
Interrelationships between gut microbiota and host: paradigms, role in neurodegenerative diseases and future prospects. Caballero-Villarraso J, Galvan A, Escribano BM, et al CNS Neurol Disord Drug Targets 017;16(8): 945e64.

GENDER DIFFERENCES IN THE CLINICAL PRESENTATION OF CLUSTER HEADACHE

Lara Ahmad, M. Allena

IRCCS Mondino Foundation; Department of Brain and Behavioral Sciences - University of Pavia – Pavia

Introduction Cluster Headache (CH) is a very well characterized primary headache disorder. CH mostly affects men but an increasing percentage of women also suffers from this disease. Available data on gender-related differences in CH are very scarce and partly discordant. The aim of this manuscript is the careful definition of clinical profile of CH between the sexes in order to identify specific gender-related variables of the disease.
Material and methods Retrospective analysis on the large clinical database of CH patients diagnosed and followed at the Pavia Headache Center, a tertiary headache clinic.
Results We collected data from 250 CH patients, 163 males (mean age 41.46 + 10.37) and 87 females (mean age 41.73 + 19.92). The mean age of CH onset was similar for both sexes but surprisingly the onset of disease often coincided with periods of abrupt fluctuations of sexual hormone levels (menarche, post-partum, menopause). During the bouts, women statistically had more attacks per day overall (p= 0.04) and a longer mean attack duration (80.9 + 50.3 minutes vs 66.01 + 32.7 minutes, p=0.008) than men. As regards autonomic associated symptoms, they were almost equally prevalent in women and men, with the exception of miosis, which was predominant in female sufferers, and enlarged temporal artery, more expressed in men. Nausea, osmophobia and vomiting were reported more frequently by women (p=0.04, p=0.037 and p=0.04, respectively). Concomitant thyroid diseases (23% vs 1.8%, p=0.001) and psychiatric disorders (17.2% vs 9.2%, p= 0.04) mostly occur in women than men. On the contrary, snoring in sleep and smoking habit is more frequent in men: 53.4% vs 19.5% (p=0.00) and 67.5% vs 49.4% (p=0.005), respectively.
Conclusion Despite an overall similar clinical presentation of cluster headache in both sexes, in women some features seem to overlap with migraine (longer duration of attacks and "migrainous" symptoms during the attacks). Moreover, CH onset in women is related with reproductive milestones (menarche, pregnancy, menopause) that usually modulates the pattern of migraine. These findings may have a relevance in terms of a pathophysiological role of sexual hormones so far unexplored in CH.

References: Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. Cephalalgia. 2018; 38 (1):1-211.
Manzoni GC. Gender ratio of cluster headache over the years: a possible role of changes in lifestyle. Cephalalgia 1998; 18:138-142
Rozen TD, Fishman RS. Female cluster headache in the United States of America: what are the gender differences? Results from the United States Cluster Headache Survey. J Neurol Sci 2012; 317:17-28.

CAN WE USE GENETICS TO DISCRIMINATE BETWEEN MULTIPLE SCLEROSIS AND ADULT-ONSET POST-INFECTIOUS NEUROLOGICAL SYNDROMES?

Riccardo Currò[1], F. Martinelli-Boneschi[2], F. Clarelli[3], G. Berzero[4], S. Santoro[3], M. Sorosina[3], L. Ferré[3], S. Peroni[3], G. Comi[3], A. Guglielmi[4], E. Vegezzi[4], I. Callegari[4], A. Cortese[4], F. Esposito[3], E. Marchioni[4]

[1] Neurology - University of Pavia – Pavia
[2] Multiple Sclerosis (MS) Research Unit and Department of Neurology - IRCCS Policlinico San Donato - San Donato Milanese, Milan
[3] Laboratory of Human Genetics of Neurological Diseases, CNS Inflammatory Unit & INSPE - IRCCS San Raffaele Scientific Institute – Milan
[4] Neuroscience Consortium - University of Pavia, Monza Policlinico and Pavia Mondino - Pavia, Italy

Background: Whilst diagnostic criteria and genetic risk scores have been clearly defined for multiple sclerosis (MS), there is still no consensus on the diagnostic criteria for postinfectious neurological syndromes (PINS) in adult patients, and few data are available about the genetic factors underlying these conditions. The aim of this study is to identify the genetic loci associated with an increased risk of PINS in adult patients, in order to establish whether they differ from the genetic loci associated with MS.
Methods: We performed a retrospective research in the institutional database of the Mondino Foundation for all patients diagnosed with PINS from 1996 to 2016. The clinical, radiological and biological characteristics of these patients were collected and reviewed. Patients available for a neurological revaluation were recruited and underwent blood sampling. Genotypes were imputed using the 1000 Genomes Project as reference panel. A weighted genetic risk score (wGRS) was calculated based on known MS loci.
Results: A total of 88 patients were included in the analyses. Neurological presentation was commonly characterized by symptoms of myelitis, whether or not accompanied by encephalic lesions. Twenty-eight patients had combined CNS and peripheral nervous system (PNS) involvement. MRI commonly disclosed inflammatory alterations located in the spinal cord (85%), in the subcortical and/or periventricular white matter (34%), and in the infratentorial region (34%). Sixty out of the 80 patients (75%) had inflammatory CSF findings. The mean follow-up duration in our cohort was 7.2 years. The disease course was monophasic in the majority of patients (67%), while a minor proportion experienced relapses (18%) or a chronic progressive course (15%). The wGRS score of PINS cases was comparable to 370 healthy controls (wGRS=20.9 vs 20.7), while significantly lower compared to 907 RRMS cases (wGRS=21.2; $p<0.0001$)
Conclusions: Differentiating PINS from MS can be challenging, especially in the case of atypical presentations. Our study confirms that MS and PINS not only differ with regard to a number of clinical and paraclinical features but also with regard to the genetic susceptibility

profile. A better discrimination between these two conditions is of paramount importance due to prognostic and therapeutic implications.

References: Marchioni E, Ravaglia S, Montomoli C, et al. Postinfectious neurologic syndromes: a prospective cohort study. Neurology 2013;80:882-889.
International Multiple Sclerosis Genetics Consortium Low-Frequency and Rare-Coding Variation Contributes to Multiple Sclerosis Risk. Cell (2018) 175:1679-87
Dale RC, de Sousa C, Chong WK, Cox TC, Harding B, Neville BG. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain. 2000;123(Pt 12):2407-22

IDIOPATHIC DIFFUSE SUPERFICIAL SIDEROSIS IN CNS: A CASE REPORT WITH APPLICATION OF RATIONAL INVESTIGATION

Giuseppe Fiamingo

Neurology - University of Pavia – Pavia

A 60-year-old man presented with a 4-year history of progressive disesthesias in the inferior limbs. The pain started in the left foot, spreaded contralaterally and raised up to both knees. Over the same period bilateral hearing loss and gait instability developed. He underwent MR imaging of head and spine that showed linear hemosiderin deposit on the brainstem, in paravermian spaces, lateral sulci, the mesial tempor-frontal lobes and the anterior regions of the medulla. A diagnosis of diffuse sovra-infratentorial and spinal siderosis was made according to classical symptoms at onset and radiological findings. No regards on etiology were supposed because of lack of major CNS bleeding evidence. The patient was started on therapeutic phlebotomies and pregabalin, waiting for admission to the IRCSS Mondino, Pavia (Italy) for further evaluation. In patientâ€™s clinical history there was no evidence of remarkable diseases related to the clinical picture, except for previous traumas (diving head concussion during childhood, back trauma skiing at age 20). Familiar history was unremarkable for neurological diseases. Neurological examination revealed normal cortical functions, right abducent nerve palsy, bilateral hypoacusia, paretic hypertonus and weakness of left lower limb, brisk reflexes in both upper and lower limbs, bilateral Babinskiâ€™s sign, slight dysmetria, disesthesias in lower limbs up to the groin on the left, hypopallestesia in the malleoli, a wide-based ataxic gait with paretic features, positive Romberg and pull test. On laboratory exams no abnormal values were found. An audiogram confirmed sensorineural hearing loss. Somatosensory and motor evoked responses revealed central conduction delay. No cognitive deficits where shown on tests. Lumbar puncture revealed raised albumin, tau and phosphor-tau levels; on spectrophotometry bilirubine was proved. The known CNS iron deposits were better established with further MR imaging of head and spine. A T2-weighted sequence revealed vascular abnormalities in posterior subdural layer from D9 to the medullary cone. Gadolinium-enhanced MR angiography suggested the presence of serpiginous vessels at that level. The patient underwent catheter spinal angiography, whose results were negative for vascular malformations. The presumptive diagnosis was superficial siderosis secondary to chronic micro-bleeding from a dural abnormality. A myelogram was performed and whole spine myelography CT was obtained, showing a pseudomeningocele in D2-D7 segment, diffuse contrast opacification and epidural abnormalities. A diagnosis of CNS superficial siderosis due to blood leakage from pseudomeningocele was performed. The patient was then referred to the neurosurgery department of Policlinico S. Matteo, Pavia (Italy) for surgical evaluation.

References: Wilson, D., Chatterjee, F., Farmer, S. F., Rudge, P., McCarron, M. O., Cowley, P., & Werring, D. J. (2017). Infratentorial superficial siderosis: classification, diagnostic criteria, and rational investigation pathway. Annals of neurology, 81(3), 333-343.

REVERSIBLE VASOCONSTRICTION SYNDROME CLINICAL AND RADIOLOGICAL SPECTRUM: A CASE SERIES

Federico Mazzacane[1], E. Rognone[2], I. Canavero[3], V. Genovese[2], E. Leuci[4], M. Zaccarelli[4], A. Morotti[5]

[1] Neurology - University of Pavia – Pavia
[2] Neuroradiology - IRCCS C. Mondino Foundation – Pavia
[3] Emergency Neurology - IRCCS C. Mondino Foundation - Pavia
[4] Stroke Unit - IRCCS C. Mondino Foundation – Pavia
[5] Neurology and Neurorehabilitation - IRCCS C. Mondino Foundation - Pavia

Background: Reversible cerebral vasoconstriction syndrome (RCVS) clinical presentation includes thunderclap headache (94-100%), focal neurological deficit, altered consciousness, seizures and posterior reversible encephalopathy syndrome. Neurovascular imaging shows diffuse, multifocal segmental stenosis of intracranial arteries. These vascular alterations should be reversible in 3 months. RCVS clinical course is typically monophasic but during the single episode, multiple attack of thunderclap headache are frequent. The main complications of RCVS are hemorrhagic or ischemic stroke and brain edema; Up to 20% of patients experience persistent neurological deficit. Death rates ranges between 0-2 %. RCVS affects mostly woman (2:1 ratio), usually aged 20 to 50 years. RCVS may be primary or secondary (25-60%); the main known triggers of secondary RCVS are vasoactive drugs. The differential diagnosis includes primary CNS vasculitis, migraine and other causes of thunderclap headache such as intracranial aneurysm with or without evidence of subarachnoid hemorrhage, cerebral venous thrombosis and cervical artery dissection.
Case Reports: 1- a women aged 51 years with unremarkable medical history presented to the ED with TCH, nonresponsive to non-steroideal anti-inflammatory drugs. CT scan ruled out acute ischemic/hemorrhagic lesions. After recurrent TCH event she underwent MRI and MRA with evidence of parieto-occipital SAH and multiple stenosis of intracranial arteries.
2- 31-years-old man with a history of migraine with and without aura and recent indomethacin abuse as symptomatic medication developed TCH, altered consciousness, and agitation that needed ICU admission. MR angiography (MRA) showed multifocal intracranial stenosis, confirmed by angiography. He was treated with intra-arterial nimodipine with good clinical and radiological response.
3- a women with 51 years with a history of migraine was evaluated at the ED for an episode of TCH; CT scan was negative. She was treated with indomethacin and alizapride and discharged. She developed a recurrent episode in the following days and underwent MRI and MRA that showed a left parietal intraparenchymal hematoma with associated SAH and vascular alteration compatible with RCVS.

Discussion: In our series we present the clinical and imaging characteristics of RCVS, underling the importance of considering this condition in patients presenting with TCH, particularly in patients with recurrent episodes of TCH. We also highlight the role of MR angiography as a valuable neuroimaging modality in the diagnosis and follow-up of these patients.

References: Anne Ducros. Reversible cerebral vasoconstriction syndrome. Lancet Neurol 2012; 11: 906-17
Calabrese LH, Dodick DW, Schwedt TJ, Singhal AB. Narrative Review: Reversible Cerebral Vasoconstriction Syndromes. Ann Intern Med. 2007;146:34-44.

SCENERY OF IDIOPATHIC GENERALIZED EPILEPSY IN THE ADULT AGE: DATA FROM A THIRD LEVEL EPILEPSY CENTRE

Elisa Micalizzi

Neurology - University of Pavia – Pavia

Objectives To describe clinical characteristics of Idiopathic Generalized Epilepsy (IGE) in adult patients followed by one single epileptologist, in order to analyze long-term outcome, the possible role of precipitant factors, the presence of atypical clinical and EEG features and the specific needs of the adult patient.
Materials and Methods Retrospective analysis of clinical data, EEG, therapy and social aspects of consecutive outpatients referred to the Epilepsy Centre of Pavia, signed in the electronic database of the Institute from 01/01/2005 to 31/12/2017, with a diagnosis and follow-up of at least 3 years made by one single epileptologist. We defined three patterns of outcome considering the time to achieve a seizure free condition (1 year, early; 5 years, late; or never remission).
Results 253 patients were selected (60,5% females), followed-up for 11.5 years (mean, range-3-39), mean age at the onset of 16.4 years old and of 37.1 years old (range 21-89) at the last clinical observation. Considering the three electro-clinical IGE syndromes, GTC only showed a higher age at onset of epilepsy (19,9 Â± 11,6 yrs, meanÂ±SD), a greater proportion of male gender (53,8%), and of precipitant factors throughout the clinical course (42%); Juvenile Absence Epilepsy (JAE) showed the higher age at the last seizure (32,4 Â± 13,1 yrs, meanÂ±SD) and Juvenile Myoclonic Epilepsy (JME) the higher proportion of photosensitivity (PPR) (52,9%). 38% of the whole sample achieved early seizure-freedom, 19% late, and 43% never reached such condition; a pattern of outcome of never remission was more likely in the JAE subgroup (p< 0.0001). Precipitating factors determining recurrence of seizures were present in 33,6% of cases. In 13,8% of patients, sleep-related seizures were reported. Moreover, atypical clinical (ictal focal signs) and EEG (asymmetrical or focal abnormalities) features were found in 16,2 % and 17,9% of cases, respectively. 27,7% of patients attempted a withdrawal of antiepileptic treatment, with recurrence of seizures in 70% of them, particularly in those with PPR. PPR was significantly associated with a less favourable outcome (p=0.04).
Discussion A remarkable proportion of adult patients with IGE have active epilepsy. According to literature, we confirm a worse prognosis of JAE compared to JME and GTC only. PPR appeared to be a significant negative prognostic factor in our sample.
Conclusion In the adult setting, it is important to consider precipitant factors and the presence of some EEG characteristics (PPR) for the clinical and therapeutic management of IGE adult patients.

References: Camfield CS, Camfield PR. Juvenile myoclonic epilepsy 25 years after seizure onset. Neurology 2009;73:1041-1045. Senf P, Schmitz B, Holtkamp M, Janz D. Prognosis of juvenile myoclonic epilepsy 45 years after onset: seizure outcome and predictors. Neurology 2013;81:2128-2133.
Holtkamp M, Kowski B, Merkle H, and Janz D. Long-Term Outcome in Epilepsy with Grand Mal on Awakening: Forty Years of Follow-up. ANN NEUROL 2014;75:298-302.

VALIDATION OF THE DYMUS SCREENING QUESTIONNAIRE TO ASSESS DYSPHAGIA IN PARKINSON'S DISEASE AND ATYPICAL PARKINSONIAN DISORDERS

Alessia Putorti[1], M. Avenali[2], C. Dagna[2], R. De Icco[2], M. Gandolfi[3], C. Solaro[4], D. Restivo[5], M. Bartolo[6], F. Meneghello[7], G. Sandrini[1], C. Tassorelli[1], - Dypak Sirn Group

[1] Department of Brain and Behavioral Sciences, University of Pavia- Pavia
[2] Unit of Neurorehabilitation, IRCCS Mondino Foundation, Pavia- Pavia
[3] Neuromotor and Cognitive Rehabilitation Research Center (CRRNC) - Verona – Verona
[4] Department of Rehabilitation, C.R.R.F. "Mons. L. Novarese", Moncrivello
[5] Department of Neurology, Garibaldi Hospital - Catania
[6] Department of Rehabilitation and Advanced Technologies, Habilita Hospital, Zingonia di Ciserano
[7] IRCCS San Camillo – Venezia

Introduction: Dysphagia is a common debilitating symptom in people suffering from extrapyramidal disorders. The DYMUS questionnaire, which has already been validated for the early screening of dysphagia in Multiple Sclerosis (Bergamaschi et al. 2008 e 2009), might also prove useful for screening dysphagia in parkinsonian syndromes.
Aims: Assessing the ability of the DYMUS questionnaire to identify, at an early stage, the presence of dysphagia in patients affected by Parkinson's disease (PD) and atypical parkinsonian disorders (APD).
Materials And Methods: This is an observational multi-centric study involving 145 patients affected by PD and ADP. All subjects filled in the DYMUS and the EAT-10 dysphagia scale and underwent a thorough clinical evaluation of dysphagia by the speech therapist. A subgroup of patients also fibroendoscopic evaluation of dysphagia.
Results: The DYMUS questionnaire showed a good level of internal consistency (Cronbach's alfa 0.77). We observed significantly higher Dymus scores in patients who were mildly (3.9±2.3) or moderately (5.3±2.8) dysphagic at the bedtest evaluation, as compared to non dysphagic subjects (1.5±1.8), with a p=0.001 value for both. ROC curve analysis showed that a DYMUS score > 2 is the cut-off for detecting a potential swallowing impairment.
Conclusion: The DYMUS questionnaire proved to be a reliabl screening tool to assess dysphagia in patients suffering from extrapyramidal diseases. It is easy and quick to administer, which makes it adequate for widespread uptake in the clinical practice.

References: Michelle R. Ciucci, CCC-SLP, Laura M. Grant, Eunice S. Paul Rajamanickam, Breanna L. Hilby, B.S., Katherine V. Blue, B.A., Corinne A. Jones. "Early Identification and Treatment of Communication and Swallowing Deficits in Parkinson Disease", Semin Speech Lang. 2013 August.
Bergamaschi R, Rezzani C, Minguzzi S, Amato MP, Patti F, Marrosu MG, Bonavita S, Grasso MG, Ghezzi A, Rottoli M, Gasperini C, Restivo D, Maimone D, Rossi P, Stromillo ML, Montomoli C, Solaro C; "Validation of the DYMUS questionnaire for the assessment of dysphagia in multiple sclerosis" DYMUS Group.

THE DIZZY PATIENT IN THE EMERGENCY DEPARTMENT: A THOUGHTFUL CLINICAL EVALUATION IS MORE EFFECTIVE THAN MRI

Francesco Turco[1], M. Versino[2]

[1] Neurology - University of Pavia – Pavia – Varese
[2] Neurology Unit and Stroke Unit, ASST Settelaghi, Circolo Hospital – DMC University of Insubria - Varese

Dizziness is a common complaint in the Emergency Department (ED) and a main reason for neurological evaluation. Differential diagnosis is wide and includes both benign self-limiting causes and serious conditions that require prompt treatment: strokes account for 3-5 % of accesses at the ED for dizziness (1), and dizzy patients are among those who are more likely to suffer from a stroke in the following 48 hours after presentation. Misdiagnosis at first evaluation is common but a standardized clinical approach, based on new paradigms, can improve diagnostics accuracy significantly.
The TiTraTE algorithm (2) prompts to consider the timing (acute or episodic), the presence of trigger factors (spontaneous or triggers) and to perform a target examination accordingly. For instance in the case of a spontaneous acute vestibular syndrome, namely the condition where a possible sroke has to be differentiated form a vestibular neuritis, the clinical HINTS+ algorithm is more sensitive and specific than MRI within a 72-hour time frame. The HINTS algorithm (3) considers 1) the nystagmus (peripheral: horizontal, pluripositional but unidirectional; central: vertical, torsional and when horizontal pluripositional but direction changing) 2) the head impulse test (peripheral: positive; central: negative) 3) test of skew by using the cover test (peripheral: negative; central positive) 4) concomitant hypoacusis (peripheral: no; central yes). When episodic vertigo is triggered by position changing, the Benign Paroxysmal Positional Vertigo (BPPV) is the most likely diagnosis: the Dix Hallpike (for the posterior and anterior canals) and the McClure (for the lateral canal) manoeuvres will rule out more serious medical condition, as Central PPB and orthostatic hypotension.

References: (1) Saber Tehrani AS, Kattah JC, Kerber KA, et al. Diagnosing stroke in acute dizziness and vertigo: pitfalls and pearls. Stroke 2018;49
(03):788-795
(2) Gurley K, Edlow JA Acute Dizziness Semin Neurol 2019;39:27-40
(3) Kattah JC, Talkad AV, Wang DZ, Hsieh YH, Newman-Toker DE. HINTS to diagnose stroke in the acute vestibular syndrome: three-step bedside oculomotor examination more sensitive than early MRI diffusion weighted imaging. Stroke 2009; 40: 3504-10

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PREVALENCE OF RIGHT-TO-LEFT SHUNT (RLS) AND VOLUMETRIC BRAIN CHANGES IN PATIENTS WITH EPISODIC AND CHRONIC MIGRAINE

Paolo Cerrone[1], F. Pistoia[2], M. Quarantelli[3], I. Frattale[2], A. Carolei[2], C. Marini[4], A. Splendiani[2], S. Sacco[2]

[1] Neurology - University of L'Aquila - L'Aquila
[2] Department of Biotechnological and Applied Clinical Sciences - University of L'Aquila - L'Aquila
[3] Biostructure and Bioimaging Institute - National Research Council – Naples
[4] Department of Life, Health and Environmental Sciences - University of L'Aquila - L'Aquila

Background Patent foramen ovale (PFO) is a relatively common condition in the general population, ranging from 15% to 35% of the healthy subjects and is the most frequent cause of right-to-left shunt (RLS). Several caseâˆ'control studies have indicated that PFO is more common in patients with migraine than in non-migraineurs, but a causal relationship between the two conditions has not been demonstrated. Migraine has also been associated with subclinical brain lesions but the association between PFO and subclinical brain lesions in migraineurs remains unclear.
Aims of the study were to evaluate the prevalence and the characteristics of the PFO in the study population and to determine if there is an association between PFO and volumetric brain changes in specific cortical and subcortical areas.
Methods Patients consecutively referring to the Regional Headache Centre of L'Aquila with a diagnosis of migraine were screened for the inclusion in the study. The diagnosis of EM or CM was made according to the criteria of the International Classification of Headache Disorders (ICHD-III beta version). Patients underwent a neuroradiological assessment through a 3T Magnetic resonance Imaging (MRI) scanner (Discovery MR750w) to acquire structural T1w volumes. Right-to-left shunt (RLS) was detected by Transcranial Doppler (TCD) sonography with the intravenous injection of agitated saline. The exam was done under basal conditions and after Valsalva maneuver.
Results Sixteen women with episodic migraine (EM) (mean age 40.44Â±9.60) and 11 women with chronic migraine (CM) (mean age 42.64Â±10.09) were included. A RLS was diagnosed in 13 patients (mean age 45.0Â±9.9 years, disease duration 25.3Â±11.2 years). No PFO was detected in the others (mean age 38.0Â±8.5 years, disease duration 12.7Â±6.9 years). Two clusters of significantly reduced gray matter (GM) in the group of patients with PFO emerged respectively within the left calcarine gyrus and encompassing both thalami.
Discussion Our findings suggest that the presence of PFO can be associated with structural changes in patients with migraine. A better characterization of such changes, which may be detected through advanced neuroimaging analyses, can lead to a better understanding of the association between migraine and PFO.

Conclusions Identifying the presence of PFO in patients with migraine and investigating its association with any grey matter changes may be extremely useful in order to elucidate the role of PFO in migraine pathogenesis and to develop more tailored management approaches in patients showing this association.

References: Ashburner J. A fast diffeomorphic image registration algorithm. Neuroimage 2007;38:95-113
Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS. A voxel-based morphometric study of ageing in 465 normal adult human brains. Neuroimage 2001;14:21-36
Mazziotta J, Toga A, Evans A, et al. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). Philos Trans R Soc Lond B Biol Sci 2001;356:1293-1322

ANTICOAGULANT-RELATED INTRACEREBRAL HEMORRHAGE: 6-YEAR DATA FROM A POPULATION-BASED STROKE REGISTRY

Enrico Colangeli[1], M. Gentile[2], R. Ornello[2], C. Tiseo[2], G. Perrotta[2], C. Scarpato[2], S. Sacco[2]

[1] Neurology – University of L'Aquila – L'Aquila
[2] Biotechnological and Applied Clinical Sciences - University of L'Aquila - L'Aquila

Background The characteristics and mechanisms of anticoagulant-related intracerebral hemorrhage (AR-ICH) are poorly studied especially in population-based settings.
Aims We compared the characteristics of patients with AR-ICH with those not related to oral anticoagulants (nAR-ICH) in a prospective population-based registry.
Materials and Methods We included in our registry all first-ever strokes occurring in residents of the district of L'Aquila. Cases were identified by active monitoring of all the available sources within the district and in nearby areas. For the purpose of this study we focused on data regarding patients with a first-ever ICH in 2011-2016. AR-ICH was defined in the presence of treatment with warfarin with INR>2.0, direct oral anticoagulants within 3 days, full-dose heparin, or non-IS systemic thrombolysis [1].
Results Out of 434 patients with ICH (58.3% men, mean age 74.4Â±13.3 years); 45 (10.4%) had AR-ICH; 39 (86.7%) were taking warfarin (mean INR at ICH onset of 2.9Â±1.0) and 6 (13.3%) were on direct oral anticoagulants. Patients with AR-ICH were older than nAR-ICH patients (79.8Â±7.9 vs 73.4Â±13.7 years; P=0.002). AR-ICHs were lobar in 19 (42.2%) patients, deep in 17 (37.8%), and in posterior fossa or multiple locations in 9 (20.0%), while among nAR-ICHs 170 (43.7%) were lobar, 163 (41.3%) deep, and 56 (14.4%) in posterior fossa or multiple locations (P=0.240). Prevalence of arterial hypertension (80.0% vs 61.2%; P=0.013) and atrial fibrillation (77.8% vs 10.5%; P<0.001) were higher in subjects with AR-ICH than in those with nAR-ICH, while prevalence of diabetes mellitus, hypercholesterolemia, and coronary heart disease was similar. NIHSS score at ICH onset did not differ between AR-ICH and nAR-ICH (P=0.739). Thirty-days (57.8% vs 34.2%; P=0.002) and 1-year (60.0% vs 41.4%; P=0.017) case-fatality rates were higher in AR-ICH than in nAR-ICH patients. The Cox regression analysis showed that stroke severity was the only independent predictor of 30-days (HR per each NIHSS point 1.07; 95% CI, 1.04-1.11; p<0.001) and 1-year (HR 1.07; 95% CI, 1.04-1.10; p<0.001) case-fatality.
Discussion and Conclusions We found a higher prevalence of arterial hypertension and atrial fibrillation and a higher 30-day and 1-year case-fatality in patients with AR-ICH compared with nAR-ICH that was independent of anticoagulant use. Notably, 86.7% of patients with AR-ICH occurred in patients on treatment with warfarin. The epidemiology of AR-ICH will likely change with the increasing use of direct oral anticoagulants.

References: Meretoja A, Strbian D, Putaala J, Curtze S, Haapaniemi E, Mustanoja S, Sairanen T, Satopaa J, Silvennoinen H, Niemela M, Kaste M, Tatlisumak T. SMASH-U: a proposal for etiologic classification of intracerebral hemorrhage. Stroke. 2012;43:2592-2597

CAROTID DISSECTION WITH EAGLE SYNDROME: A CASE REPORT

Ciro Scarpato[1], G. Perrotta[2], R. Ornello[2], C. Tiseo[2], E. Colangeli[2], B. Orlandi[3], F. De Santis[3], F. Notturno[3], S. Sacco[2]

1 University of L'Aquila – L'Aquila
2 Department of Applied Clinical Sciences and Biotechnology - University of L'Aquila - L'Aquila
3 Department of Neurology and Stroke Unit - AZH - ASL1 AZ-SU-AQ – Avezzano

Background Cervical artery dissection (CAD) is a dangerous clinical entity causing several and life-threatening neurological deficits, including ischemic stroke. Cervical artery dissection can be traumatic or spontaneous. Neck traumas may cause dissection with formation of an intramural hematoma resulting in thrombosis or vascular stenosis or occlusion.
Methods We report a case of right internal carotid artery (ICA) dissection caused by a blunt trauma of the neck in a patient with stylocarotid artery syndrome (Eagle syndrome).
Discussion A 52-year-old male with a medical history of arterial hypertension and nephrolitiasis was admitted to the Emergency Department for an acute onset of trouble speaking and disphagia associated with right ptosis. Ten days before, the patients complained pain on the right side of the neck after playing a football match in which he reported extreme head rotation. At admission, the patient was alert, with right ptosis and miosis and disorder of the glossopharyngeal nerve causing right deviation of the tongue, rhinolalia. There was no associated weakness or other focal neurological deficit. Non-contrast head computed tomography (CT) was unremarkable. CT angiography (CTA) of the head and neck showed decreased flow in the right ICA in the cervical-petrous tract with an hypodense ring and eccentric true lumen, suggesting for intramural hematoma. Magnetic resonance imaging (MRI) showed no acute infarction on diffusion-weighted imaging; however, magnetic resonance angiography (MRA) showed decreased flow in the right ICA. With the support of tridimensional CTA reconstructions, a calcified right stylohyoid ligament was found near the carotid artery. The patient was diagnosed with posttraumatic right carotid artery dissection and received anticoagulation with no further disturbances. CTA at 6 months showed improved flow in the right cervical ICA.
Conclusions Eagle syndrome is caused by an elongated styloid process or a calcified stylohyoid and stylomandibular ligament. The elongated styloid process may compress the glossopharyngeal nerve and surrounding structures, causing recurrent odynophagia and cervical pain. The identification of the pathophysiology underlying CAD is required in order to estimate the risk of recurrent cerebral ischemia and to select optimal treatment methodology. Although Eagle syndrome is a rare cause of CAD, it needs to be investigated, expecially in young patients with blunt trauma of the neck.

References: Piagkou M, Anagnostopoulou S, Kouladouros K, Piagko G. Eagleâ€™s syndrome: a review of the literature. Clin Anat 2009;22:545-58.
Eagle WW. Symptomatic elongated styloid process: report of two cases of styloid process-carotid artery syndrome with operation. Arch Otolaryngol 1949;49:490-503
Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. Lancet Neurol 2009;8:668-78.

SYNAPTIC VESICLE PROTEIN 2A TUMORAL EXPRESSION PREDICTS LEVETIRACETAM ADVERSE EVENTS

Carmen Calvello[1], M. Romoli[1], M. Mandarano[2], M. Romozzi[1], P. Eusebi[3], C. Bedetti[1], E. Nardi Cesarini[1], A. Verzina[1], E. Loreti[2], A. Sidoni[2], P. Giovenali[2], P. Calabresi[1], C. Costa[1]

[1] Neurology - University of Perugia – Perugia
[2] Department of Experimental Medicine, Section of Anatomic Pathology and Histology - University of Perugia – Perugia
[3] Department of Medical and Surgical Specialties and Public Health - University Hospital of Perugia – Perugia

Background: Levetiracetam (LEV), an antiepileptic drug targeting synaptic vesicle protein 2A (SV2A), is a first line treatment for brain tumor related epilepsy (BTRE)[1]. Despite SV2A tumoral expression influences drug effectiveness [2], little is known regarding its impact on the occurrence of neuropsychiatric adverse events (NPAEs).
Aims: We aimed to correlate the expression of SV2A in tumoral and peritumoral tissue of patients with glioma and BTRE to the occurrence of NPAEs of LEV.
Materials and Methods: Specimens from patients enrolled in the multicenter COMPO study, with glioma and BTRE treated with LEV, undergoing neurosurgery were retrieved. Immunohistochemistry-based expression of SV2A in tumoral and peritumoral tissue was scored in a 4-point scale from absent (score=0) to strong (score=3). Low immunoreactivity (IR) corresponded to scores<2. Staining ratios (tumoral SV2A IR/peritumoral SV2A IR) were grouped into low (â‰¤0.5) and high (>0.5). NPAEs were assessed longitudinally with the Neuropsychiatry Inventory 12 test (NPI-12)[3].
Results: Overall, 18 patients were eligible for analysis. All received LEV monotherapy, with 67% developing NPAEs. Patients with NPAEs had significantly lower median SV2A intensity score compared to patients without NPAEs (score 1 vs 0, p=.025). Low staining ratio (â‰¤0.5) associated with higher NPAEs occurrence compared to SR>0.5 (85.7% vs 0%, p<.01). A SR‰0.5 predicted a consistent increase in risk of NPAEs (OR 45.0; 95%CI 1.8-1128; p=.02).
Discussion and Conclusion: SV2A expression in tumoral and peritumoral tissue correlates with the occurrence of LEV-related NPAEs. Thus, considering that SV2A expression also influences LEV effectiveness [2], SV2A staining might help in tailoring treatment to patients.

References: Maschio M, Dinapoli L, Sperati F, et al. Levetiracetam monotherapy in patients with brain tumor-related epilepsy: Seizure control, safety, and quality of life. J Neurooncol 2011;104:205-14.
De Groot M, Aronica E, Heimans JJ, et al. Synaptic vesicle protein 2A predicts response to levetiracetam in patients with glioma. Neurology 2011;77:532-9.
Bedetti C, Romoli M, Maschio M, et al. Neuropsychiatric adverse events of antiepileptic drugs in brain tumour-related epilepsy: an Italian multicentre prospective observational study. Eur J Neurol 2017;24:1283-9.

VALIDATION OF THE ITALIAN VERSION OF HIV-DEMENTIA SCALE: A SCREENING TOOL FOR THE DETECTION OF SUBCORTICAL COGNITIVE DEFICITS

Roberta Rinaldi[1], C. Montanucci[2], P. Eusebi[2], N. Salvadori[2], V. Lisetti[2], P. Calabresi[3], L. Parnetti[2]

[1] Neurology - University of Perugia – Perugia
[2] Centre for Memory Disturbances, Lab of Clinical Neurochemistry, Section of Neurology - University of Perugia – Perugia
[3] Clinical Neurology, Department of Medicine - University of Perugia – Perugia

Background: Mini Mental State Examination (MMSE), the most popular neuropsychological screening tool for the assessment of global cognitive functioning, lacks of sensitivity in detecting cognitive deficits associated with subcortical dysfunctions. The HIV-Dementia Scale (HDS)1, a screening tool originally created for detecting cognitive impairment in HIV patients, has proved to be useful in other neurological diseases characterized by subcortical damage2. Until now the Italian version is lacking.
Aims: We aimed at: 1) validating the HDS Italian version in a cohort of cognitively healthy elderly subjects by calculating criterion validity and test-retest reliability; 2) exploring the suitability of HDS in detecting subcortical cognitive deficits in subjects with neurological diseases associated with subcortical damage.
Materials and Methods: HDS was translated from English into Italian by using forward-backward translation. The test is composed of 4 items: item 1-attention (max score=4), item 2-psychomotor speed (max score=6), item 3-memory recall (max score=4) and item 4-construction speed (max score=2). We administered both HDS and MMSE to 104 consecutive cognitively healthy, functionally independent subjects (age:71.1Â±4.2; 46M, 58F) recruited as volunteers, and to 29 patients with subcortical neurological disorders 14 subcortical ischemic vascular disease, 9 normal pressure hydrocephalus and 6 HIV infection; age:69.3Â±10.1; 21M, 8F).
Results: In the healthy group, HDS score was negatively associated to age (rS=-0.21, pË,0.01) and positively to education (rS=0.52, pË,0.001). The HDS distribution in healthy subjects was close to the original manuscript (12.8Â±3.1) and it was different from patients (8.6 Â± 3.8, p<0.001). Has been found a significant correlation with MMSE both in patients (rS=0.73, p<0.001) and in healthy subjects (rS=0.37, p<0.001); in patients well performing MMSE (>24), HDS was poorer compared to controls (9.5Â±4.0 vs. 12.8Â±3.1, p<0.001). Test-retest reliability was tested in a subset (n=34) of cognitively healthy subjects (Spearman coefficient equal to 0.69, p<0.001). A ROC analysis adjusted for age as confounder yielded an optimal cut-off value for an HDS score of 11, which provided sensitivity equals to 0.88 and a specificity of 0.76.

Discussion and Conclusions: Our results show that the Italian version of the HDS has psychometric properties analogous to the original. Patients showed poorer scores on the HDS compared to healthy individuals, even when their global cognitive functioning measured by MMSE was within normal values. Our results support the use of HDS as a screening tool for detecting subcortical cognitive deficits, being complementary to MMSE in clinical practice.

References: Power C., Selnes O.A., Grim J.A., McArthur J.C. HIV Dementia Scale: a rapid screening test. Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology. 1995 Mar 1; 8 (3): 273-278.
van Harten B, Courant MNJ, Scheltens P. Validation of the HIV Dementia Scale in an Elderly Cohort of Patients with Subcortical Cognitive Impairment Caused by Subcortical Ischaemic Vascular Disease or a Normal Pressure Hydrocephalus. Dementia and Geriatric Cognitive Disorders. 2004 Apr 14; 18 (1): 109-114.

CASES OF DEMENTIA WITH CONFABULATIONS: ALZHEIMER OR NOT ALZHEIMER?

Elisabetta Belli

Neurology – University of Pisa – Pisa

Objective: Confabulations, also known as false memories, have already been associated with various diseases involving mainly the frontal areas, such as Wernicke-Korsakoff syndrome or frontal epilepsy. The neuropsychological dysfunctions underlying mechanisms of confabulation are not well known. We describe two patients with dementia both presenting confabulations at the onset of the disease speculating about neuropsychological correlates.
Method: The first patient is a 77-year-old woman with late onset of memory impairment who did not show any awareness of her memory deficits. The second patient is a 57-years-old man with an early onset of memory deficit and clear consciousness of it, whose clinical onset was characterized by behavioural disturbances and confabulations. A neuropsychological battery including the Confabulation Battery was administered to both patients. Moreover, they performed neuroimaging and cerebral FDG-PET.
Results: The woman was diagnosed with amnestic MCI; FDG-PET highlighted a mild hypometabolism in temporo-mesial, posterior dorsolateral parietal region and in precuneus bilaterally and in temporo-lateral region on the right side. The neuropsychological pattern of the man suggested a diagnosis of the behavioural variant of frontotemporal dementia; his FDG-PET showed wide and moderate hypometabolism in parietal and temporal areas, mainly right, and at the anterior cingulate cortex. At Confabulation Battery, both patients showed absence of provoked confabulations in coexistence with florid spontaneous confabulations reported by relatives.
Discussion: The woman presented a late onset MCI with prevalent involvement of memory functions and without awareness of her memory deficits; her cognitive and imaging profile suggested a conversion to typical AD phenotype. The younger male patient presented a clinical-neuropsychological profile showing a significant involvement of frontal functions, with full awareness of his memory deficits, rising the hypothesis of a possible overlapping between AD and FTD. At FDG-PET, the right hemisphere was mostly impaired in both patients. Self-consciousness and realty evaluations are known to be regulated by common anatomical areas; nevertheless, in our patients this correspondence between disease-awareness and confabulations was not respected.
Conclusions: Despite the exact anatomical correlation of confabulations is still not defined, the imaging analysis performed in our patients is coherent with recent theories according to which at the origin of confabulatory tendency in AD there is an impairment of the connections between crucial hubs in frontal and mediotemporal areas, mainly involving the right hemisphere. Besides, it would be reasonable to hypothesize that self-awareness and realty interpretation should not be considered as necessarily associated dimensions.

SLEEP MICROSTRUCTURE AND COGNITIVE DECLINE IN MILD COGNITIVE IMPAIRMENT: A NOVEL BIOMARKER

Alessandro Schirru, L. Carnicelli, M. Maestri Tassoni, F. Giorgi, G. Tognoni, U. Bonuccelli, E. Bonanni

Pisa Department of Clinical and Experimental Medicine, Section of Neurology - University of Pisa – Pisa

Aims: Since the population is getting older in Western countries and the percentage of elderly subjects is increasing, a broad interest has developed towards neurological disease of aging, in particular dementia. Several conditions of increased risk of dementia have been identified; the principal one being mild cognitive impairment (MCI). MCI has been defined as a transitional state between normal aging and dementia, of which it may represent a prodrome. The specific transition between normal ageing and MCI can be quite subtle and the distinction between MCI and early dementia can be challenging. Aims of our study were to evaluate if sleep variables (both conventional and microstructural) in subjects with MCI, are eventually associated with conversion to dementia.
Materials and Methods:We enrolled nineteen subjects with MCI (mean age 68.5Â±7.0 years) and 11 cognitively intact healthy elderly individuals (mean age 69.2Â±12.6 years). The patients and the healthy controls underwent ambulatory Polysomnography (PSG) for the evaluation of nocturnal sleep architecture and CAP parameters. The subjects were clinically and cognitively reevaluated after two years, during routine follow-up, and the MCI subjects were divided into MCI converters and non-converters.
Results: After 2 years of follow up, 11 MCI converted in dementia (57.8%). Compared with healthy elderly, MCI showed disrupted sleep with decreased REM sleep, CAP rate and CAP slow wave related phases (A1 index). Standard sleep architecture analysis did not show significant differences between the two subgroups of MCI, except for an increased REM Latency in MCI converters, whereas CAP analysis pointed out significantly decreased CAP rate, A1 index and A3 index in converters compared with non-converters. Discussion: Our data confirm impaired sleep in MCI, in line with previous studies reporting sleep alterations associated with neurodegeneration, particularly when considering more refined sleep parameters.
Conclusions: Sleep structure in neurodegenerative disorders should not been considered only an epiphenomenon, but rather also a potential factor in the various mechanisms underlying an interplay between sleep, cognitive function, and cognitive decline in the context of neurodegeneration, and argue for a role as biomarkers in the diagnosis and prognosis of early-phase cognitive impairment.

References: Petersen RC, Roberts RO, Knopman DS, Boeve BF, Geda YE, Ivnik RJ, Pag. 1 Sleep microstructure and cognitive decline in Mild Cognitive Impairment: a novel biomarker Smith GE, Jack CR Jr. Mild cognitive impairment: ten years later. Arch Neurol. 2009 Dec; 66(12):1447-55. doi: 10.1001/archneurol.2009.266

Parrino L, Ferri R, Bruni O, Terzano MG. Cyclic alternating pattern (CAP): the marker of sleep instability. Sleep Med Rev. 2012 Feb;16(1):27-45. doi: 10.1016/ j.smrv.2011.02.003. Epub 2011 May 26. Review
Maestri M, Carnicelli L, Tognoni G, Di Coscio E, Giorgi FS, Volpi L, Economou NT, Ktonas P, Ferri R, Bonuccelli U, Bonanni E. Non-rapid eye movement sleep instability in mild cognitive impairment: a pilot study. Sleep Med. 2015 Sep;16(9): 1139-45. doi: 10.1016/j.sleep.2015.04.027

A POSSIBLE ROLE OF PALMITOYLETHANOLAMIDE COMBINED WITH LUTEOLINE IN FRONTOTEMPORAL DEMENTIA TREATMENT: A CLINICAL AND NEUROPHYSIOLOGICAL STUDY

Martina Assogna[1], C. Motta[2], S. Bonnì[3], E. Casula[3], I. Borghi[3], M. Minei[3], F. Di Lorenzo[3], A. Martorana[2], G. Koch[3]

[1] Neurology – University of Study of Rome Tor Vergata – Rome
[2] Department of Systems Medicine - University of Rome Tor Vergata – Roma
[3] Non Invasive Brain Stimulation Unit/Department of Behavioral and Clinical Neurology - Santa Lucia Foundation IRCCS – Rome

Background and aims: Frontotemporal dementia (FTD) is a frequent cause of presenile neurodegenerative dementia and there is no effective pharmacological treatment to slow its progression. A link has been proposed between neuroinflammation and specific forms of FTD, suggesting that neuroinflammation is an important component of the disease since the early phases of the disease. We aim to investigate efficacy and safety of Palmitoylethanolamide combined with Luteoline (PEA-LUT) in a sample of FTD patients to reduce behavioral disturbances and improve the activities of daily living.
Methods: We enrolled 10 patients with a diagnosis of probable FTD. We performed cognitive and neurophysiological evaluations at baseline (T0) and after 4 weeks (T1) treatment with PEA-LUT 700 mgx2/day. To evaluate the cognitive effects of PEA-LUT administration we used a battery of tests including the MMSE, the Frontal Assessment Battery (FAB), the Neuropsychiatric Inventory (NPI) and the screening for aphasia in Neurodegeneration (SAND). We measured change on synaptic transmission using SICI-ICF, LICI and SAI paired-pulse TMS protocols over the primary motor cortex. We used iTBS protocol to measure changes in cortical plasticity. We used combined TMS/EEG methods to evaluate changes in DLPFC cortical oscillatory activity.
Results: We observed an improvement in NPI mean score (p=0.018) and FAB score (p=0.038). Neurophysiological evaluation showed a restoration of LICI (p=0.040), in particular at ISI 100ms (post-hoc p=0.035), suggesting a modulation of GABA(B) activity. We observed an increase of LTP-like cortical plasticity (p=0.079) and of DLPFC oscillatory activity in beta/gamma range.
Discussion and Conclusion: PEA-LUT could reduce behavioural disturbances and improve executive function in FTD patients through the modulation of cortical excitability and GABAergic transmission.

References: Zhang J. Mapping neuroinflammation in frontotemporal dementia with molecular PET imaging. J Neuroinflammation. 2015 May 29;12:108
Lall D, Baloh RH. Microglia and C9orf72 in neuroinflammation and ALS and frontotemporal dementia. J Clin Invest. 2017 Sep 1;127(9):3250-3258
Filiano AJ, Martens LH, Young AH, Warmus BA, Zhou P, Diaz-Ramirez G, Jiao J, Zhang Z, Huang EJ, Gao FB, Farese RV Jr, Roberson ED. Dissociation of frontotemporal dementia-related deficits and neuroinflammation in progranulin haploinsufficient mice. J Neurosci. 2013 Mar 20;33(12):5352-61

DIAGNOSTIC CHALLENGE IN RAPIDLY PROGRESSIVE DEMENTIA: A CASE REPORT

Maria Rosaria Bagnato, A. Castelli, M. Pierantozzi, C. Bonomi, M. Conti, L. Boffa, N. Mercuri

Neurology – University of Study of Rome Tor Vergata – Rome

In January 2019, a 45 years old woman from Ukraine, previously affected by an ischemic stroke in October 2018, came to our hospital because of a generalized tonic-clonic seizure. Her neurological history had begun with progressive aphasia characterized by difficulty in finding vocabulary and deficiency of fixation memory, since summer 2018. These symptoms were so disabling to compromise her normal social and work activities. By neurological examination, we observed cognitive and motor slowing, aphasia characterized by phonological and semantic paraphasias in her native language, prominent difficulty in understanding and speaking italian (for this reason MMSE execution was impossible), non-reactive mydriatic pupils, postural instability and hyperreflexia. Multiple instrumental and laboratory tests were performed: the EEG showed slow and paroxysmal anomalies on bilateral fronto-center-temporal regions and so we started treatment with valproate 400 mg x 2. Brain MRI documented the previous nucleocapsular stroke and periventricular leukoaraiosis, a lumbar puncture showed minimal increase in LCR-proteins (53 mg/dl), amyloid-beta42 244 pg/ml, tau 79 pg/ml, 14-3-3 protein absent, we performed a tb-PET-CT to exclude paraneoplastic cause of the disease, which was negative. Because of low levels of Thiamine and because of aspecific increase of phlogosis indexes we added vitamin B1 and Ceftriaxone 2 gr to therapy. During hospitalization, after about ten days of treatment, we observed an improvement of clinical conditions both in motor and cognitive side; the woman was partially able to ambulate without any support, and her language disorder got better to the point that we could execute MMSE (score 25/30). We observed EEG improvement too, with reduction of slow and paroxysmal components and greater stability of the background rhythm. Meanwhile, laboratory findings revealed the serological positivity of Treponema Pallidum, leading to diagnosis of neurosyphilis.

Although infections-associated dementia is rare, it must be considered in the differential diagnosis of rapidly progressive dementias, especially when there are other suggestive elements (young age, epilepsy, stroke). Syphilis causes meningovascular damage, parenchymal atrophy and consequent glial proliferation. The possibility of reverting Treponema-correlated damage is related to the extent of damage, to the timeliness of the diagnosis and thus to the timeliness of therapy. Neurosyphilis is misdiagnosed in more than 70% of cases. Treponema also interacts with neuronal metabolism by sequestering Thiamine, and by producing amyloid-beta42 protein precipitation. In syphilis-related dementia, known as general paresis, AB42-LCR values are comparable to those of AD. These interactions Treponema-neurons may be considered useful prognostic-therapeutic markers.

References: Tong ML1, Liu LL, Zeng YL, Zhang HL, Liu GL, Zheng WH, Dong J, Wu JY, Su YH, Lin LR, Yang TC, Laboratory findings in neurosyphilis patients with epileptic seizures alone as the initial presenting symptom, Diagnostic Microbioly Infectous Disease, April 2013, 75(4):377-80
Luo X1, Shi H, Hou L, Zhong X, Chen X, Zhang Y, Zheng D, Tan Y, Hu G, Mu N, Chen J, Fang Y, He H, Ning Y., Different cerebrospinal fluid levels of Alzheimer-type biomarker AÎ²42 between general paresis and asymptomatic neurosyphilis., Eur J Neurol. 2015 May;22(5):853-8
Bian J, Tu Y, Wang SM, Wang XY, Li C, Evidence that TP_0144 of Treponema pallidum is a thiamine-binding protein, J Bacteriol. 2015 Apr;197(7):1164-72

SENSORY INVOLVEMENT IN MOTOR MULTIFOCAL NEUROPATHY EXPLORED WITH SUDOSCAN: A SINGLE-CENTRE EXPERIENCE

Francesco Barbato, A. Romano, G. Bisogni , A. Di Paolantonio, P. Rossini, M. Sabatelli, S. Servidei, G. Granata, M. Luigetti

Neurology – Catholic University of the Sacred Hearth - Rome

Introduction: Motor Multifocal Neuropathy (MMN) is a rare inflammatory neuropathy characterized clinically by exclusive or predominant motor involvement, usually as mainly distal, asymmetric limb weakness with predilection for upper limbs, and neurophysiologically by the presence of conduction blocks (CBs) [1]. Antibodies to gangliosides appear to be implicated in the pathogenesis of this disorder, being moderate to high titers of anti-GM1 reported in 40-85% of cases [2]. The disease appears to be slowly progressive in the majority of cases, but the rate of progression, the degree of functional impairment, and the mortality may vary consistently in different studies. Corticosteroids and plasma exchange typically are not effective, while treatment with intravenous immunoglobulin (IVIg) and/or cyclophosphamide generally delays or stops disease progression [3]. Sensory involvement is typically absent or can be sub-clinical after a long-course disease [3]; indeed, sural nerve biopsies have shown minimal changes, perhaps suggestive of demyelination, in some cases [2]. Although pain has been reported in this setting [17], small fibre involvement has never been specifically investigated. In this study, we prospectively evaluated a cohort of MMN patients in order to investigate the presence of small fibre dysfunction by sudoscan.
Objective: to evaluate the presence of small fibre dysfunction in a cohort of patients affected by Motor Multifocal Neuropathy (MMN) using sudoscan.
Patients and Methods: we enrolled all adult MMN patients regularly followed by our Neurology Department. All subjects underwent clinical visit and neurophysiological examination with nerve conduction studies (NCS) and sudoscan.
Results: NCS showed a reduction of sensory nerve action potential amplitude was observed in 3/7 patients, while low-borderline values were detected in 2/7. Sudoscan showed low-borderline ESC values in 3/7 patients: low-borderline ESC values were always in upper limbs, accordingly to clinical and neurophysiological impairment.
Conclusions: our results confirm that sensory involvement may be found in MMM MMN and that this occurrence doesn't exclude this diagnosis. Sensory involvement in this setting is not confined to large fibres, but it can also involve the small ones.

References: E. Nobile-Orazio, Multifocal motor neuropathy, J. Neuroimmunol. 115 (2001) 4-18.
J.-T.H. Van Asseldonk, H. Franssen, R.M. Van den Berg-Vos, J.H.J. Wokke, L.H. Van den Berg, Multifocal motor neuropathy, Lancet Neurol. 4 (2005) 309-319. doi:10.1016/S1474-4422(05)70074-0.
L. Vlam, W.-L. van der Pol, E.A. Cats, D.C. Straver, S. Piepers, H. Franssen, L.H. van den Berg, Multifocal motor neuropathy: diagnosis, pathogenesis and treatment strategies, Nature Reviews Neurology. 8 (2012) 48-58. doi:10.1038/nrneurol.2011.175.

ATYPICAL PRESENTATION AND RESPONSE TO THERAPY IN SPORADIC LATE-ONSET NEMALINE MYOPATHY (SLONM)

Giovanni Colacicco, G. Primiano, C. Sancricca, G. Severa, S. Servidei

Neurology – Catholic University of the Sacred Hearth – Rome

Backgroud and Aims: SLONM is a rare acquired, subacute myopathy with onset in adult age characterized by proximal weakness, normal or low CK level, myopathic EMG with spontaneous activity, monoclonal gammopathy and, as pathological hallmark, nemaline bodies on muscle biopsy.
Materials and methods: A 68 year old Caucasian woman developed progressive dysphagia and dysphonia, and rapid weight loss (15 kg). Six months later the patient was hospitalized for pneumonia. Pneumonia of ab ingestis type was caused by a MRSA and the patient was treated with intravenous antibiotics. Neurological examination showed deficit of mimic muscles, severe dysphagia for both solids and liquids, dysphonia, but not weakness of other muscles. She was put on enteral nutrition through nose-gastric feeding tube. In the hypothesis of a neuromuscular disease she underwent EMG, MRI and muscle biopsy.
Results: Blood CK levels was below 15 UI/L (n.v. 43-145). EMG showed myopathic abnormalities with spontaneous activity. Neuromuscular transmission was normal. Scintigraphic study of deglutition revealed a severe failure of oropharyngeal and esophageal peristalsis. Muscle MRI demonstrated a moderate fat substitution of paraspinal muscles and bilateral STIR hyperinthensity of tibialis anterior bilaterally. Muscle biopsy (quadriceps) showed diffuse muscle hypotrophy with type 1 predominance and the presence of characteristic nemaline rods that react positively for phalloidin. A monoclonal IgG lambda gammopathy was detected by immunoelectrophoresis. In the hypothesis of a SLONM the patient was treated with intravenous immunoglobulin (IVIg) at the dose of 2g/Kg. In the following three months she exhibited a remarkable improvement and was able to resume oral feeding with a significant weight gain.
Discussion: This report is an example of the variability of clinical presentations of SLONM, broadening the spectrum of associated phenotypes. Isolated dysphagia and dysphonia, in fact, have never been reported so far. Of note in our case is the dramatic response to IVIg therapy with complete remission in few months. According to the data from the literature and our own experience, this extremely favorable outcome is unusual. SLONM patients in fact generally need a prolonged immunosuppressive multidrug therapy. This supports the importance to start the therapy as soon as possible and the central role of an inflammatory process in the pathogenesis of SLONM.
Conclusions: A diagnosis of SLONM should be taken in account also in presence of isolated dysphagia without segmental muscle weakness. Treatment with IVIg represents the gold standard and a prompt diagnosis, that includes muscle biopsy, is necessary for the best outcome.

SPECIFICITY AND SENSITIVITY OF A SINGLE CSF-RESTRICTED IGG BAND CUT-OFF AS A MARKER OF MULTIPLE SCLEROSIS

Francesco Antonio Losavio[1], M. Lucchini[1], M. Loiodice[1], V. Nociti[1], C. De Fino[1], V. Di Carlo[2], T. De Michele[2], M. Mirabella[1]

1 Institute of Neurology - Catholic University of the Sacred Heart – Rome
2 Institute of pathology and clinical biochemistry - Catholic University of the Sacred Heart – Rome

Abstract. A single CSF-restricted IgG band cut-off for positive oligoclonal bands raises the sensitivity as a marker of Multiple Sclerosis with a lower impact on sensitivity.
Background. Intrathecal IgG synthesis defined as the presence of CSF-specific oligoclonal bands (OCB) visualized after isoelectric focusing and subsequent immunoblotting of the cerebrospinal fluid (CSF) and serum has been recently introduced in the diagnostic criteria for Multiple Sclerosis (MS) as substitute for demonstration of dissemination in time [1]. The classical cut-off for the positivity of OCB is the presence of at least two CSF-restricted bands.
Aims. We retrospectively analyzed the results of the OCB search in a cohort of patients to determine their sensitivity and specificity as a marker of MS and the impact of a single CSF-restricted IgG band cut-off to these parameters.
Materials and Methods. We collected data from 1125 patients, admitted to the neurological department of the "Policlinico Universitario A. Gemelli" Foundation IRCSS during the past 10 years, that underwent a lumbar puncture with search for OCB during their diagnostic work-up. Each patient diagnosis was assigned to 8 main categories: multiple sclerosis, neuromyelitis optica (NMO) and NMO spectrum disorders, other inflammatory disease of the CNS, peripheral nerves inflammatory disease, non-inflammatory neurological disease, symptomatic controls, CNS tumors and CNS infections.
Results. 627 patients were diagnosed with MS, 11 with NMO or NMO-SD, 154 with other inflammatory disease of the CNS, 73 with peripheral nerves inflammatory disease, 189 with non-inflammatory neurological disease, 21 as symptomatic controls, 34 with CNS tumors and 16 with CNS infections. Of the entire population 487 showed two or more OCB, 91 a single restricted OCB and 547 absence of OCB. When we considered the OCB positivity cut-off as 2 or more bands it showed a 72.9% sensitivity and a 94.0% specificity as a marker for MS. When we considered the OCB positivity cut-off as 1 or more band its sensitivity raised to 83.4% and its specificity decreased to 89.0%. Among the 91 patients with a single-CSF restricted band, sixty-six (72,5%) were diagnosed with MS.
Discussion and conclusions. Lowering the cut-off for the positivity of the OCB to one or more bands raises its sensitivity as a marker for MS of 10.5% and lowers its specificity of 5%. In case of a strong suspect for MS, the presence of a single CSF-restricted IgG band, in an adequate setting, could be taken into account as a possible marker of disease.

References: Thompson AJ, Banwell BL, Barkhof F et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 2018 Feb;17(2):162-173.

SYMPTOMATIC INTRACRANIAL ATHEROSCLEROTIC DISEASE: AN ULTRASOUND 2-YEAR FOLLOW-UP PILOT STUDY

Giuseppe Reale

Neurology – Catholic University of the Sacred Hearth – Rome

Background and Aims The objective of this single-center pilot study was to assess wheter symptomatic intracranial atherosclerotic disease (ICAD) ultrasound features change through the 2 years following an acute ischemic stroke or TIA, being ICAD a relevant cause of acute ischemic stroke or TIA, linked to high rates of recurrent stroke.
Methods We consecutively enrolled 48 patients with acute ischemic stroke or TIA with symptomatic ICAD detected by trans- cranial color-coded duplex sonography (TCCS) and confirmed by MR-angiography and/or CT-angiography. We set a neurosonological and clinical follow-up at 3, 6, 12, and 24 months (T0, T1, T2, T3, and T4).
Results We observed that the hemodynamic effect of the stenosis changed during the 2-year follow-up, as revealed by the modifications of Peak Systolic Velocity (PSV) (Friedman-ANOVA test, $p < 0.001$). The pairwise post-hoc analysis showed a statistically significant difference between PSV at T0 and PSV at T3 ($p = 0.005$) and between PSV at T0 and PSV at T4 ($p < 0.001$) being PSV at T3 and T4 lower than PSV at T0. Seven patients had a new event in the first 12 months.
Conclusions The high rate of recurrent stroke or death among ICAD patients seems to be independent of progressive arterial narrowing. A wide multicenter follow-up study is needed in order to identify the factors that, alongside the hemodynamic features, contribute to the high risk of recurrent stroke among patient with symptomatic ICAD.

References: Holmstedt CA, Turan TN, Chimowitz MI (2013) Atherosclerotic intracranial arterial stenosis: risk factors, diagnosis, and treatment. Lancet Neurol 12:1106-1114
Baumgartner RW, Mattle HP, Schroth G (1999) Assessment of >50% and <50% intracranial stenoses by transcranial color-coded duplex sonography. Stroke 30:87-92

CRYPTOGENIC STROKE - CLINICAL FEATURES, DIAGNOSIS, PROGNOSIS AND THERAPY

Giuseppe Reale

Neurology – Catholic University of the Sacred Hearth – Rome

Backround About 20-30% of strokes are cryptogenic, that is a category of ischemic stroke for which no probable cause is found despite a thorough diagnostic evaluation (standard vascular and cardiac serologic evaluation). More than 200 causes of cryptogenic stroke are known.
Aims To summarize the main clinical, radiological, diagnostic and therapeutic features of cryptogenic stroke.
Materials and Methods Review of the Literature.
Results Cryptogenic stroke accounts about 10-40% of all ischemic stroke. New diagnostic algorithms will reduce the incidence of cryptogenic stroke to 10% (highly cryptogenic stroke). Possible mechanisms are: Cardiac embolism (occult AF, aortic atheromatous disease or other cardiac sources); Paradoxical embolism (PFO, atrial or ventricular septum defects, extracardiac arterovenous malformations); Undefined thrombophilia (APL syndrome, occult cancer); Substenotic cerebrovascular disease (<50%, dissections, reversible cerebral vasoconstriction syndrome). Special attention should be paid to the subgroup ESUS (Embolic Stroke of Undetermined Source). Diagnostic work-up starts with a thorough history and ends up with TEE, body CT. The prognosis of cryptogenic stroke is better than cardioembolic stroke but worse than lacunar stroke. Therapy gold-standard is Aspirin, despite several trials assessing anticoagulation vs antiplatelet therapy.
Discussion and conclusion Cryptogenic stroke is frequently observed and is a challenge in terms of diagnosis and secondary prevention.

References: TOAST classification, Adams HP et al, Stroke 1993
Cryptogenic stroke, Saver JL, NEJM 2016

MELKERSSON-ROSENTHAL SYNDROME IN AN ITALIAN FAMILY: EVIDENCE OF AUTOSOMAL DOMINANT TRANSMISSION?

Eleonora Rollo, G. Tasca

Neurology – Catholic University of the Sacred Hearth – Rome

Melkersson-Rosenthal Syndrome (MRS) is a rare disorder characterized by a triad of symptoms: orofacial edema, recurrent facial nerve palsy and fissured tongue, although only in rare cases all the symptoms occur simultaneously. Isolated IgE hypogammaglobulinaemia is described in association with this triad. The etiology and pathophysiology of this condition are still largely unknown. A recent report described a variant in the gene SLC27A1 in the affected members of a Chinese family suggesting a possible mendelian mechanism of transmission. Nevertheless further reports demonstrated the clinical and genetic heterogeneity of this condition. We present the case of a 44 year-old woman with bilateral recurrent facial nerve palsy and fissured tongue. She had never experienced orofacial edema. Earlier episodes of facial nerve palsy completely remitted after corticosteroid treatment. Interestingly, her level of serum IgE was in the lower normal limit. The diagnosis of MRS was suspected on a clinical basis. Her family history showed a segregation compatible with an autosomal dominant transmission of the fissured tongue phenotype, which was present in at least one member in four consecutive generations. Furthermore, multiple cases of recurrent or single facial nerve palsy occurred in at least three generations of her relatives. These palsies all remitted, partially or completely, after steroid treatment. Systematic genetic testing through Whole Exome Sequencing as well as collection and analysis of other families with similar phenotype is needed to clarify whether specific genetic defects contribute to cause MRS.

ONSET OF CREUTZFELDT-JAKOB DISEASE MIMICKING AN ACUTE CEREBROVASCULAR EVENT

Eleonora Sabatelli

Neurology – Catholic University of the Sacred Hearth – Rome

Creutzfeldt-Jakob disease (CJD) is a rare, rapidly progressive degenerative encephalopathy, caused by a pathologically altered form of the prion protein (PrP). It is characterized by variable association of cognitive and behavioural impairment, ataxia, myoclonus, pyramidal and extra-pyramidal signs. Acute onset mimicking ischemic stroke may be the initial manifestation of the disease. We present the case of a 65 years old woman, who presented a sudden gait disturbance and a rapidly progressive episodic memory disorder, associated with mental confusion and vivid dreams. Clinical manifestations worsened rapidly and within a few months the patient lost her autonomy in walking and of the social interaction. Brain MRI showed asymmetric hyperintensity of the cortex and the subcortical white matter, of the thalamus, caudate and putamen at DWI and FLAIR sequences. Repeated EEG examinations did not reveal significant alterations. The 14-3-3 protein and the RT-QuIC were detected in the cerebrospinal fluid confirming a diagnosis of Creutzfeldt-Jakob disease.

A DYNEIN GENE MUTATION ASSOCIATED WITH SPORADIC NON-PROGRESSIVE SPINAL MUSCULAR ATROPHY LOWER EXTREMITY PREDOMINANT (SMALED1)

Eleonora Torchia[1], D. Tiziano[2], G. Primiano[1], C. Sancricca[1], S. Servidei[1]

[1] Neurology – Catholic University of the Sacred Hearth – University Hospital Foundation Policlinic IRCCS Gemelli - Rome
[2] Genetic - Catholic University of the Sacred Hearth – University Hospital Foundation Policlinic IRCCS Gemelli – Rome

Background. Spinal Muscular Atrophy (SMA) is an autosomal recessive disorder characterized by progressive proximal muscle weakness caused by SMN1 deletions. Recently some rare autosomal dominant (AD) variants have been identified predominantly affecting the lower extremities (SMALED) that occur in early childhood with slowly progressive weakness of both proximal and distal muscles mainly in the lower limbs. SMALED can be associated with mutations in DYNC1H1 (SMALED1) and BICD2 (SMALED2) genes.
Patients and methods. A 38-year-old man presented at birth with bilateral congenital clubfoot and flaccid paresis of the lower limbs. During motor development he has reached the crawling phase, but was never able to stand on his legs or walk autonomously. Based on clinical and EMG findings a diagnosis of SMA was made. Over the years the clinical picture has remained substantially stable. Currently, by using long orthopedic braces, the patient maintains satisfactory balance and walking skills and can autonomously manage normal daily life activities. He was admitted at our Neurology department for a diagnostic work-up.
Results. Neurological examination documented flaccid paresis and atrophy of the lower limbs with predominant involvement of the ileopsoas, quadriceps and distal lower limb muscles. In addition there was scapular winging, but preserved muscle strength of the upper limbs. Muscle MRI documented almost complete fat replacement of thigh and leg muscles bilaterally, partially sparing the thigh adductor and the long finger extensor, severe fatty infiltration of the shoulders muscles, and notable signs of hypo/atrophy of abdominal wall, dorsal paravertebral and gluteal muscles. EMG and muscle biopsy demonstrated signs of chronic neurogenic lesion. Cognitive functions and brain MRI were normal. Genetic analysis by targeted sequencing panel revealed an heterozygous mutation in the DYNC1H1 gene.
Discussion. Mutations in both BICD2 and DYNC1H1 genes have been so far identified in familiar cases with AD transmission. In our patients, however, the mutation seems de novo as both parents are unaffected. Dominant DYNC1H1 changes have been described in heterogeneous phenotypes including, beside SMALED, congenital form with intellectual disability and neuronal migration defects, CMT2O, and spastic paraplegia. Our patient manifests congenital onset of pure severe neurogenic atrophy with preserved cognitive function expanding the spectrum of DYNC1H1-linked phenotypes.

Conclusion.The presence of neurogenic weakness affecting mostly lower limbs and involving both proximal and distal muscle should suggests to analyze SMALED-associate genes, in sporadic cases too. Phenotypic characterization even of single patients may help to better define this newly identified group of ultrarare diseases.

UPDATE ON MUTATIONAL SPECTRUM OF PRIMARY FAMILIAL BRAIN CALCIFICATION

Ilenia Andreini[1], I. Taglia[1], A. Mignarri[2] , C. Battisti[1] , A. Federico[1], M. Dotti[1]

[1] Unit of Neurology and Neurometabolic Disorders, Department of Medicine, Surgery and Neurosciences - University of Siena – Siena
[2] Unit of Neurology - Misericordia Hospital – Grosseto

Primary familial brain calcification (PFBC) is a rare neurodegenerative disorder with characteristic bilateral brain calcification and a variable clinical presentations, including movement disorders, progressive cognitive impairment and neuro-psychiatric disturbances, although PFBC patients also may be clinically asymptomatic. So far, four causative genes have been discovered: SLC20A2, PDGFRB, PDGFB and XPR1 accounting for approximately 50% of cases (Ramos et al., 2017). More recently, mutations in MYORG gene have been linked to an autosomal recessive form of PFBC (Yao et al., 2018). In 2014, we reported results from a genetic screening for PFBC in seven unrelated families, which led to the discovery of three SLC20A2 mutations accounting for this familial disorder (Taglia et al., 2014). In this study, we aimed to expand mutational screening in patients recruited in our center from 2014.

We recruited five unrelated families and twenty-six apparently sporadic cases, a total of thirty-one index patients which fulfilled diagnostic criteria of primary brain calcification: 1) the presence of cerebral calcification; 2) exclusion of other causes of brain calcification, as infectious, autoimmune, endocrine and mitochondrial disorders. All patients underwent clinical and genetic analysis, including Sanger sequencing of SLC20A2, PDGFRB, PDGFB, and XPR1.

The mutational analysis in our cohort of patients led to the identification of four mutations in SLC20A2 (p.Ile123Thr; p.626-629dupWFVT; p.Trp101Cysfs3*; p.E368GFs*44) in three familial cases and in one sporadic patient, and a novel mutation (p.R611H) in XPR1 in one family. No mutations were found in PDGFRB and PDGFB. In our cohort of patients we observed a high clinical variability, even in patients within the same family. However, confirming our previous report a similar the neuro-imaging pattern in members of the same family has been detected. We found SLC20A2 mutations in 13% of cases, confirming that this gene provided the highest contribution, followed by XPR1. Our study confirmed also that the genetic cause of the majority of cases remains unknown, therefore further studies in our cohort of patients will include the mutational screening of MYORG gene.

References: Ramos EM, Oliveira J, Sobrido MJ, Coppola G. Primary Familial Brain Calcification. GeneReviews (Internet). Seattle: University of Washington; 2004. Last Update: August 24, 2017
Yao XP, Cheng X, Wang C, Zhao M, Guo XX, Su HZ, Lai LL, Zou XH, Chen XJ, Zhao Y, Dong EL, Lu YQ, Wu S, Li X, Fan G, Yu H, Xu J, Wang N, Xiong ZQ, Chen WJ . Biallelic Mutations in MYORG Cause Autosomal Recessive Primary Familial Brain Calcification. Neuron. 2018 Jun 27;98(6):1116-1123.
3) Taglia I, Mignarri A, Olgiati S, Menci E, Petrocelli PL, Breedveld GJ, Scaglione C, Martinelli P, Federico A, Bonifati V, Dotti MT. Primary familial brain calcification: Genetic analysis and clinical spectrum. Mov Disord. 2014 Nov;29(13):1691-5.

ANTI-NMDA-RECEPTOR ENCEPHALITIS: TWO CASES WITH ATYPICAL COURSE AND GOOD RESPONSE TO EARLY IMMUNOTHERAPY

Virginia Cancelloni[1], C. Battisti[1], A. Cerase[2], M. Dotti[1]

[1] Unit of Neurology and Neurometabolic Disorders, Department of Medicine, Surgery and Neuroscience - University of Siena – Siena
[2] Neuroimaging and Neurointervention Unit, Department of Neurological and Sensorineural Sciences - Policlinico "Santa Maria alle Scotte", Azienda Ospedaliera Universitaria Senese – Siena

Background: Anti-NMDA-receptor encephalitis is a rare form of autoimmune encephalitis that typically presents with prominent psychiatric manifestations followed by heterogeneous neurological symtomps. Up to one third of patients have an underlying tumour, mostly an ovarian teratoma. With early first-line immunotherapy and tumor resection, if present, up to 53% of patients experience im-provement within 4 weeks.
Clinical cases: A 23-year old woman (case 1) suddenly developed incoming focal and generalized seizures. Progressively spatial disorientation, psychiatric syntomps, short-term memory deficits and cognitive-motor slowing emerged. A 60-year old woman (case 2) suddenly developed fever, temporo-spatial disorientation and decreased level of consciousness. Within 2 days tachycardia and tachypnea with resulting cardiac and respiratory failure appeared, requiring respiration and hemodynamic support in Intensive Care Unit.
Materials and Methods: Blood and CSF analysis (including infectious disease work-up for principal neurotropic agents), brain MRI, EEG, anti-neuronal and anti-surface antibodies testing and oncological screening (including pelvic MRI, mammary and ginecological ultrasound, gastro- and colonscopy and total body CT) were performed.
Results: Blood and CSF analysis were normal for both patients. At EEG typical extreme delta brush pattern (case 1) and diffuse slow and disorganized activity (case 2) were evident. Brain MRI T2/FLAIR images pointed out hyperintensity of right thalamus and occipital-temporal-parietal lobes and left cerebellar cortex (case 1) and hyperintensity of bilateral hippocampal cortex and fronto-temporal mesial lobes (case 2). Antibody testing was positive for anti-NMDAR antibodies only in serum. Oncological screening did not detect underlying tumor. Both patients received first-line immunotherapy with clear improvement of EEG and brain MRI alterations.
Discussion: Both patients presented with an atypical course of anti-NMDAR encephalitis, with prominent seizures and dysautonomic disorders. In contrast to other reported cases, CSF testing was normal. Anti-NMDAR antibodies were detected only in serum, probably due to too early antibody testing. Moreover, brain MRI showed T2/FLAIR alterations in both patients, supposedly associated with brain inflammatory and postcritical processes. After first-line immunotherapy, a significant functional improvement and reduction of EEG and MRI alterations emerged.

Conclusions: Anti-NMDA-receptor encephalitis usually begins with prominent psychiatric syntomps followed by great constellation of neurological dysfunctions. However, our cases report confirms the broad variability of the clinical course. The recognition of characteristic symptom con-stellations is crucial because early immunotherapy may be life-saving being strongly associated with good outcome and fewer relapses.

References: Newman M.P. et al, Autoimmune encephalitis. Internal Medicine Journal 2016;148-156.
Dalmau J. et al, Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurology 2008;7:1091-98.

NECROTIZING AUTOIMMUNE MYOPATHY REVEALING AN UNDETECTED MITOCONDRIAL MYOPATHY

Antonio Covelli[1], I. Di Donato[1], E. Cardaioli[1], P. Brunori,[2] A. Malandrini[1], M. T. Dotti[1]

[1] Unit of Neurology and Neurometabolic Disorders, Department of Medicine, Surgery and Neurosciences - University of Siena – Siena
[2] Unit of Neurofisiopatologia - Azienda Ospedaliera di Perugia – Perugia

Necrotizing autoimmune myopathy (NAM) is a rare inflammatory myopathy characterized by severe proximal weakness and necrotic muscle fibers with little muscle inflammation. Autoantibodies against 3-hydroxy-3-methylglutaryl-coenzyme-A reductase (HMGCR) have been often reported in patients with NAM, especially in association with statin therapy.
A 13-years-old boy was recently referred to our reference center for neuromuscular disorders for the presentation, a couple of months before during a Mycoplasma Pneumoniae infection, of very severe muscle weakness (MRC 1-2) and extremely high CK levels with peack value 15 800 U/L. His previous history was unremarcable. Our neurological examination showed a tall (185 cm), thin (45Kg) boy with mild bilateral ptosis, proximal muscles weakness, scapular winging, hypotonia, waddling gait, absence of deep tendon reflexes and positive Gower's maneuver. Myopathic changes were detected at EMG examination. Muscle biopsy showed necrotic fibers and some inflammatory infiltrates. Moreover, ragged-red fibers and 20% COX-negative fibers were evident. Serum positivity for anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGCR) antibodies was found. High dose corticosteroid therapy (1mg/kg) was started and further improvement was observed at one month follow up. Pediatric necrotizing myopathy associated with anti-HMGCR antibodies is a very rare condition. Unlike in adults, a previous exposure to statin therapy is lacking and CK levels are usually higher. Clinicopathologic features are similar to adult patients with muscle biopsy findings typical of a paucimmune necrotizing myopathy. Favorable response to immunotherapies is reported. The occurrence in this patient of an inflammatory myopathy let us to discover a previously asymptomatic mitochondrial myopathy. It may be speculated that the underlying metabolic muscle pathology could have influenced the severity of clinical expression of the inflammatory myopathy.

References: Wen-Chen Liang et al, Pediatric necrotizing myopathy associated with anti-3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies, Rheumatology (2017); 56; 287-293
Yves Allenbach et al, Anti-HMGCR Autoantibodies in European Patients With Autoimmune Necrotizing Myopathies Inconstant Exposure to Statin, Medicine (2014); 93; 150 – 157
Payam Mohassel and Andrew L. Mammen , Anti-HMGCR Myopathy, Review, Journal of Neuromuscular Diseases 5 (2018) 11-20

NEURONAL CEROIDOLIPOFUSCINOSIS: CLINICAL AND GENETIC HETEROGENEITY IN RELATION WITH INNOVATIVE THERAPEUTIC OPPORTUNITIES

Stefania Dallagiacoma, A. Malandrini, I. Di Donato, M. T. Dotti

Department of Medicine, Surgery and Neurosciences - University of Siena – Siena

Background and aims: Neuronal ceroidolipofuscinosis (CLN) is a rare, autosomal recessive, neurodegenerative disease resulting in intracellular accumulation of autofluorescent lipopigments in neurons, retina and other tissues. CLN disease has various age at onset which are typical but not exclusive of each subtype. CLN2, resulting from TPP1 gene mutation, has a late-infantile onset in its classical presentation, while CLN1, that results from PPT1 gene mutation, has a classic infantile onset. Drug resistant epilepsy, psychomotor regression, and visual disturbances worsening to blindness are the typical clinical hallmarks. We here describe two cases with a slowly progressive phenotype and review the main clinical features, the diagnostic steps and the therapeutic challenges.
Cases report: case1, a 8-year-old boy with progressive regression of the acquired skills since the age of 30 months. High frequency drug-resistant seizures appeared after 3 years of age. Neurological examination showed ataxo-spastic gait, vocal and motor stereotypies, and severe language delay. Brain MRI showed cerebellar and thalamic atrophy and supratentorial white matter hyperintensity. Fundus oculi showed bilateral disc pallor and moderate dystrophy of posterior pole. Molecular genetic testing using NGS panel revealed heterozygous pathogenic mutations of TPP1 gene. Case 2, a 34-year-old-woman first came to our attention at the age of 25 years. She had a regular psycho-motor and cognitive development until the age of 15 years when she presented slowly progressive cognitive, language, and motor deterioration, bilateral blindness, sensorineural hypoacusia and drug-resistant seizures. Brain MRI showed diffuse cerebral and cerebellar atrophy. Skin biopsy showed accumulation of autofluorescent lipopigments. Molecular genetic testing using NGS panel revealed homozygous pathogenic mutations of PTT1 gene.
Discussion and Conclusion: CLN should be suspected in all cases with refractory epilepsy in association to neurological deterioration. Of particular interest in both patients the slowly progressive clinical course, only exceptionally observed in the classical late-infantile CLN2. Early diagnosis is crucial for a new therapeutic chance with enzyme-replacement therapy (Cerliponase Alfa), a recombinant proenzyme form of human TPP1 administered by intraventricular infusion. This treatment, which has been started in case 1, has been documented to significantly slow the disease progression.

References: 1 Williams RE, Adams HR, Blohm M, et al. Management Strategies for CLN2 Disease. Pediatr Neurol. 2017;69:102-112.
2 Schulz A, Ajayi T, Specchio N, de Los Reyes E, Gissen P, Ballon D, Dyke JP, Cahan H, Slasor P, Jacoby D, Kohlschütter A; CLN2 Study Group: Study of IntraventricularCerliponase Alfa for CLN2 Disease. N Engl J Med. 2018;378:1898-1907.
3 Kousi M, Lehesjoki AE, Mole SE: Update of the mutation spectrum and clinical correlations of over 360 mutations in eight genes that underlie the neuronal ceroidlipofuscinosis. Hum Mutat. 2012;3:42-63.

GAIT ATAXIA, PYRAMIDAL INVOLVEMENT AND LEUKOENCEPHALOPATHY: WHAT'S UNDERNEATH?

Chiara Manfredi[1], I. Di Donato[1], A. Covelli[1], A. Cerase[1], F. Santorelli[2], M. Dotti[1]

[1] Unit of Neurology and Neurometabolic Disorders, Department of Medicine, Surgery and Neurosciences - University of Siena – Siena
[2] Molecular Medicine - IRCCS Fondazione Stella Maris – Pisa

Novel sequencing technologies have been crucial in expanding our understanding of the genetics of rare diseases. Recently, mutations in the genes encoding the subunits of RNA polymerase III (Pol III), POLR3A and POLR3B, have been identified as new genetic causes for autosomal recessive spastic ataxia.
We here report the case of two adult siblings (65 and 59 years respectively) with adolescent-onset slowly progressive spastic ataxia and intention tremor. Neurological examination showed in both similar clinical characteristics with inability to walk, severe intention tremor, dysmetria, dysarthria, areflexia and bilateral extensor plantar response. No cognitive impairment was present. The parents were unrelated and there was no family history of neurological diseases.
Extensive laboratory and metabolic investigations resulted negative. EMG was normal and the muscle biopsy specimen showed no abnormalities. Brain MRI revealed both supratentorial and infratentorial diffuse mild white matter T2 hyperintensity, with focal involvement of the pontine tegmentum and the dentate nuclei. No mutations in causative genes of hereditary spastic paraplegias, spinocerebellar ataxia and Friedreich ataxia were found. Subsequently, a panel target resequencing for ataxias identified compound heterozygous POLR3A mutations (c.4073G>A, c.1909+22G>A) in both siblings, thus suggesting a POL III-related condition.
Interestingly, it has been recently described (Brain 2017) that patients carrying the c.1909 + 22G>A variant (the same observed in our patients), in combination with a second POLR3A mutation, share homogenous phenotype, characterized by adolescent onset and slow progression of a combination of ataxia and pyramidal involvement. Compared to the infantile-onset phenotype, a lower rate of dental, gonadal and cognitive abnormalities is observed.
In conclusion, we report an interesting family with autosomal-recessive mutations in POLR3A gene. POLR3A encodes the largest subunit of human RNA polymerase III (RPC1) which is crucial for tRNA synthesis and tRNA levels in the brain. Previous studies have linked this gene to a wide phenotypic spectrum of hypomyelinating leukodystrophies including tremor ataxia with central hypomyelination (TACH), ataxia, delayed dentition and hypomyelination (ADDH), hypomyelination, hypodontia and hypognadotropic hypogonadism (4H), leukodystrophy with oligodontia, and hypomyelination with cerebellar atrophy and hypoplasia of the corpus callosum (HCAHC). The present report is a confirmation of an extensione of the phenotypic

spectrum linked to POLR3A. The typical MRI features of POLR3A-associated leukodystrophies, namely hypomyelination with or without thinning of the corpus callosum and atrophy of the cerebellum, need to be carefully checked to address the diagnosis of hereditary spastic-ataxia.

References: Minnerop M, Kurzwelly D, Wagner H, Soehn AS, Reichbauer J, Tao F, et al. Hypomorphic mutations in POLR3A are a frequent cause of sporadic and recessive spastic ataxia. Brain 2017; 140: 1561-78.
Rydning SL, Koht J, Sheng Y, Sowa P, Hjorthaug HS, Wedding IM, et al. Biallelic POLR3A variants confirmed as a frequent cause of hereditary ataxia and spastic paraparesis. Brain 2019; 142: 1-5
Gauquelin L, Tetreault M, Thiffault I, Farrow E, Miller N, Yoo B, et al. POLR3A variants in hereditary spastic paraplegia and ataxia. Brain 2017; 141: e1.

TWO CASES OF LGI1-ANTIBODIES ENCEPHALITIS: CLINICAL CHARACTERISTICS AND THE ROLE OF IMMUNOTHERAPY

Maria Teresa Sollazzo[1], C. Battisti[1], R. Marconi[2], M. Dotti[1]

1 Unit of Neurology and Neurometabolic Disorders, Department of Medicine, Surgery and Neurosciences - University of Siena – Siena
2 Unit of Neurology, Cardio-Neuro-Vascular Department - P. O. Grosseto, Azienda USL Toscana Sud-Est – Grosseto

LGI1-antibodies encephalitis is a rare autoimmune disorder associated to neuronal voltage-gated potassium channel complex (VGKC)-antibodies. We present two cases of LGI1-antibodies encephalitis in order to underline the main clinical characteristics and to improve therapeutic strategies.
Case 1. A 68-year-old woman came to our attention after a convulsive status epilepticus, treated in Intensitive Care and preceded two days before by faciobrachial dystonic seizures (FBDSs). She had three weeks history of rapid short-term memory decline and of behavior and sleep disorders. Intercritical EEG was normal. MRI indicated hyperintensities on T2-weighted sequences in insula and in the fronto-mesial region of the left hemisphere. The CSF was normal. LGI1-Abs were positive both in liquor and serum; the biomarkers of the other AE, tumor markers and paraneoplastic neuronal antibodies were all negative. After combined treatment with intravenous immunoglobulin and glucocorticoid, resolution of the MRI hyperintensities was observed. For persistent memory impairment and FBDSs, Rituximab was prescribed with complete disappearance of FBDSs. Case 2. A 78-year-old man came to our evaluation for a twenty days history of visual hallucinations, FBDSs and episodic bilateral choreiform movements with repeted falls. CSF, MRI and EEG were normal. LGI1-Abs were positive in the serum; tumor markers and paraneoplastic neuronal antibodies were all negative. He was treated with intravenous glucocorticoid and Haloperidol with resolution of the clinical manifestations.
LGI1-antibodies interrupt VGKC function, resulting in CNS hyperexcitability with seizures and limbic encephalitis. Main clinical features include memory dysfunction, psychiatric disturbances and FBDSs, manifesting as involuntary movements of the arm and ispilateral hemiface or leg. Generalized seizures, observed only in the first patient, are rare. In the second patient we found a peculiar combination of movement disorders, with typical FBDSs and episodic choreiform movements. It remains controversial whether FBDSs are seizures or just an abnormal paroxysmal extrapyramidal manifestation.
MRI can show increased signal on T2-weighted FLAIR imaging in hippocampus or in medial temporal lobes. In the first patient MRI abnormalities were observed, but they could have been caused by seizures not by inflammation. Only a few cases are refractory to first-line immunotherapy, like the first one. Rituximab has been associated with long-term remission of

symptoms in refractory patients, but a consensus on its optimal use is lacking, therefore randomized clinical trials are needed for LGI1-antibodies and other autoimmune encephalitis.

References: Lehong Gao, Aihua Liu, Shuqin Zhan, Li Wanga, Liping Li, Le Guan, Xin Zhao, Xiating Zhang, YupingWang: Clinical characterization of autoimmune LGI1 antibody limbic encephalitis. Epilepsy & Behavior. 2016; 56: 165-169
J.William L. Brown, Peter J. Martin, John W. Thorpe, AndrewW. Michell, Alasdair J. Coles, Amanda L. Cox, Angela Vincent, Michael S. Zandi: Long-term remission with rituximab in refractory leucine-rich glioma inactivated 1 antibody encephalitis. Journal of Neuroimmunology 2014; 271: 66-68

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SEIZURES IN ALZHEIMER DISEASE: A CASE REPORT HELPING IN DIFFERENTIAL DIAGNOSIS

Angela Mariaelena Alicino, R. Leone, M. Parisi, L. Bollo, G. Candida, M. Narracci, T. Francavilla, M. Guido, G. Libro, R. Pellicciari, M. Trojano, I. Simone

Department of Basic Medical Sciences, Neurosciences and Sense Organs - University of Bari Aldo Moro – Bari

Abstract: A case report showing how neurological infective diseases could be misdiagnosed in the elderly. Background: Seizures in Alzheimer Disease have a great variability in the lifetime prevalence and have a 6- to 10-fold increased risk of appearance. Patients with a younger age of AD onset are more susceptible to seizures. This could be explained by higher prevalence of familial AD in younger patients, which has been associated with higher seizures rates or by a more aggressive AD course in younger AD patients.
AIMS: In patients with dementia the clinicians may mistakenly consider seizures activity to be related to the underlying dementia.
Case Report: A 64 years' woman was diagnosed with Alzheimer Disease on January 2018 and because of her high familiarity for dementia there was suspicion for Familial AD. On the 03/19/2019 she was admitted to our Neurology department for an acute epileptic crisis. A similar episode occurred in the Emergency Room. On her admission she was awake, aware, not oriented to time and space, with mixed aphasia. No meningeal signs. Head CT excluded ischemic lesions. EEG showed spikes and atypical spikes and waves most on left frontotemporal areas with tendency to diffusion and focal paroxysmal anomalies, most on the right. Patient showed hyperpyrexia, that was initially treated with Paracetamol and Hydrocortisone with partial response. Valproate therapy was started. Chest Xray showed a pulmonary infective process, so iv antibiotic therapy with Teicoplanin and Piperacillin-Tazobactam was started. Persisting aphasia and appearance of meningeal signs lead to add iv therapy with Ceftriaxone and Aciclovir. MRI showed left temporal, hippocampal-insular and right temporomesial-insular T2 hyperintensity and T1 hypointensity with contrast enhancement of meninges. CSF Lymphocytic pleocytosis, DBBE and HSV1 PCR positivity lead to diagnose HSV1 meningoencephalitis. On her discharge she still had mixed aphasia. She developed left lateral hemianopia.
Discussion and conclusion: In the reported case, diagnosis of meningoencephalitis was delayed because clinicians thought seizures to be symptomatic of Alzheimer Disease in a patient with suspiscion of Familial AD and fever caused by a pneumonia. It's important clinicians to recognize clinical signs and symptoms of the infection and to start an early treatment.

References: D. Pandis, N. Scarmeas Seizures in Alzheimer disease: clinical and epidemiological data Epilepsy Curr, 5 (2012), pp. 184-187
C Hommet, K Mondon, V Camus, B De Toffol, S Constan Epilepsy and dementia in the elderly Dement Geriatr Cogn Disord, 25 (2008), pp. 293-300 Friedman D, Honig LS, Scarmeas N. Seizures and epilepsy in Alzheimer's disease, CNS Neurosci Ther , 2012, vol. 18 (pg. 285-94)

IMMUNOADSORPTION AS RELAPSE THERAPY IN NMOSD PATIENTS: RELATIONSHEEP BETWEEN CLINICAL OUTCOME AND MOG-IGG AND AQP4-IGG TITER.

Luca Bollo, P. Iaffaldano, M. Mastrapasqua, M. Ruggieri, A. Manni, R. Sgobio, D. Paolicelli, I. Simone, A. Frigeri, M. Trojano

Department of Basic Medical Sciences, Neuroscience and Sensory Organs - University of Bari-Medical School - Bari-Italy

Background: Neuromyelitis optica spectrum disorders (NMOSD) are frequently associated to the presence of serum anti-aquaporin4 (AQP4-IgG) and anti-myelin oligodendrocyte glycoprotein (MOG-IgG) autoantibodies (Abs). Severe NMOSD relapses can be treated with immunoadsorption (IA), recognized as an alternative to therapeutic plasma exchange. Cell-based assay (CBA) is the gold standard for the detection of AQP4-IgG and MOG-IgG Abs.
AIMS: To correlate the serum MOG-IgG and AQP4-IgG Abs titer with clinical and radiological outcome during and after IA treatment.
Materials and Methods: Clinical and lab features of 4 NMOSD patients treated with IA were collected. MOG-IgG and AQP4-IgG Abs were detected using an in-house CBA and the serum titer was determinated using a fluorescent ratiometric method, ranging between 0 to 1 (cut-off values : 0.02 for MOG-IgG and 0.02 for AQP4-IgG). Patients were treated with several cycles of IA (median number=10, range 7-13). Antibody titers were evaluated before the first cycle of IA (T1), 2 weeks after the beginning of IA (T2) and at 2-4 weeks from the last apheresis cycle (T3).
Results: Four NMOSD patients, 3 of them misdiagnosed as multiple sclerosis, came to our attention for a severe relapse, with no recovery after a standard intravenous methylprednisolone pulse. Immunoadsorption as relapse therapy in NMOSD patients: relationsheep between clinical outcome and MOG-IgG and AQP4-IgG titer. Two NMOSD patients were MOG-IgG positive: a 26 years-old woman (Case1) with an acute bilateral optic neuritis (ON) at onset , whose antibody titers dropped from 0.98 at T1, to 0.8 at T2 and 0.7 at T3, and a 26 years-old man (Case2) with a clinical history of congenital rubella syndrome, who developed an acute bilateral ON. His antibody titers decreased from 0.96 at T1 to 0.25 at T2, and below the cut-off at T3. Two NMOSD patients were AQP4-IgG positive: a 39 years-old woman (Case 3) with dyencefalic lesions and a cerebral salt-wasting syndrome at onset, who came to our attention for a longitudinal extensive transverse myelitis (LETM). She had a titer of 0.90 at T1 that decreased to 0.65 at T2 and 0.7 at T3, and a 44 years-old woman (Case 4) with a clinical onset as area postrema syndrome followed by a LETM, whose antibodies titers dropped from 0.50 at T1, to 0.6 at T2 and below the cut-off at T3. In 3/4 of cases the IA treatment determinated a complete or partial clinical recovery,
Discussion and Conclusion: Serum MOG-IgG and AQP4-IgG Ab titers seem to be related to clinical outcomes and may be useful to monitor treatment response in NMOSD patients.

References: Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin. J Neuroinflammation. 2016 26;13(1):279.

Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, et al. MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: Epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation. 2016 27;13(1):280.

Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke K-D, Hellwig K, et al. Apheresis therapies for NMOSD attacks: A retrospective study of 207 therapeutic interventions. Neurol Neuroimmunol Neuroinflamm. 2018 Nov;5(6):e504.

INTRA-HOSPITAL DELAY IN ACUTE ISCHEMIC STROKE: IMPACT OF STANDARDIZED-INTERDISCIPLINARY LOCAL PROTOCOL

Giusy Candida, M. Petruzzellis, G. Scaglione, A. Manni, M. Trojano, I. Simone

Neurology Unit, Department of Basic Medical Sciences, Neurosciences and Sense Organs, University of Bari 'Aldo Moro'

Intravenous and endovascular treatment IVT and EVT) are effective therapies for acute ischemic stroke (AIS), although strictly time-sensitive. The recommended door-to-needle(DTN) timeâ‰¤60 minutes is reached for a minority of patients in real life. By using an intra-hospital shared AIS protocol, we assessed the effects of performing all the time-sensitive diagnostic and therapeutic procedures in a single location on the modified Rankin score(mRS), the rates of symptomatic intracerebral hemorrhage(sICH) and mortality, all evaluated at three months.
Materials and Methods: Starting from January 2018, an interdisciplinary AIS early warning protocol was introduced in our Centre: all patients with possible AIS were directly admitted from the emergency room to the CT suite, where both neurological examination and CT scan+CT-angiography were performed. We compared an intervention group(IG) of 368 patients admitted at our Department in 2018, prospectively studied, with a control group(CG) of 352 patients treated in 2017, retrospectively analyzed. Indicators of the quality of stroke management were time from DTN (when bridging with IVT) and time from door to groin(DTG).
Results: IVT was performed in 34 in the IG and 53 patients in the CG. EVT was performed in 43 in the IG and 35 patients in the CG. Bridging treatment was performed in 39 in the IG and 15 patients in the CG. Good functional outcome (mRS 0-2) was achieved by 63.6% of patient in the IG compared to 59.6% of the CG(p=0.25) and excellent functional outcomes (mRS 0-1) in 49% of IG, compared to 44.9% in the CG(p=0.28). Three months mortality was 12.4% in CG and 12.3% IG, while sICH was reduced from 2.9%(CG) to 0%(IG). The median DTN-time was reduced from 136.5 min(CG) to 110 min(IG), as well as the median DTG-time, from 180 min(CG) to 110 min(IG).
Discussion: Performing AIS workflow in a single location, allowed us to reduce of 17.58% the DTN-time and of 38.9% the DTG-time. The bridging therapy (gold standard in large vessel occlusion-related AIS) was performed in a higher number of patients in the IG (10.60%,vs 4.26% in the CG).
Conclusion: Our analysis showed that using an intra-hospital shared early warning protocol, that reduces the delay between diagnosis and treatment, a better clinical outcome was obtained even if not statistically significant.

References: AHA/ASA Guideline - 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association 'Stroke Room': Diagnosis and Treatment at a Single Location for Rapid Intraarterial Stroke Treatment. Ragoschke-Schumm A1, Yilmaz U, Kostopoulos P, Lesmeister M, Manitz M, Walter S, Helwig S, Schwindling L, Fousse M, Haass A, Garner D, KÃrner H, Roumia S, Grunwald I, Nasreldein A, Halmer R, Liu Y, Schlechtriemen T, Reith W, Fassbender K - Cerebrovasc Dis. 2015;40(5-6):251-7. doi: 10.1159/000440850. Epub 2015 Oct 21.

PROBABLE SPORADIC CREUTZFELDT-JAKOB DISEASE MISDIAGNOSED AS DEPRESSION AND ANXIETY

Nicola Davide Loizzo, L. Bollo, A. Alicino, G. Candida, I. Simone, M. Trojano

Department of Basic Medical Sciences, Neurosciences and Sense Organs - University of Bari Aldo Moro – Bari

Creutzfeldt-Jakob disease (CJD) is the prototype of a family of rare and fatal human degenerative conditions, known as prion diseases. Sporadic CJD (sCJD) is the commonest human prion disease, accounting for around 85% of cases. The peak incidence is in the seventh decade, and younger (20-40s) or older (>80) cases are less common. sCJD is characterized by prominent neurological symptoms, including a rapidly-progressing dementia, myoclonus, ataxia, and a median disease duration of 4.5 months. At the onset, many neurological symptoms can be easily misdiagnosed as psychiatric, in particular in young patients. Only long-term follow-up can suggest the diagnosis as in the following case report that we present. A previously-healthy, 55-year-old woman initially complained of acute subjective vertigo and postural instability with frequent falls. Due to the persistence of these symptoms, seven days later she went to the Emergency Department of another Hospital. Neuroimaging evaluation didn't reveal any suspicious signs except for an arachnoid cyst at the right cerebellopontine angle. Moreover, the patient didn't show any sign of cognitive impairment performing her business and household activities. The psychiatric evaluation diagnosed depression and anxiety and prescribed Paroxetine and Etizolam while ear-nose-and-throat specialist prescribed Betahistine but neither of them brought lasting benefits. Two months later, she came to our attentions complaining severe impairment of gait and peripheral jerks. At first, our investigations were directed towards an autoimmune or paraneoplastic neurological disease but the results were negative. One week later, patient showed spontaneus or elicited by auditory stimuli suggesting sCJD diagnosis. EEG showed periodic and triphasic sharp wave complexes, mainly on the right side of the brain. DWI of MRI displayed high signal intensity areas on bilateral caudate and cortical ribboning sign primarily on right cortex and frontal left cortex. In addition to these findings, she showed visual impairment, limbs' hypertonus in flexing and bradykinesia. Finally, elevated 14-3-3 protein in the CSF was confirmed. It is important to underline that diagnosis of probable sCJD was made 4 months later the onset of the disease when the clinical picture was significantly worse, requiring assistance with all personal care. In this case report, we highlight the importance to following patients with uncertain neurological signs and not misdiagnosing them as psychiatric solely on the basis of low probability of alternative diagnoses.

References: Mackenzie G and Will R. Creutzfeldt-Jakob disease: recent developments [version 1; peer review: 2 approved]. F1000Research 2017, 6(F1000 Faculty Rev):2053

INTRATHECAL ADMINISTRATION OF NUSINERSEN IN ADULT POPULATION: A REAL LIFE SAFETY ASSESSMENT

Giammarco Milella, E. D'Errico, A. Fraddosio, I. Tempesta, A. Mastronardi, A. Morea, G. Scaglione, M. Trojano, I. Simone

Department of Basic Medical Sciences, Neurosciences and Sense Organs - University of Bari Aldo Moro – Bari

Background: Spinal Muscular Atrophy (SMA) is an autosomal recessive motorneuron disease associated with progressive muscular atrophy due to a homozygous deletion or mutation in the survival motor neuron 1 gene (SMN1) causing insufficient levels of SMN protein. Nusinersen is an antisense oligonucleotide (ASO) drug that modifies the pre-mRNA splicing of SMN2,a gene copy that differs from SMN1 by only five basepairs, to promote increased production of the functional SMN protein. Because of the lacking ability of ASOs to cross the blood-brain barrier, Nusinersen is administered by intrathecal injections (II). In clinical trials Nusinersen has led to a clinical improvement in children with SMA type 1 or type 2 compared with placebo groups, with only 5 cases of communicating hydrocephalus in 1437 patients treated worldwide. In 2017 Nusinersen was approved for the treatment of pediatric and adult SMA. To date literature data on the safety of Nusinersen in adults SMA are very limited.
Aim of the study:to assess the feasibility and safety of the treatment in adults with SMA.
Materials and methods: Eleven patients with SMA type 3, aged between 20-73-years, were recruited for treatment with Nusinersen. Two of 11 patients were excluded because of severe neuromyopathic scoliosis and spondylodesis. According to a standardized protocol, LPs was performed under sterile conditions in lateral decubitus by using a 22-gauge needle. For the IT of Nusinersen, conventional, fluoroscopy-assisted and computer tomography (CT)-guided LP were used on request. After local anaesthesia, 5ml of CSF were removed and the drug was administered intrathecally. Vital signs were monitored during and after 24 hours from procedures. CSF analyses and cultures were performed in all samples. Results: The total number of LPs was 42 of which 21 conventional, 19 fluoroscopy-assisted, 2 CT-guided LPs. Adverse events were headache, back pain and dizziness all of which are reported common complications of lumbar punctures. No serious adverse effects were reported. The CSF analysis did not show any signs of infection (normal leukocytes count and CSF/serum glucose index, only slight increase of QAlbumin in 4 patients). CSF cultures were all negative.
Conclusion: Neverthelessthe presence of scoliosis and spondilodesis in all patients, the injection of Nusinersen was well-tolerated, independently on age. Only in two patients the procedure couldn't be performed for severe spinal impairment. No patient stopped the treatment. According to CTCAE, the reported adverse events were mild and clearly related to LP. Considering the medical and logistic difficult of treatment, an interdisciplinary cooperation between neurologists, anesthesiologistsand neuroradiologistsis mandatory.

References: Stolte B, Totzeck A, Kizina K, Bolz S, Pietruck L, Mönninghoff C, Guberina N, Oldenburg D, Forsting M, Kleinschnitz C, Hagenacker T. Feasibility and safety of intrathecal treatment with nusinersen in adult patients with spinal muscular atrophy.
Ther Adv Neurol Disord. 2018 Oct 5;11:1756286418803246. doi: 10.1177/1756286418803246. eCollection 2018.
Brazilian Medical Association; Antonio Silvinato, Participant; Wanderley M Bernardo, Participant Spinal muscular atrophy 5Q "Treatment with nusinersen Rev. Assoc. Med. Bras. vol.64 no.6 Sao Paulo June 2018
Common Terminology Criteria for Adverse Events (CTCAE) v5.0 Publish Date: November 27, 2017

VEMURAFENIB FOR BRAFV600E-MUTATED PILOCYTIC ASTROCYTOMA IN YOUNG ADULTHOOD: A CASE REPORT

Milena Narracci, M. Narracci, E. D'Errico, T. Perillo, M. Trojano, I. Simone

Department of Basic Medical Sciences, Neurosciences and Sense Organs - University of Bari Aldo Moro – Bari

Pilocytic Astrocytomas (PAs) are low grade gliomas (WHO grade I) with peak incidence in young adults. No standard treatment exists beyond post-surgical progression, but in tumors with a known driver mutation, targeted therapy is currently evaluated. We present an infrequent case of BRAF V600E mutation-positive PA receiving Vemurafenib, with 12-months event-free-survival (EFS) and ongoing clinical benefit. PAs 10-years survival reaches more than 90% in children, with no relapse after complete surgery, low recurrence rate after incomplete resection and rare malignant transformation. Adults PAs are less frequent but more aggressive. Cystic lesions with solid mural component and rare intratumoral hemorrhage are common. Cerebellum and diencephalon are typical locations, while spine only in 4%. BRAF gene V600E point mutation, detected in 2-9% of PAs, encodes for a constitutively active serine/threonine kinase, specifically targeted by Vemurafenib kinase inhibitor, currently evaluated in phase 2 trials. Targeted therapy is more cancer selective than chemotherapy and represents a good therapeutic option, especially in children. We describe a case of progressive BRAF V600E mutation-positive PA treated with Vemurafenib. A 14-years old caucasian boy with progressive scoliosis, spastic paraparesis and left muscle hypotrophy, sphincter dysfunction and lower limbs dysaesthesia was diagnosed with intramedullary C7-D9 BRAF V600E+ PA, in June 2013. He underwent partial surgical resection in another hospital, than he came to our attention for post-operative polichemotherapy from July 2013 to January 2015. 40-months from surgery, MRI showed cystic enlargement, hemorrhage, higher contrast enhancement and oedema. 18-months later, paraparesis with left limb fasciculations, feet paraesthesia and sacral dysaesthesia appeared, with consequent social withdrawal. He started targeted therapy with BRAF V600E kinase inhibitor Vemurafenib in May 2018 (550 mg/mq/bid orally). Neurologic and radiologic response was detected 1-month from first Vemurafenib dose. Adverse events included: skin maculopapular rash, alopecia, asymptomatic QTc prolongation and hypercholesterolaemia. In November 2018, MRI detected mild caudal cystic enlargement. In April 2019 paraparesis worsening, hypoaesthesia below D7 level and extremities apallesthesia developed, with radiologic increase of tumor oedema, not always connected with progression, and mild cystic growth. He continued Vemurafenib and all symptoms improved with dexamethasone 4 mg/die and baclofene. Now he's 20 and attends a secondary school, with good social inclusion. Targeted therapy with Vemurafenib, in a BRAF V600E+ progressive spinal PA, was associated with 12-months EFS, persistent radiologic and clinical response and manageable toxicity.

References: Del Bufalo F. Ceglie G. Cacchione A. Alessi I. Colafati G. Carai A. Diomedi-Camassei F. De Billy E. Agolini E. Mastronuzzi A. Locatelli F. BRAF V600E Inhibitor (Vemurafenib) for BRAF V600E Mutated Low Grade Gliomas. Front Oncol. 2018 Nov 14;8:526. Kaley T. Touat M. Subbiah V. Hollebecque A. Rodon J. Lockhart AC. Keedy V. Bielle F. Hofheinz RD. Joly F. Blay JY. Chau I. Puzanov I. Raje NS. Wolf J. DeAngelis LM. Makrutzki M. Riehl T. Pitcher B. Baselga J. Hyman DM. BRAFÂ Inhibition inÂ BRAFV600-Mutant. Gliomas: Results From the VE-BASKET Study. J Clin Oncol 2018 Dec10;36(35): 3477-3484. Jones DTW. Kieran MW. Bouffet E. Alexandrescu S. Bandopadhayay P. Bornhorst M. Ellison D. Fangusaro J. Fisher MJ. Foreman N. Fouladi M. Hargrave D. Hawkins C. Jabado N. Massimino M. Mueller S. Perilongo G. Schouten van Meeteren AYN. Tabori U. Warren K. Waanders AJ. Walker D. Weiss W. Witt O. Wright K. Zhu Y. Bowers DC. Pfister SM. Packer RJ. Pediatric low-grade gliomas: next biologically driven steps. Neuro-Oncology, Volume 20, Issue 2, February 2018, Pages 160-173.

IS PROTEIN S DEFICIENCY A POSSIBLE ARTERIAL THROMBOSIS RISK FACTOR?

Rossana Sgobio, M. Petruzzellis, S. Lamberti, D. Mezzapesa, M. Savarese, B. Tartaglione, L. Pascazio, S. D'Alessandro, A. Lalla, G. Milella, G. Falcicchio, M. La Cava, F. Caputo, M. Trojano, I. Simone

Department of Basic Medical Sciences, Neurosciences and Sense Organs - University of Bari Aldo Moro – Bari

Protein S is the cofactor of activated protein C which, together with antithrombin system, is a major regulator of blood coagulation. Protein S deficiency is an important risk factor for venous thrombosis but it is a rare cause of recurrent ischemic stroke in young population. We reported a case of a 45-year-old north-african man with acute ischemic stroke and left upper limb ischemia related to protein S deficiency. The patient was admitted to the Neurological Unit of a peripheral hospital for acute onset of right hand motor impairment (time of onset non defined). Brain computed tomographic (CT) scan was negative. Three days after, he developed acute aphasia, right hemiplegia, and clinical evidence of arterial ischemiae of left upper limb. Brain-CT demonstrated a small left insulo-parietal ischemic lesion, and CT angiography showed left tandem internal carotid artery (ICA), middle cerebral artery (MCA) and brachial artery occlusion. He was admitted to our Stroke Unit. His past medical history was unremarkable except for smoking. Arterial hypertension was revealed, previously unknown. Considering the clinical-MRI DWI mismatch, endovascular treatment of left ICA and MCA was performed. Then left brachial artery embolectomy was also executed. The day after, do to left brachial artery and ICA reocclusion, ICA endoarterectomy (CEA) and brachial embolectomy were tried, but with unsuccessful. During CEA, MCA occlusion occurred, which was successfully treated with endovascular thrombectomy. After nine days the upper limb was amputated. An extensive diagnostic work-up was negative except for very low protein S levels. Subsequently a total body CT scan demonstrated multiple simultaneous arterial and venous thrombosis, particularly right pulmonary artery thromboembolism, so warfarin therapy was started. Genetic test was not performed according to geneticist- because family history was negative for venous and arterial thrombosis. At the discharge to rehabilitation clinic severe disability was present (mRS 5). In the present case, it is likely that there is close relationship between the venous and arterial thrombosis and protein S deficiency because no other cause was demonstrated. However further studies are needed to determine the role of protein S deficiency as a risk factor for arterial thrombosis.

References: Girolami A1, Simioni P, Lazzaro AR, Cordiano I., Severe arterial cerebral thrombosis in a patient with protein S deficiency (moderately reduced total and markedly reduced free protein S): a family study. Thromb Haemost. 1989 Feb 28;61(1):144-7

Zhao-Hui Wang, Zhi-Jun Zhao, Kang Xu, Guo-Bing Sun, Lin Song, Hong-Xiang Yin, Xiao-Qi Chen, Hereditary protein S deficiency leads to ischemic strok. Mol Med Rep. 2015 Sep; 12(3): 3279-3284

Wiesel ML1, Borg JY, Grunebaum L, Vasse M, Levesque H, Bierme R, Sie P., Influence of protein S deficiency on the arterial thrombosis risk. Presse Med. 1991 Jun 8;20(22):1023-7

ACCUMULATION OF PROTEINACEOUS MATERIAL IN SKELETAL MUSCLE FIBERS OF A YOUNG MAN WITH SPINAL MUSCULAR ATROPHY TYPE III: COMMON FINDING OR RARE ASSOCIATION?

Irene Tempesta, L. Bollo, A. Alicino, M. Ucci, A. Manni, G. Scaglione, G. Milella, A. Amati, F. Girolamo, M. Trojano, I. Simone

Department of Basic Medical Sciences, Neurosciences and Sense Organs - University of Bari Aldo Moro – Bari

Background: Spinal Muscular Atrophy (SMA) encompasses a group of autosomal recessive inherited degenerative neuromuscular disorders associated with spinal motor neuron loss, caused by mutations in the SMN1 gene. Myofibrillar Myopathies (MFM) are a clinically and genetically heterogeneous group of progressive muscle diseases characterized by distinctive histopathology of abnormal protein aggregations and myofibrillar disintegration. Most of the diseases are autosomal dominant and adult-onset, and the clinical presentation is characterized by muscle weakness which can be accompanied by cardiomyopathy with or without respiratory insufficiency.
Case-report: An eighteen-year-old boy complained weakness in the proximal lower limbs, especially when getting up, and fatigue during sport activity since he was sixteen years old. He was able to walk about 3-4 Km. He also referred progressive muscle hypotrophy and cramps of the lower limbs. His family history and previous medical history were unremarkable. Neurological exam showed gait abnormalities because of lower limbs weakness, muscle hypotrophy of both quadriceps, areflexia in the lower limbs while tendon reflexes were reduced in the upper limbs. Laboratory tests revealed high serum creatine kinase levels (1299 U/L). Respiratory and cardiological evaluation were normal. Electromyography showed both myopathic changes and chronic denervation in the four limbs muscles. A muscle biopsy was performed and numerous target fibers had been demonstrated at routine stainings, together with abnormal accumulation of dense proteinaceous material and inclusions of fragmented filaments. These inclusions appeared stained by myosins and dystrophin arising the possible coexistence of a myofibrillar myopathy. Finally, genetic test revealed exon 7 and 8 deletions in the SMN1 gene on chromosome 5q, so the patient received a diagnosis of SMA. Currently he is treated with nusinersen and has already received four loading doses and one maintenance dose, with a slight improvement of muscle weakness.
Conclusions: In our patient increase of creatine kinase, electrophysiological signs and muscle biopsy could suggest a MFM, but the genetic test led to SMA diagnosis. Nowadays muscle biopsy is no longer routinely performed to diagnose SMA, so further studies are needed to assess whether our findings are common features among SMA patients or this is a rare case of comorbidity between Spinal Muscular Atrophy and Myofibrillar Myopathy.

References: Yagishita S, Itoh Y. "Target-targetoid phenomenon of the human muscle fibers. A histological, histochemical and ultrastructural study". Virchows Arch A Pathol Anat Histol. 1977 Aug 9;375(1):13-22
Arnold WD, Kassar D, Kissel JT. "Spinal muscular atrophy: diagnosis and management in a new therapeutic era". Muscle Nerve. 2015 Feb;51(2):157-67

LOWER LIMBS NEUROPATHY DUE TO NON-HODGKIN'S LYMPHOMA OF THE ILIOPSOAS MUSCLE MIMICKING A CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

Maria Ucci, R. Sgobio, L. Pascazio, M. Savarese, P. Milzi, D. Mezzapesa, M. Petruzzellis, B. Tartaglione, S. Lamberti, M. Trojano, I. Simone

Department of Basic Medical Sciences, Neurosciences and Sense Organs - University of Bari Aldo Moro – Bari

Introduction Diffuse large B-cell lymphoma (DLBCL) is one of the most common forms of non-Hodgkin's lymphoma (NHL) and extra-nodal involvement represents one third of cases. Skeletal muscle DLBCL is a rare presentation of NHL, accounting for 0.1% of NHL, and is associated with poor prognosis. We describe a case of lower limbs neuropathy due to an undiagnosed non-Hodgkin's lymphoma of the iliopsoas muscle which mimicked a chronic inflammatory demyelinating polyneuropathy.
Case report A 75-year-old man two years ago developed sudden lumbar and right leg pain with lower limbs weakness. The symptoms gradually worsened so he was admitted to Duisburg-Essen Hospital in Germany. Spine MRI was performed and showed enhancement of left and right L3-S2 roots and of the cauda. On CSF examination the protein level were raised with mild pleocytosis. Bone marrow biopsy and S1 right root biopsy were performed and showed no blastic or neoplastic cells. The patient was presumed to have CIDP and treated with six session of plasmapheresis with mild improvement of the hyposthenia. After a period of clinical wellness, in december 2017 he complained lower limb pain and hypoesthesia of right leg, so he received 0.4 g/kg of intravenous immunoglobulins for five days, without any response. He was admitted the first time to our department in April 2018 for a reacutization of symptoms and underwent eight session of plasmapheresis with partial improvement of pain and motor deficiency. The electroneurography showed: decreased CMAP amplitude and MCV of both external popliteal sciatic (EPS) nerve with right prevalence; normal SNCV and SNAP of left superficial peroneal nerve, decreased SCV of left sural nerve; absent SNAP in right superficial peroneal nerve and sural nerve. In October 2018 the patient was admitted for the second time in our department. Neurological examination showed severe muscle straight deficiency in left and right leg (with left prevalence), areflexia and pain of the lower limbs. Total body CT showed a mass of 4,5 cm diameter into the left iliopsoas muscle extended from inguinal region to the L2-L3 intervertebral foramen. Then FDG-PET identified enhancement of the iliopsoas mass and locoregional lymphnodes. The histological examination of muscle biopsy demonstrated non-Hodgkin's Diffuse large B-cell lymphoma.
Discussion This case illustrates a rare compressive/paraneoplastic neuropathy caused by a primary skeletal muscle lymphoma, misdiagnosed and treated as a CIDP for two years. This report emphatizes the importance of performing an early and correct diagnosis, essential for patient prognosis.

References: Merindol J, et al. Isolated muscle hypertrophy revealing diffuse large B-cell lymphoma. Joint Bone Spine (2019)
Li J-Y, Li C-L, Lu C-K. Skeletal muscle lymphoma presenting with chroniccompartment syndrome of leg after trauma. Case Rep Oncol Med2018;2018:4078672.

FAHR'S DISEASE: IDENTIFICATION OF AN UNCOMMON SLC20A2 MUTATION

S. Arena[1], S. Toscano[1], G. Mostile[1], C. Rascunà[1], G. Portaro[1], A. Nicoletti[1], M. Zappia[1]

[1] Neurology Clinic, Department "G.F. Ingrassia", Section of Neurosciences, University of Catania, Catania, Italy.

Background Fahr's disease is a rare neurological condition characterized by symmetric and bilateral calcification, mainly calcium carbonate and calcium phosphate, in basal ganglia, thalamus, hippocampus, cerebral cortex and dentate nucleus. Several mutations of genes (***SLC20A2, XPR1, PDGFB, and PDGFRB)*** can be involved with different modes of inheritance and may produce various phenotypes [1]. In this report, we describe the case of a male patient with positive family history for gait disturbances and tremor.

Case Report A 72 years old man reported a 7 years history of rest and kinetic tremors, followed by gait disturbances, postural instability with some fall, hyposmia, memory impairment, anxiety and irritability in the latest 2 years. He had a positive family history on the paternal side for gait disturbances with tremor (two uncles) and for parkinsonian disorder with a good response to levodopa treatment, associated with multiple cerebral calcifications (a cousin). Neurological examination showed mild parkinsonism and presence of rest and kinetic tremors in left arm, characterized by changing in frequency and amplitude and disappearing with distraction maneuvers. Brain MRI T2- fast field echo (FFE) sequences showed diffuse low intense signal in basal ganglia, as for deposits of paramagnetic mineral substances. Moreover, brain CT showed multiple and bilateral calcifications in basal ganglia and thalamus. Dopamine transporter single-photon emission computed tomography (DAT SPECT) imaging confirmed nigrostriatal cell loss with extra-striatal uptake. Moreover, Acute Levodopa Challenge Test showed a poor motor response. Neuropsychological assessment established mild memory impairment. Blood tests were negative for biochemical abnormalities of calcium-phosphate homeostasis and for infectious disease. On the basis of his strong positive family history, we suspected an autosomal dominant inheritance involvement. DNA was extracted from peripheral blood. Sequencing of SLC20A2 identified missense heterozygous mutation c.82G>A (p-Asp28Asn), predicted to be disease causing with a high probability (99.99%) in a Mutation Taster analysis [2].

Conclusion Although its rarity, Fahr's disease should be always suspected in presence of bilateral multiple calcifications, progressive neurological dysfunction (as parkinsonism) and/or psychiatric symptoms (as psychogenic tremor), absence of biochemical abnormalities and positive family history. Moreover, etiology is not completely understood. Mutation c.82G>A is a relatively new finding in the scenario of Fahr's disease and has been described only in few cases, both familiar and sporadic [2]. Moreover, it is tipically associated with concomitant calcifications and outstanding resistance to levodopa treatment [3]. Due to various phenotypes, Fahr's disease is a challenging diagnose.

References: Saleem, et al. *Fahr's syndrome: literature review of current evidence*. Orphanet Journal of Rare Diseases 2013, 8:156.
Chen, et al. *Novel SLC20A2 mutations identified in southern Chinese patients with idiopathic basal ganglia calcification*. Gene 529 (2013) 159–162.
Jaworski, et al. *Fahr Syndrome – an Important Piece of a Puzzle in the Differential Diagnosis of Many Diseases*. Pol J Radiol, 2017; 82: 490-493.

MALIC ENZYME 2 GENE AND THE POSSIBLE SUSCEPTIBILITY TO GENETIC GENERALIZED EPILEPSIES (GGES): A CASE REPORT

Giulia Battaglia, L. Giuliano, G. Mainieri, A. Guccione, V. Sofia, M. Zappia

Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia" Section of Neurosciences - University of Catania

Genetic generalized epilepsies (GGEs) are a group of frequent and polygenic disorders with a tipical onset during childhood or adolescence, clinical manifestations and electroencephalogram (EEG) features. Due to their complex genetic architecture, identification of candidate genes has been difficult.

Clinical Case: A 21-year-old young woman was admitted to our clinic because of different types of seizures with a daily recurrence, poorly controlled by pharmacological therapy. She experienced the first GTCS at the age of 14 years during sleep, followed by other episodes during wakefullness. At the same age she started to present frequent absence seizures with sudden onset and offset, sometimes preceded by epigastric aura and followed by subsequent confusion. For this reason, she started different antiepileptic treatments in different combinations (valproate, topiramate and levetiracetam) without a good clinical response. Carbamazepine and lamotrigine were introduced with an initial good response. However, after an increase of dosage of carbamazepine, she started reporting brief jerks of both hands. During the hospitalization in our Unit a standard EEG showed normal background activity and the absence of epileptic discharges; the Wechsler Adult Intelligence Scale showed a I.Q. of 67. The patient also underwent a brain MRI showing no abnormalities, except for a cerebellar lesion of uncertain significance. Long-Term Video EEG Monitoring (LTM) during sleep showed the presence of long sequences of 3 to 4 Hz generalized spikes and polyspikes wave discharges, especially during N2 phase. An isolated spike and wave discharge was associated with a myoclonic jerk of the upper limbs on polygraphic recording. For this reason, carbamazepine was withdrawn and progressively replaced by perampanel with a decrease of seizures and a disappearance of jerks. Due to peculiar EEG features in sleep we also performed a genetic panel and a missense mutation in malic enzyme (ME2) (c. 580C>T) was found. ME2, which is indirectly implicated in the synthesis of GABA, is one of the genes that seems to be linked with an higher susceptibly for GGEs (Wang, Greenberg and Stewart, 2019). Furthemore a missense mutation in the same gene involving c.1072A> G and c.1090C>G. in a patient with generalized epilepsy has been previously described (Wang, Greenberg and Stewart, 2019) In conclusion our results support the notion that the link between genes and GGE is complex and that different coding variants of the same gene can be involved.

References: Wang, M., Greenberg, D. A. and Stewart, W. C. L. (2019) "Replication, reanalysis, and gene expression: ME2 and genetic generalized epilepsy", Epilepsia, 60(3), pp. 539-546. doi: 10.1111/epi.14654

MUSICOGENIC EPILEPSY: CASE REPORT

Antonella Guccione, A. Guccione, L. Giuliano, G. Mainieri, G. Battaglia, V. Sofia, M. Zappia

Department G.F. Igrassia, section of Neurosciences - University of Catania

Background: musicogenic epilepsy, firstly described in 1937 by Critchley, is a rare form of reflex epilepsy with an estimated prevalence of 1/10,000,000 people. The mean age of onset is 28 years with a female predominance (1). We describe the case of a patient who presented the association between temporal lobe epilepsy of unknown etiology with music-induced seizures, type 1 diabetes mellitus (T1DM) and IgA deficiency.
Clinical case: a 20 years old italian man with a positive family history of epilepsy reported a 1 year history of seizures characterized by epigastric aura or fear sensations followed by impairment of consciousness, oromandibular automatisms, repetitive left hand movements, headache and mental confusion. He never had a secondary generalization.
Seizure frequency was of 5-6 episodes per month. Ictal events occurred spontaneously or were precipitated by listening, thinking and evoking memories of music.
In the same period type 1 diabetes mellitus was diagnosed and insulin replacement therapy was started. EEG showed irregular slow waves over left temporal areas increasing during hyperpnea. During long-term video-EEG monitoring we recorded an ictal event triggered by listening Italian national Mameli's Anthem in normoglycemia conditions. Blood tests showed that the anti-glutamic acid decarboxylase antibodies (GAD-Abs) were negative (2) and the presence of IgA deficiency (<6 mg/dL). Neuropsychological evaluation, brain MRI and FDG-PET were unremarkable.
Levetiracetam treatment was started (2,000 mg daily) with an initial clinical benefit. After a few months, for the reappearance of weekly seizures, lacosamide was added (200 mg/day) with reduction in seizure frequency.
Conclusions: in the last years it was often observed the association between epilepsy and diabetes mellitus but the relationship is unclear. GAD-Abs have been associated with T1DM and a large variety of neurological conditions, including epilepsy, although their real pathogenetic mechanism in neurological diseases is still unknown (3). However, several etiological factors may contribute to this condition such as autoimmune diseases, gene mutations and metabolic factors.

References: 1) M. J. Maguire. Music and epilepsy: a critical review. Epilepsia (2012); 53(6):947-961
2) M. Falip, L. Rodriguez-Bel, S. CastaÃ±er, J. Miro, S. Jaraba, J. Mora, J. Bas, M. Carreé. Musicogenic reflex seizures in epilepsy with glutamic acid decarbocylase antibodies. Acta Neurol Scand (2018); 137:272-276
3) A. Verrotti, A. Scaparrotta, C. Olivieri and F. Chiarelli. Seizures and type 1 diabetes mellitus: current state of knowledge. European Journal of Endocrinology (2012); 167: 749-758

SEVERE COGNITIVE FLUCTUATIONS AND HALLUCINATIONS AS CLINICAL PRESENTATION OF ALZHEIMER'S DISEASE: A CHALLENGING DIAGNOSIS THAT MIMICS OTHER PRIMARY DEMENTIAS

Salvatore Gulizia, A. Luca, R. Manna, C. D'Agate, A. Nicoletti, M. Zappia

Department of Medical, Surgical and Advanced Technology "G.F. Ingrassia" - University of Catania - Catania

Background: Alzheimer's disease (AD) is the most common neurodegenerative disease. The neuropathological hallmarks are extracellular deposits of beta amyloid and intracellular neurofibrillary tangles. Usually, it manifests as a progressive cognitive decline typically involving episodic memory. However, some cases may present with non-amnesticfeatures defining the "atypical" variants of AD[1]. We reported a case of frontal variant of AD (fv-AD) presenting with hallucinations and marked cognitive fluctuations that mimics other primary disorder such as Lewy Body Dementia (LBD) and behavioral variant of Fronto-Temporal Dementia (bv-FTD).
Clinical Case History: 72 years old housewife with hypertension. Familiar history for neurological disease (a brother with multiple sclerosis). Patient's daughter reported a 5 year-history of behavioral changes characterized by suspiciousness, irritability and delusions. Moreover, the patient complained that even if she known it was not possible, sometimes, her dead bother "came to visit her, just to spend time together". After 2 years, psychomotor retardation, distractibility, lapses and episodes of fluctuating "confusions" occurred. The abilities of daily living were spared even if she complained some difficulties with handling money and using telephone. Neurological examination and neuropsychological assessment: neurological examination was normal apart from the presence of bilateral palmo-mental and snout reflex. Age and education adjusted Mini Mental State Examination and Frontal Assessment Battery were 14.2 and 6.8 respectively. In the verbal memory test both immediate and delayed recall were altered. Poor logical-deductive abilities were evident at the Colored Raven's Matrixes. The Clock Drowing Test showed constructive apraxia. Neuroimaging: Brain MRI showed frontal and temporal lobe atrophy. Brain perfusion scintigraphy resulted unremarkable and brain SPECT DaTScan showed only mild extra-striatal uptake. Cerebro-spinal fluid investigations: routine CSF analysis were normal. The research of AD biomarkers in CSF showed low levels of 1-42 beta-amyloid fragment (59 pg/ml, normal values >599) and high levels of tau (413 pg/ml; normal values 8.1) defining an A+/T+/N+ profile.
Conclusion Due to the "atypical", the diagnosis of fv-AD with behavioral onset may be very challenging. In this specific case, the clinical onset with hallucinations and the marked cognitive fluctuations could suggest a diagnosis of Lewy Bodies Dementia[2]. On the other hand, the behavioral changes may fit with a bv-FTD diagnosis[3]. In this regard, an early diagnosis could be reached with CSF biomarkers analysis.

References: Villain N, Dubois B, Alzheimer's Disease Including Focal Presentations, Semin Neurol. 2019 Apr;39(2):213-226
Perri R, Monaco M, Fadda L, Caltagirone C, Carlesimo GA., Neuropsychological correlates of behavioral symptoms in Alzheimer's disease, frontal variant of frontotemporal, subcortical vascular, and lewy body dementias: a comparative study, J Alzheimers Dis. 2014;39(3):669-77 Stephanie Wong, Jessica Strudwick, Emma Devenney, John R. Hodges, Olivier Piguet & Fiona Kumfor (2019): Frontal variant of Alzheimer's disease masquerading as behavioural-variant frontotemporal dementia: a case study comparison, Neurocase, 2019 may: 48-58

AN UNCOMMON ASSOCIATION BETWEEN JUVENILE MYOCLONIC EPILEPSY AND MULTIPLE SCLEROSIS: A CASE REPORT

Roberta Manna, S. Lo Fermo, V. Sofia, G. Mainieri, A. Luca, S. Gulizia, M. Zappia

Department "G.F. Ingrassia", Section of Neurosciences, - University of Catania – Catania

Background The prevalence of epilepsy in MS was recently estimated at 3.1% compared to 0.6% in the general population. In Sicily, incidence rate of epilepsy among MS was 285/100,000 person years at risk. Previous studies reported a high frequency of focal epilepsy in MS. To the best of our knowledge, to date only one report of juvenile myoclonic epilepsy (JME) in MS has been reported.

Case presentation A 15-years-old boy presented to the E.R. on April 2018 for T-C seizures preceded by fencing posturing. In the last weeks, he frequently complained dropping his phone off his hands, especially on awakening and while playing videogames, in a dark room. Moreover, in the last two months, he referred blurred vision in his left eye. When he was admitted to our department, his neurological examination showed only a reduced visus in the left eye (16/20). He underwent an EEG and polyspikes and waves complex were found, especially after intermittent photic stimulation and hyperpnoea activation maneuvers. JME was diagnosed and valproate therapy 1200 mg/die was started. As routinary practice, MRI was performed. Unexpectedly, not enhanced bulbo pontine sulcus, left cerebellar puduncle, right temporomesial periventricular region, left anterior temporal periventricular, posterior internal right capsule, orbital part of the left eye, as well as C1 and C2-C3 spinal tracts hyperintensities were found. Demyelinating disease was suspected and other investigations were carried out. PEV showed increased latency of P100 wave in the left eye (148.5 msec). PESS were normal. CSF investigation was normal. After the spinal tap, the boy had nausea and headache. The neurological examination showed flapping tremor with absence of meningeal irritation signs. Another EEG was made and slow waves and triphasic waves were demonstrated. A iatrogenic encephalopathy was suspected, valproate was reduced and lamotrigine was added with an improvement of the symptoms and disappearance of the flapping tremor.

Follow-up: six months later, he came to our department for exotropia in the right eye, lateral gaze and upbeat nystagmus, spontaneous diplopia in all directions. He was treated with methylprednisolone bolus for five days with complete recovery. According to Mc Donald's criteria, multiple sclerosis was diagnosed. Interferon-Î² was started, in off label regimen, because of the age of the boy. Up to date, he had no adverse events or relapses. Conclusion: this is the second case reported in literature on the association between JME and MS.

AN UNCOMMON NEUROLOGICAL PRESENTATION OF BREAST CANCER

Roberta Manna, V. Sofia, R. Terranova, A. Luca, M. Zappia

Department of Medical, Surgical and Advanced Technology "G.F. Ingrassia" "Ingrassia" - University of Catania – Catania

Clinical Case: A 58 years old woman complained about diplopia, severe headache, back pain, episodes of sweating, confusion, and sudden falls, followed by tremors in the limbs. For these symptoms, she started levetiracetam 1000 mg/die without benefit. MRI revealed an increased ventricular volume and patient was recovered in the Neurosurgery department of our hospital. A lumbar puncture was performed and the CSF analysis revealed high level of proteins, albumin, oligoclonal bands. Then, she was admitted to our department.
Neurological examination showed bilateral lateral rectum paralysis, postural instability with a positive Romberg sign. EEG showed slow background rhythm and slow waves in both frontal regions. Lacosamide 100 mg/die was added. CFS flowmetry MRI was performed and the hypothesis of a normal pressure hydrocephalus was advanced.
A column MRI showed inflammation signs of cauda equina and intracranial nerves and "salt and pepper" appearance of the bones. For this reason, we hypothesized aematological disease, in particular multiple myeloma, although the patient, in her blood test, had only a slight anemia. An osteomedullary biopsy was made and it showed metastatic cells of "signet ring cell" adenocarcinoma. A total body CAT scan showed an enlargement of the uterus with an irregular contrast enhancement. A total body FDG-PET showed enhancement in the pyloric region, in the uterus, in axillary lymph nodes. The patient underwent hysteroscopy and signet ring cells were found. On mammal examination nipple retraction on the left was evidenced and a retroareolar nodule was present. An agobiopsy was performed and it showed pleomorphic lobular and duttular carcinoma with signet cells.
Conclusions: We described a very rare and complex case of pleomorphic breast cancer presentation. The patient complained only neurological deficits (headache, cranial nerves deficit and epilepsy) and for this reason diagnosis was difficult. Collaboration between different specialists is always necessary and it is very important to think of the patients as a whole.

DIFFERENCES IN 3D SPATIO-TEMPORAL AND KINEMATIC GAIT PARAMETERS BETWEEN IDIOPATHIC NORMAL PRESSURE HYDROCEPHALUS ASSOCIATED WITH PARKINSONISM AND PARKINSON'S DISEASE PATIENTS

Giacomo Portaro, G. Mostile, V. Dibilio, F. Contrafatto, P. Cunsolo, G. Raudino, F. Certo, A. Nicoletti, G. Barbagallo, M. Zappia

Department G.F. Igrassia, section of Neurosciences - University of Catania

Background: Gait dysfunction is a common feature in patients with Parkinson's Disease (PD) as well as in patients with Idiopathic Normal Pressure Hydrocephalus (iNPH) associated with parkinsonism, leading to clinical overlap. There are some evidences of distinctive gait features in iNPH as compared to PD, including reduced gait speed and step length, increased asymmetry in step length as well as alterations in kinematic parameters related to dynamic instability. However, results remain still heterogeneous.
Objectives: To evaluate differences in 3D spatio-temporal and kinematic gait parameters between iNPH associated with parkinsonism and PD patients.
Methods: We used the BTS GaitLab system to evaluate gait kinetic and kinematic parameters in a group of patients with iNPH associated with parkinsonism, who were diagnosed based on clinical characteristics as well as for the radiological evidence of cerebral ventriculomegaly. They were compared to a cohort of patients affected by PD diagnosed according to Gelb et al., who were tested with the same system in their "practical on" motor state if pharmacologically treated.
Results: We enrolled N=7 iNPH patients with parkinsonism (age: 72.3 years; UPDRS-ME score: 29.7) to be compared with N=39 PD patients (age: 65.8 years; UPDRS-ME score: 31.1), of whom N=34 (87.2%) L-dopa treated. At univariate analysis, we observed a significant increase in right double support phase while a significant reduction in gait speed, bilateral gait cycle length and dorsi-plantar flexion of left ankle in iNPH patients as compared to PD. Multivariate analysis confirmed reduction in both left gait cycle length and dorsi-plantar flexion of left ankle as independent kinetic-kinematic factors differentiating the two conditions.
Conclusions: Our results showed a reduction of gait speed and stride lenght in patients affected by iNPH compared to PD and an alteration in kinematic parameters with a worse foot-to-floor clearance. These results confirm that gait analysis may help to differentiate clinical overlap between iNPH and PD.

References: Bugalho P, Alves L, Miguel R. Gait dysfunction in Parkinson's disease and normal pressure hydrocephalus: a comparative study. J Neural Transm (Vienna). 2013 Aug;120(8):1201-7
Stolze H, Kuhtz-Buschbeck JP, Drücke H, Jöhnk K, Illert M, Deuschl G. Comparative analysis of the gait disorder of normal pressure hydrocephalus and Parkinson's disease. J Neurol Neurosurg Psychiatry. 2001 Mar;70(3):289-97

RETINAL THICKNESS AND MICROVASCULAR PATTERN IN EARLY PARKINSON'S DISEASE

Cristina Rascunà[1], C. Terravecchia[1], A. Russo[2], G. Mostile[1], C. Cicero[1], A. Luca[1], N. Castellino[2], A. Longo[2], T. Avitabile[2], M. Reibaldi[2], M. Zappia[1], A. Nicoletti[1]

1 Department GF Ingrassia - University of Catania
2 Department of Ophthalmology - University of Catania

Background: In human retina dopamine is physiologically released by amacrine cells(ACs). Dopamine takes part in contrast sensitivity, visual acuity and colour vision by modulating ganglionic
cells signaling. Retinal dopaminergic depletion observed in Parkinson's Disease(PD) could partly explain the visual symptoms experienced in PD patients. Several spectral-domain optical-coherence-tomography(SD-OCT) studies reported a thinning of intraretinal layers in PD patients compared to healthy controls(HC), especially in retinal nerve fiber layer(RNFL), ganglionic cells layer(GCL) and inner plexiform layer(IPL) (1). However, few studies have focused on possible correlation between retinal thickness and retinal microvascular pattern (2).
Aims: To detect changes in retinal thickness and their possible correlates with microvascular pathway in early PD patients compared to HC. Materials and methods: Patients fulfilling UK-Brain-Bank criteria for PD were recruited. HC were also enrolled. Exclusion criteria were ocular/retinal diseases, systemic diseases impairing visual system (diabetes, uncontrolled hypertension/hypotension, cardiovascular diseases) and other neurological diseases. Retinal microvascular pattern was analysed using OCT-angiography(OCT-A) and segmentation analysis of retinal layers using SD-OCT. Retinal microvasculature was automatically divided into superficial and deep capillary plexus (SCP and DCP). Multivariate analysis was performed to evaluate the possible confounding role of age, sex and hypertension on the retinal layers thickness found significantly different between PD and HC. A possible correlation between retinal thickness and microvascular pattern was analysed using Pearson correlation. Results: Twenty-one right eyes from 21 PD patients and 33 eyes from 17 HC were evaluated. A significant thinning of RNFL, GCL, IPL and INL was found in PD patients compared to HC, adjusting for age, sex and hypertension. Among PD patients a positive correlation between RNFL, GCL and IPL thickness and microvascular density was found in the foveal region, both into SCP and DCP.
Discussion and conclusion: Recent studies demonstrated Î±-synuclein deposition not only along the wall of blood vessels (3) but also in the inner-retina, especially in GCL, IPL, and in the interface between IPL and inner nuclear layer(INL), where ACs are located. Consistent with these data, we found a thinning of intraretinal layers in PD patients compared to controls. Moreover, in PD patients we observed an interesting positive correlation between microvascular density and inner retinal layers thickness in the foveal region. Foveal involving

could, at least partly, explain visual symptoms described in the early PD. It is unclear whether retinal impairment is due primarily to a cellular neurodegeneration or microvascular damage. Nevertheless, such findings suggest an intriguing role of retina as possible biomarkers of early PD.

References: Satue M. et al. Optical Coherence Tomography as a Biomarker for Diagnosis, Progression, and Prognosis of Neurodegenerative Diseases. 2016. J Ophthalmol. 2016; 2016: 8503859.
Kwapong W.R. et al. Retinal Microvascular Impairment in the Early Stages of Parkinson's Disease. Invest Ophthalmol Vis Sci. 2018 Aug 1;59(10):4115-4122.
Price D.L. et al. Longitudinal live imaging of retinal alpha-synuclein: GFP deposits in a transgenic mouse model of Parkinson's disease/dementia with Lewy bodies. Sci Rep. 2016; 6:29523

EXPLORATORY ANALYSIS OF ELECTROCORTICAL SIGNAL COMPLEXITY IN PATIENTS WITH PROGRESSIVE SUPRANUCLEAR PALSY AND CORTICOBASAL SYNDROME

Roberta Terranova, G. Mostile, L. Giuliano, A. Luca, G. Donzuso, G. Portaro, C. Rascunà, V. Sofia, A. Nicoletti, M. Zappia

Neurology – G.F. Ingrassia – University of Catania – Catania

Background Complexity is a characteristic of self-similar fractal phenomena, which have been described in biological processes. It has been hypothesized that a topographic increased level of neuronal organization can be evaluated by analyzing self-similarity property of site-specific electrocortical activity as expression of brain signal complexity. In untreated Parkinson's disease subjects, an increased level of fronto-temporal neuronal organization has been observed. No data are available for patients clinically affected by suspected tauopathies with dementia and parkinsonism.
Aims We evaluated self-similarity of electrocortical activity as expression of brain signal complexity in patients clinically affected by Progressive Supranuclear Palsy (PSP) and Corticobasal Syndrome (CBS).
Methods We analyzed data of N=14 patients affected by Progressive Supranuclear Palsy with Richardson's syndrome (PSP-RS) and N=7 patients with Corticobasal Syndrome (CBS) who underwent standardized EEG. We selected also two groups of healthy controls [Group 1: N=10 subject (mean age: 25.2 ± 5.8)]; Group 2: N = 27 subject (mean age: 68.8 Â± 1.2)] with normal EEG, no parkinsonism and with a MMSE score greater than 24 points. Patients groups were age-matched with Group 2. A Welch's periodogram was applied to site-specific electroencephalographic signal epochs. To investigate self-similarity of electrocortical activity, the power law exponent was computed for each selected coordinate as minus the slope of power spectrum versus frequency in a Log-Log scale.
Results We compared first power law exponent in the two different age groups of healthy controls and we found a significant increase of values in bilateral parietal and occipital regions as well as in right temporal regions in Group 2. Then, we analyzed differences in values between PSP-RS and CBS patients. PSP-RS subjects presented significant overall lower values among all sites of recordings as compared to controls (Group 2). CBS patients presented instead significant lower values in the posterior temporal-parietal-occipital regions bilaterally with respect to controls (Group 2), while no significant differences were observed in the frontal regions.
Conclusions We found a physiological increase in power law exponent values through aging with an antero-posterior gradient among the evaluated sites of recording. In the two analyzed pathological conditions (PSP-RS and CBS), we found a decrease of this index with different pattern of distribution among the evaluated brain regions. We hypothesized that site-specific changes in electrocortical organization could represent adaptive mechanisms of spared cortex areas in patients affected by suspected tauopathies with dementia and parkinsonism, in the opposite direction to physiological changes.

INITIAL TREATMENT CHOICE IN A LARGE ITALIAN COHORT OF RELAPSING REMITTING MULTIPLE SCLEROSIS PATIENTS

Aurora Zanghì, E. D'Amico, C. Chisari, S. Toscano, S. Arena, S. Lo Fermo, F. Patti, M. Zappia

Department G.F. Ingrassia - University of Catania

Background: Multiple Sclerosis (MS) treatment landscape has changed considerably during the last few years with the addition of new disease-modifying treatments (DMTs).
Aims: To evaluate the effectiveness and the persistence of first-choice DMT in a large Italian cohort of Relapsing-Remitting MS (RRMS) patients.
Materials and Methods: Were enrolled all patients afferent to the tertiary MS center of Catania, Italy, who received a diagnosis of RRMS according to the 2010 revision of the McDonald criteria from January 1, 2010, to December 31, 2015. The last follow up was settled on December 31, 2018.
Patients were divided into two groups: Group A, including RRMS patients who have continued their first prescribed DMT until the last follow-up; Group B, including RRMS patients who discontinued their first DMT during the observation period. Data were extracted from a computerized database, iMedé software (iMedé, Merck-Serono SA; Geneva). The following data were collected: demographical (sex, age), clinical (the type of disease onset, number of relapses and level of disability obtained by Expanded Disability Status Scale, EDSS) and radiological data (number of T2 and T1-gadolinium lesions on Magnetic Resonance Imaging, MRI). Time-to-first-relapse between the two groups was compared with survival analysis. Subsequently, a Cox regression model was built to identify any predictor.
Results: From a total sample of 704 patients, 392 were enrolled in the study. Out of them, 183 were in Group A (46.7%) and 209 in Group B (53.3%). Group B showed a higher number of patients with multifocal onset, a higher number of T1-gadolinium lesions on MRI than Group A (for all $p<.05$). The time-to-first-relapse was lower in patients in Group B (34.6 vs 84.6 months, $p=.04$, Log-Rank 4.2).
Cox-regression-model retained as predictors: age (ExpB 15.3, CI 2.6-86.7, $p=0.002$), number of relapses (ExpB 5.3, CI 1.4-19.7, $p=0.01$) and number of T1-gadolinium lesions on MRI (ExpB 3.2, CI 1.2-9.3, $p=0.03$) in the year before diagnosis.
Discussion and Conclusions: in our cohort, 46.7% of RRMS patients maintained the first prescribed DMT during the entire follow-up. Age and level of disease activity in the year before diagnosis were predictors of a higher discontinuation rate. We conclude that demographic, clinical and radiological information helps predict individual response to DMTs at the time of their commencement. The contemporary approach to personalized MS therapy depends on evidence-based prognostication and evaluation of early treatment responses to identify the need to switch therapy.

References: Granqvist M, Boremalm M, Poorghobad A, et al. Comparative Effectiveness of Rituximab and Other Initial Treatment Choices for Multiple Sclerosis.
JAMA Neurol. 2018;75(3):320-327. doi:10.1001/jamaneurol.2017.4011
Brown JWL, Coles A, Horakova D, et al. Association of Initial Disease-Modifying Therapy With Later Conversion to Secondary Progressive Multiple Sclerosis. JAMA. 2019;321(2):175-187.
doi:10.1001/jama.2018.20588
Rotstein, D. and X. Montalban. "Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis." Nature Reviews Neurology.
2019; 15(5): 287-300

EFFICACY AND SAFETY OF PERAMPANEL IN A "REAL WORLD" CONTEXT

Francesco Fortunato, I. Sammarra, A. Giugno, A. Quattrone, A. Pascarella, A. Labate, A. Gambardella

Institute of Neurology - Magna Graecia University - Catanzaro

Background: Adjunctive treatment with once-daily perampanel was effective in improving seizure control in patients 12 years and older with refractory focal and generalized seizures.1-2
Aim: To assess efficacy and safety of perampanel (PER) as add on therapy in patients with focal or generalized epilepsy in a real-world context.Materials and methods: Thirty-two patients have been prospectively enrolled since May 2017: 26/32 (87%) were affected by focal epilepsy e six/32 (13%) affected by generalized epilepsy. All patients performed a baseline visit, a visit at three months and six months after enrollment. The inclusion criteria were: male or female patients of age ï‚³ 12 years with focal seizures with or without evolution to bilateral convulsion, or generalized seizures, which were inadequately controlled by one or more antiepileptic drugs (AEDs). In all patients, seizure frequency was assessed by a diary during follow-up visits. PER was started with 2 mg/day at bedtime and was up-titrated by 2 mg/day every 2-6 weeks. Efficacy, as measured by responder rates (>50% reduction in seizure frequency), retention rates, and adverse effects, was analyzed.
Results: All patients were taking a median of 2 AEDs (range: 1-4) when starting on PER. The median dose of PER was 6 mg (range: 2-10 mg). Nineteen/32 (59%) patients were classified as responders, and 4/19 (21%) patients experienced sustained seizure freedom. About two-thirds of patients complained side effects, and the most common were fatigue, nausea, vomiting, ataxia, dizziness, behavioral irritability, and sedation. Five/32 (16%) patients withdrew PER during the study period, with four of them (80%) withdrawing due to intolerable adverse effects, especially irritability and aggressive behavior. Discussion and conclusion: Adjunctive PER can achieve clinically meaningful improvement in many patients with refractory focal or generalized epilepsy. Further studies are warranted to explore the tolerability profile, with particular attention to psychiatric adverse events.

References: 1. Steinhoff BJ, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: A pooled analysis of three phase III studies. Epilepsia 2013; 53:1481-89.
2. French JA, et al. Perampanel for tonic-clonic seizures in idiopathic generalized epilepsy. Neurology 2015; 85:950-57

USEFULNESS OF 24-HOUR AMBULATORY EEG MONITORING IN THE DIAGNOSIS OF TYPICAL ABSENCES

Alessia Giugno, F. Fortunato, M. Sturniolo, I. Sammarra, A. Pascarella, A. Quattrone, M. Mancini, M. Cretella, F. Pucci, A. Labate, A. Gambardella

Institute of Neurology - Magna Graecia University – Catanzaro

Background. Voluntary hyperventilation (VH) is believed to be highly successful to elicit typical absences (TAs), especially in patients with genetic generalized epilepsies (GGE) and absences, including childhood and juvenile absence epilepsy (CAE and JAE) respectively.1 Failure in recording TAs may lead to diagnostic uncertainties and therapeutic difficulties in clinical practice.2- Thus, the aim of this study was to evaluate the diagnostic yield of 24-hour ambulatory EEG monitoring (EEG/DIN) compared with VH, in patients with suspected or definite TAs/GGE. We also evaluated if any clinical factors might influence VH efficacy.
Materials and Methods. The study group included 108 consecutive individuals (53 women, mean age 12.6Â±5.4 years) clinically suspected of having TAs, who were enrolled between January 2011 and December 2018. All underwent EEG recording with VH for 4-5 min of maximal effort from the subject, with monitoring of respiratory excursions and encouragement by the EEG technologist. If standard EEG was uninformative, they were investigated with EEG/DIN. Results. Three distinct groups were defined on the basis of HV and EEG/DIN findings: -i, In 61/108 (56%) subjects (41/61 with CAE, 20/61 with JAE, 43/61 on antiepileptic drugs [AEDs]), HV triggered TAs. -ii. In 36/108 (34%) individuals (17/36 with CAE, 19/36 with JAE; and 26/36 on AEDs), HV was unsuccessful, but EEG/DIN showed TAs or electrophysiological hallmarks of them. -iii. The remaining 11/108 patients had normal EEG with HV and EEG/DIN, and the diagnosis of TAs/GGE was ruled out in 9/11 of them. AED was discontinued in 2/4 individuals on therapy at the time of the study.
Discussion and conclusions. The results of this study have illustrated a higher diagnostic yield of EEG/DIN than HV in individuals with TAs/GGE. Moreover, HV was less effective in JAE, regardless of AED therapy. Overall, these findings give evidence that EEG/DIN greatly help establish the diagnosis and monitor TAs, especially in JAE.

References: Wirrell FC, et al. Will a critical level of hyperventilation-induced hypocapnia always induce an absence seizure? Epilepsia 1996; 37:459-62.
Seneviratne et al. The electroencephalogram of idiopathic generalized epilepsy. Epilepsia 2012; 53:234-48

ANTI-RI-ASSOCIATED PARANEOPLASTIC OPHTALMOPLEGIA-ATAXIA SYNDROME IN A WOMAN WITH BREAST CANCER

Manuela Mancini[1], A. Quattrone[1], M. Casaletto[2], A. Pascarella[1], A. Giugno[1], A. Labate[2], A. Gambardella[2]

[1] Institute of Neurology - "Magna Graecia" University – Catanzaro
[2] Institute of Molecular Bioimaging and Physiology – University National Research Council – Catanzaro

Introduction: Paraneoplastic neurological syndromes (PNS) are rare disorders associated with cancer, not caused by direct invasion, metastasis or consequences of treatment. PNS have been associated with antibodies to intracellular onconeuronal proteins, and must not be overlooked because of potential therapeutic relevance. We report a 72-year-old woman with subacute ophthalmoplegia-ataxia syndrome subsequently diagnosed with breast cancer and anti-Ri antibodies.
Case description: The patient is a 72-year-old right-handed woman with three-month onset of blurred vision, diplopia and progressive gait disturbance. Neurological examination showed severe gait and truncal ataxia preventing walking, with limbs relatively spared; pupillary responses were normal, there was an asymmetric bilateral horizontal gaze paresis, left worse than right, and horizontal nystagmus. The neurological examination was otherwise normal. Extensive laboratory investigation including brain MRI was unremarkable. Cerebrospinal fluid examination showed mild lymphocytic pleocytosis (30 cells/mm3) and oligoclonal bands. Afterwards, the patient performed onconeural antibodies, Ri was positive, and whole-body CT scan revealed a nodular opacity under the left nipple and axillary adenopathy. The echo-guided biopsy of the axillary node confirmed lymph node metastasis and she underwent a breast-conserving surgery, lumpectomy with left axillary node dissection.
Discussion and Conclusion: The present case further illustrates that recognition of PNS is important, since neurological symptoms almost invariably predate direct symptoms of the primary tumor, and treatment at early stages may provide better chance of good outcome. The presence of anti-Ri antibody typically identifies women with opsoclonus/myoclonus and ataxia who usually suffer from breast cancer. We have now illustrated the occurrence of anti-Ri even in the absence of opsoclonus, thus enlarging its clinical spectrum. In this way, our findings further reinforce the belief that opsoclonus/myoclonus cannot be considered syndromic of anti-Ri-antibody-associated paraneoplastic syndrome.

References: Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Eng J Med. 2003; 349:1543-54
Voltz R. Paraneoplastic neurological syndrome: an update on diagnosis, pathogenesis and therapy. Lancet Neurology 2002; 1:294-305
Pittock SJ et al. Anti-neuronal nuclear autoantibody type 2: paraneoplastic accompaniments. Ann Neurol. 2003; 53:580-7

INCIDENCE OF EARLY POST-STROKE SEIZURES DURING REPERFUSION THERAPIES IN PATIENTS WITH ACUTE ISCHEMIC STROKE: AN OBSERVATIONAL, PROSPECTIVE STUDY

Giovanni Mastroianni[1], V. Belcastro[2], E. Ferlazzo[3], S. Gasparini[3], G. Ferrigno[3], S. Lattanzi[4], P. Banfi[5], M. Versino[5], F. Carimati[5], S. Vidale[2], G. Grampa[2], F. Brigo[6], G. Gigli[7], F. Bax[7], G. Merlino[7], M. Valente[7], U. Aguglia[3]

1 Institute of Neurology - "Magna Graecia" University – Catanzaro
2 Neurology Unit - S. Anna Hospital – Como
3 Department of Medical and Surgical Sciences – "Magna Graecia" University – Catanzaro
4 Department of Experimental and Clinical Medicine - Marche Polytechnic University – Ancona
5 UOC Neurology and Stroke Unit - Insubria University – Varese
6 Department of Neuroscience - University of Verona – Verona
7 Clinical Neurology Unit - University of Udine – Udine

Abstract: Stroke is the main cause of epilepsy in the adult and elderly population. The intravenous administration of recombinant tissue plasminogen activator (rtPA; intravenous alteplase) or mechanical thrombectomy represent established and highly effective treatments of acute ischemic stroke. In the literature data on the risk of early post-stroke seizures (EPSS) in patients undergoing treatment with rtPA or thrombectomy are scarce and conflicting. Aim of this real-world clinical practice study was to prospectively investigate the incidence and the predictors of EPSS (within 7 days of stroke) in patients with ischemic stroke undergoing or not intravenous rtPA and/or mechanical thrombectomy.
Methods: during a 12-months period, a total of 516 patients (262 who underwent reperfusion therapies and 253 untreated patients) were consecutively enrolled in 5 Italian Stroke Units (Como, Varese, Ancona, Reggio Calabria, Udine). Clinical data and stroke etiologies were analyzed. Age, sex, NIHSS before treatment and 1 week after the acute event, vascular risk factors (hypertension, smoke, atrial fibrillation, diabetes and hypercholesterolemia) and early hemorrhagic transformation were considered as possible predictors.
Results: EPSS occurred in 16 patients (total incidence=3,1%), without significant differences between treated and untreated patients (3,8% vs. 2,3%, p=0,45). None of the examined demographic, clinical and neuroimaging variables was significantly different between patients who experienced EPSS and those without seizures. Logistic regression did not identify any predictor of EPSS.
Conclusions: EPSS were rare in both treated (rtPA and/or thrombectomy) and untreated patients. The occurrence of EPSS was not predicted by any of the examined variables.

SUBACUTE CENTRAL-VARIANT POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME: A CASE REPORT

Angelo Pascarella, A. Giugno, M. Mancini, A. Quattrone, A. Gambardlla, A. Labate

Institute of Neurology - University Magna Graecia - Catanzaro

Abstract: Central-variant posterior reversible encephalopathy syndrome (PRES) is a very uncommon entity [1]. Rapid diagnosis is important because prompt treatment can induce complete clinical and radiological resolution [1,2].
Background: PRES is a clinicoradiological syndrome characterized by acute onset of neurological symptoms associated to typical MRI findings of white matter vasogenic edema. PRES recognizes a variety of etiologies and it is usually reversible with a favorable prognosis after removing underlying predisposing factor [1,2]. Atypical distribution with exclusive involvement of brainstem, basal ganglia or periventricular white matter with sparing of the parietooccipital regions, termed as "central-variant", has been rarely reported [1-3].
Aims: here we describe a case of central variant PRES due to severe hypertension.
Materials and Methods: Subject: a 66-year-old man with no significant past medical history presented with a 2 months history of progressive visual deterioration with "blurred vision" and dizziness. Neurological examination was unremarkable. Physical examination revealed a high blood pressure (220/160 mmHg).
Methods: complete laboratory tests (including autoimmune and infectious markers), fundoscopy, standard electroencephalogram (EEG), visual evoked potential (VEP) and brainstem auditory evoked potential examination (BAEP) and brain MRI were performed.
Results: all laboratory tests were unremarkable except for a slightly high serum creatinine (1.42 mg/dl) and proteinuria (30 mg/dl). Fundoscopy revealed slightly monolateral right papilledema and bilateral cotton-wool spots. EEG, VEP and BAEP were normal. Brain MRI showed diffuse areas of not enhancing hyperintensity on T2-weighted fluid attenuation inversion recovery (FLAIR) images over bilateral semi-oval centre, corona radiate and periventricular white matter area, bilateral thalami, right cerebellar hemisphere and the entire pons, which appeared swollen. All above lesions had isosignal intensity on diffusion-weighted images (DWI). Blood pressure normalized (125/80 mmHg) within 48 hours after treatment. All symptoms disappeared a few days later. Brain MRI six weeks after onset showed complete regression of previous signal alterations.
Discussion and Conclusion: Central-variant PRES represent a very uncommon condition [1-3]. The exact pathophysiological mechanism of PRES and the cause of atypical distribution in central variant PRES remains still unknow [2,3]. However severe acute hypertension seems to be the most frequent precipitating factor for central-variant PRES [2,3]. Although, the very mild clinical features despite a wide extension and severity of MRI abnormalities, represents a typical feature of brainstem PRES [3], a prompt antihypertensive treatment is fundamental

to prompt solve the clinical features [1-3]. Imaging together with clinical features are mandatory to distinguish PRES from other possible entities avoiding unnecessary invasive exams and give an appropriate management.

References: 1. McKinney AM, Jagadeesan BD, Truwit CL. Central-variant posterior reversible encephalopathy syndrome: brainstem or basal ganglia involvement lacking cortical or subcortical cerebral edema. AJR Am J Roentgenol. 2013; 201:631-8.
2. Ou S, Xia L, Wang L, Xia L, Zhou Q, Pan S. Posterior Reversible Encephalopathy Syndrome With Isolated Involving Infratentorial Structures. Front Neurol. 2018; 9:843
3. Ferrara M, Di Viesti P, Inchingolo V, Latino RR, Popolizio T, De Cosmo SA, Pugliese F, Leone MA. Isolated pons involvement in Posterior Reversible Encephalopathy Syndrome: Case report and review of the literature. eNeurologicalSci. 2016; 6:51-54.

PREVALENCE OF HIPPOCAMPAL MALROTATION IN PATIENTS WITH TEMPORAL LOBE EPILEPSY: AN UPDATE

Ilaria Sammarra, A. Giugno, F. Fortunato, A. Pascarella, A. Quattrone, A. Gambardella, A. Labate

Institute of Neurology - Magna Graecia University – Catanzaro

Abstract: Backgrounds: Hyppocampal malrotation (HIMAL), consequence of incomplete folding of medial temporal structures during embryonic brain development, could be a neuroradiological marker of predisposition for epileptogenesis in mesial temporal lobe epilepsy (MTLE)1.
Aims: To evaluate the prevalence of HIMAL in healthy controls (HC) and to compare it with the prevalence in patients with MTLE.
Material And Methods: Two-hundred and three patients with MTLE and one-hundred and twenty-two age- and sex-matched HC underwent a 3 Tesla MRI protocol including whole-brain, 3D T1-weighted, spoiled gradient recall echo (TE/TR = 3.7/ 9.2 ms, flip angle 12°, voxel size= 1Ã—1Ã—1 mm3). Images were visually inspected by two expert raters, instructed to assess the presence of eight criteria for HIMAL identification2: (1) medial positioning with respect to temporal horn; (2) round, globular shape and vertical orientation; (3) empty choroid fissure; (4) misplaced fimbria on the dorsolateral edge of Ammon's horn; collateral sulcus (5) deep and verticalized or (6) protruding into empty choroid fissure; (7) reduction of parahippocampal gyrus upper horizontal portion adjacent to hippocampal fissure; (8) thickened subiculum. Presence of HIMAL was recorded if at least 3 out of 8 criteria were present.
Results: Inter-rater agreement between the two experts was 98%. HIMAL was present in 41 out of 203 MTLE patients (20.1%) and in 11 out of 122 HC (9%). Twenty-nine patients had left HIMAL (14.3%), 5 had right HIMAL (2%) and 7 had bilateral HIMAL (3.5%). Eight HC showed left HIMAL (6.6%), while 3 showed right HIMAL (2.5%). Among MTLE patients, there was discordance between side of HIMAL and side of epileptogenic focus in 26 out of 41 cases.
Discussion And Conclusion: Prevalence of HIMAL is 2.3 times higher in MTLE patients than in HC, suggesting that it might represent a vulnerability factor in patients experiencing epileptic seizures.

References: 1. Yeghiazaryan NS. Temporal lobe epilepsy and hippocampal malrotation: Is there a causal association? Epilepsy & Behavior, 2010; 18:502-504.
2. Bernasconi N, Kinay D, Andermann F, Antel S, Bernasconi A. Analysis of shape and positioning of the hippocampal formation: an MRI study in patients with partial epilepsy and healthy controls. Brain, 2005; 128:2442-2452.

GIANT PONTINE TELANGIECTASIA PRESENTING AS HEADACHE

Domenico Santangelo, G. Demonte, T. Garcea, A. Gambardella, F. Bono

"Mater Domini" Institute of Neurology - Magna Graecia University – Catanzaro

Abstract: Although it is well understood that structures of the brainstem are involved in the mechanisms of the headache attack, there is still no clear evidence that venous malformations such as telangiectasia are the cause of headache attack. Background: Vascular malformations of the parenchyma are frequently classified as arteriovenous malformations, venous malformations, cavernous angiomas, or capillary telangiectasia.
Aims: We here report the case of a woman with headache associated with a giant telangiectasia of the pons.
Materials and Methods: A 45-year-old woman complained of the recent onset of vertigo and tinnitus associated with severe headache attacks. The head pain was localized in the occipital, parietal and temporal regions. The headache occurred 3-4 times a month, lasted 24-48 hours, and it did not respond to the common analgesic drugs. Neurological examination during the interictal phase showed nystagmus in the gaze of extreme left laterality. Results: A brain MR showed the presence of areas of small patchy hyperintensity in the right paramedian anterior pontine region; these MR findings indicated the presence of a giant capillary telangiectasia of the pons. The brain PET-MRI did not show alteration of the metabolism of the brainstem. The blink reflex recovery cycle showed a persistent facilitation of the trigeminal nociception on the right.
Discussion and Conclusion: The blink reflex recovery cycle shows a trigeminal nociceptive facilitation on the right, suggesting a functional disfunction of the brainstem in this case. Moreover, the brain MR indicates the presence of the pontine malformation near regions involved in the modulation of the nociception, such as the locus coeruleus and the raphe nuclei. Taken together these data suggest that the clinical manifestations, such as headache attacks associated with vertigo and tinnitus, may be due to the presence of the giant telangiectasia of the pons in this patient.

References: Knight YE1, Goadsby PJ. The periaqueductal grey matter modulates trigeminovascular input: a role in migraine? Neuroscience. 2001;106(4):793-800.
Zaza Katsarava, Thomas Egelhof, Holger Kaube, Hans- Christoph Diener, Volker Limmoroth. Symtomatic migraine and sensitization of trigeminal nociception associated with contralateral pontine cavernoma. Pain,2003; 381-384
Goadsby PJ. Neurovascular headache and a midbrain vascular malformation: evidence for a role of the brainstem in chronic migraine. Cephalalgia. 2002 Mar;22(2):107-11.

CLINICAL FEATURES IN A COHORT OF ITALIAN MUSK-MG PATIENTS IN A LONG TERM FOLLOW-UP

Carmen Bonanno, S. Messina, G. Nicocia, A. Lupica, A. Toscano, C. Rodolico

Department of Clinical and Experimental Medicine - University of Messina – Messina

Background: Muscle specific kinase Myasthenia Gravis (MuSK-MG) is a distinctive, frequently more severe, subtype of MG. The prevalence varies among countries and ethnic groups, 30% to 70% in European anti-AChR antibody negative patients and between 2.5% and 3% in Asian countries. MuSK-MG usually demonstrates an acute bulbar onset with rapid progression within a few weeks.
Aims: We report clinical features, treatment outcomes and follow-up data of 31 Italian MuSK-MG patients. Patients and methods: We retrospectively evaluated 31 patients (17 F, 14 M) diagnosed with MuSK-MG who attended our outpatient Department between January 1995 and January 2019. Ages at presentation ranged from 10 to 70 years old. Serological diagnosis was performed showing Anti MuSK antibodies positivity in 31/31 patients. According to Osserman criteria, the majority of patients at onset showed a type-2 MG (23/31), 4 patients type-1 MG, 3 patients type-3 and only one patient type-5. Results: Follow up time in our cohort ranged from six months to 23 years. Six patients experimented respiratory insufficiency. Five underwent thymectomy and none of them benefited from surgery. To every patient was administered prednisolone with a partial initial response. 19/31 were also treated with azathioprine, 3 of whom in association with a second immunosuppressant. Rituximab was given to 3 patients with severe phenotypes and 1 out of 3 showed a complete stable remission at six months follow up.
Discussion and conclusions: In our centre, patients with MuSK-MG are 4.1 % of the whole MG population with a female/male ratio of approximately 1:1. Among them, 12.9 % of pure ocular form was found, which is confirmed as severe and resistant to treatment. The posterior neck weakness was present at the onset in 19.3%. A long-term follow-up of our MUSK-MG patients allowed to asses: 1) variability of clinical presentations, 2) rituximab effectiveness, 3) identification of osteoporosis as the main long-term complication of steroids often causing pathological fractures

References: Morren J, Li Y. Myasthenia gravis with muscle-specific tyrosine kinase antibodies: A narrative review. Muscle Nerve. 2018 Sep;58(3):344-358
Guptill JT, Sanders DB, Evoli A. Anti-MuSK antibody myasthenia gravis: clinical findings and response to treatment in two large cohorts. Muscle Nerve. 2011 Jul;44(1):36-40.

HOMOZYGOSITY FOR THE GLU89GLN MUTATION IN TTR GENE: FIRST REPORT OF AN ITALIAN FAMILY

Francescopaolo Cucinotta[1], L. Gentile[1], G. Fabrizi[2], F. Taioli[2], C. Stancanelli[1], M. Aguennouz[1], M. Russo[3], G. Vita[1], A. Toscano[1], A. Mazzeo[1]

1 Unit of Neurology and Neuromuscular Diseases, Department of clinical and Experimental Medicine - University of Messina – Messina
2 Department of Neurosciences, Biomedicine and Movement Sciences - University of Verona – Verona
3 Clinical Centre for Neuromuscular Diseases - Nemo Sud – Messina

Abstract We describe a case of cardiac and autonomic involvement in ATTR, associated with Glu89Gln transthyretin mutation, with an early onset and a rapid course of disease. Background Hereditary ATTR have been related to different point mutations in the 127-amino acid TTR. Despite inheritance is autosomal dominant, homozygosity has been also reported.
Aims To our knowledge this is the first case of ATTR homozygous for the amyloidogenic Glu89Gln gene. Materials and methods A 39-year-old man with previous bilateral carpal tunnel syndrome at the age of 32, had a 2-year history of dyspnea and left ventricular wall thickening. Family history was positive for heart failure: the mother and 2 of her brothers. They died at 53 to 63 years of age, and onset of symptoms had been at 45 to 56 years of age. His two sons, 13- and 19-years-old, are referred asymptomatic to date. An electrocardiogram revealed sinus-rhythm and low-voltage of the QRS complexes. A transthoracic echocardiogram showed concentric hypertrophy of both ventricles. Then he received the diagnosis of hypertrophic cardiomyopathy. Two years later, he was inserted in transplant list and at the age of 40 he underwent cardiac transplantation. During the following years he complained of sexual disturbances and manifested others features of progressive and severe autonomic involvement with orthostatic hypotension and constipation alternating with diarrhea. At the age of 47 he referred mild ataxic gait. For this reason at the age of 49 he was referred to our clinic.
Results Neurological examination showed mild ataxic gait, and positive Romberg sign. Reflexes were reduced. He showed mild weakness in ankle dorsiflexion (MRC 4) and reduced pinprick and vibration sensation distally in lower limbs. He died at the age of 49 for sudden cardiac death. Genetic test for TTR-FAP was performed, and the homozygous for Glu89G was detected (C265G).
Discussion In our single-center experience in Sicily, Glu89Gln mutation is characterised by 5th - 6th decade onset, neuropathy as presenting symptom with heart dysfunction. In our case homozygosity for the Glu89Gln mutation is associated with an earlier onset at the age of 32 with bilateral carpal tunnel syndrome, and a rapid course of disease which led to the patient's death at the age of 49 despite heart transplantation. TTR gene analysis should be considered in young patients with heart disease especially in presence of family history of cardiopathy of unknown cause or in young patients with heart disease and autonomic disfunction.

References: Ikeda S, Nakano T, Yanagisawa N, Nakazato M, Tsukagoshi H. Asymptomatic homozygous gene carrier in a family with type I familial amyloid polyneuropathy. Eur Neurol. 1992;32(6):308-13.
Anna Mazzeo, Massimo Russo, Gianluca Di Bella et al. Transthyretin-Related Familial Amyloid Polyneuropathy (TTR-FAP): A Single-Center Experience in Sicily, an Italian Endemic Area. Journal of Neuromuscular Diseases 2 (2015) S39-S48
Iglika Yordanova, Zornitza Pavlova, Andrey Kirov et al. Monoallelic expression of theTTRgene as a contributor to the age at onsetand penetrance of TTR-related amyloidosis. Gene 705 (2019) 16-21

MANDRAGORA INTOXICATION MIMICKING ACUTE STROKE: A CASE REPORT

Ludovica Ferraù, F. Grillo, C. Dell'Area, R. Musolino, A. Toscano

Department of Medical and Experimental Medicine - University of Messina – Messina

Abstract: We report the case of a 82 years old female presented to Emergency Department with sudden onset of stupor, aphasia and facial palsy about one hour after dinner. In the suspicion of stroke the patient was centralized to our Stroke Unit. After clinico-radiological work-up acute stroke has been ruled out. Three family members who had dinner with the patient suffered confusional state and was hospitalized for acute mandragora intoxication.
Background: Mandragora spp. are a group of solanaceas plants found in Mediterranean regions[1]. An inappropriate use can cause serious toxic effects due to their atropine-like activity[2].
Aims: To emphasize that alteration of mental status and anticholinergic symptoms[3] can be observed in this kind of poisoning and confused with acute stroke leading to misdiagnosis.Materials and Methods: The patient, whit history of hypertension and diabetes, arrived to the provincial hospital with palpitations, xerostomia, right hemiparesis, aphasia, dizziness and delirium. On admission the blood pressure was 160/70 mmHg, oxygen saturation was 92% in room air, electrocardiogram showed sinus tachycardia at 115 pulse/min, blood test was unremarcable. In the suspicion of stroke, the patient was transferred to the Stroke Unit of Messina University and the neurologist noted delirium whit speech disturbance, xerostomia, bilateral mydriasis, moderate right hemiparesis with a National Institute of Health Stroke Scale (NIHSS) score of 10. Brain Computer Tomography (bCT), brain Magnetic Resonance Imaging and Carotid Ultrasound ruled out acute stroke. The patient underwent to complete blood tests panel and cardiological evaluation.
Results: No lesions suggestive of stroke were found at a bCT after 3 days. She presented progressive recovery in a few days without neurological sequelae after medical therapy and adequate hydration. After two days the son's patient informed us that other 3 relatives were hospitalized for confusional state to another hospital. All the patients had dinner together eating the same plant from the countryside. Analyses of the plant confirmed diagnosis of acute mandragora intoxication.
Discussions and Conclusion: Aphasia and hemiparesis are benchmarks of stroke. Nevertheless aphasia can be difficult do diagnose in the case of acute confusional state. However the presence at the same time of mydriasis, xerostomia and tachycardia could suppose a different diagnosis. We can't explain hemiparesis. In our knowledge mandragora intoxication had never been reported as stroke mimic and are often unrecognized and misdiagnosed. It is important to ensure that physicians are aware of the possible effects of this herb to reach the correct and prompt diagnosis, avoiding unnecessary diagnostic and therapeutic procedure.

References: 1. Saxe TG: Toxicity of medicinal herbal preparations. Am Fam Physician 1987, 35:135-142
2. Hanus LO, Rezanka T, SpÃ-zek J, Dembitsky VM: Substances isolated from Mandragora species. Phytochemistry 2005 66:2408-241
3. Piccillo GA, Mondati E, Moro PA: Six clinical cases of mandrag- ora poisoning: diagnosis and treatment. Eur J Emerg Med 2002

RECURRENT VERTEBRO-BASILAR STROKES: A SUGGESTIVE CASE OF PRIMARY ANGIITIS OF THE CENTRAL NERVOUS SYSTEM

Giulia Fiume, F. Giammello, F. Grillo, A. Toscano, R. Musolino

Department of Clinical and Experimental Medicine - University of Messina – Messina

Abstract: We report the case of P.G., a 59-year-old man with a history of recurrent vertebro-basilar infarctions. First diagnosis deposed to cryptogenetic, but in according to symptoms evolution and to the imaging and laboratory findings, we considered diagnosis of Primary Angiitis of the Central Nervous System (PACNS).

Background: PACNS is an inflammatory disease affecting the vessels of the Central Nervous System (CNS) in the absence of evidence of systemic vasculitis [1]. It causes approximately 3-5% of strokes in subjects under 50 years-old with a slight prevalence in men. The etiology is unknown.

Aims: To describe a diagnostic pathway of an unusual case of recurrent vertebro-basilar infarctions in the context of rare causes of stroke.

Materials and Methods: The patient was hospitalized in March, June and August of 2018, for recurrent strokes. After excluding common causes of stroke, we considered some rare ones and we applied the diagnostic protocol proposed by Beuker et al. [2] which includes the analysis of clinical features, laboratory tests, cerebrospinal fluid (CSF), magnetic resonance tomography (MRI), digital subtraction angiography
(DSA) and biopsy in the suspicion of PACNS.

Results: Clinical picture at admissions included: recurrent nuchal headache, asthenia and visual disturbance in the right eye. Neurological examination showed: dysarthria, right homonymous lateral hemianopia and a Mini-Mental State Examination (MMSE) of 19.74 (normal >23). Laboratory routine tests, acute phase reactants, rheumatoid factor, antinuclear antibodies, anti-neutrophil cytoplasmic antibodies, antiphospholipid antibodies, and viral antibodies for CMV, EBV and Herpes Simplex 1-2 were normal. CFS showed 1 cell/ml (range 0-5); total protein concentration 84 mg/dL (range 20-50) and presence of oligoclonal bands. During each hospitalization MRI showed new multifocal bilateral ischemic lesions at T2 and FLAIR sequences in the cortical and subcortical structure in the occipital lobe, hippocampus and cerebella in both hemispheres and a left thalamic lesion. After somministration of gadolinium, multiple lesions showed pathologic impregnation not objectivable to subsequent checks. DSA got refused. At discharge the patient started a corticosteroid therapy with prednisone at a dose of 1mg/Kg, as maintenance therapy reported in licterature [3].

Discussion and Conclusions: Although DSA and biopsy have not been performed, we have satisfied 4 to 6 criteria of Beuker et al. for PACNS diagnosis. Moreover, at present, after 9 months of corticosteroid therapy the patient haven't had other relapses from August 2018 up to now.

References: Hajj-Ali RA. Primary angiitis of the central nervous system: differential diagnosis and treatment. Best Pract Res Clin Rheumatol. 2010 Jun;24(3):413-26.
Beuker C, Schmidt A, Strunk D, et al. Primary angiitis of the central nervous system: diagnosis and treatment. Ther Adv Neurol Disord. 2018; 11:1756286418785071.
Boysson H, Zuber M, Naggara O, et al. Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the french cohort of patients with primary vasculitis of the central nervous system. Arthritis Rheum 2014; 66: 1315-1326.

CLINICAL FEATURES OF AN ITALIAN COHORT OF PATIENTS WITH VERY LATE-ONSET MYASTHENIA GRAVIS

Giulia Nicocia, A. Lupica, S. Messina, C. Bonanno, T. Brizzi, S. Sinicropi, G. Vita, A. Toscano, C. Rodolico

Department of Clinical and Experimental Medicine - University of Messina – Messina

Background: Myasthenia gravis is an autoimmune disorder of neuromuscular junction characterized by fluctuating muscle weakness and faticability [1]. In the last few years an unexpected increased incidence of elderly-age MG was found, in part due to improved diagnostic methods and an aging population [2]. Very late onset MG can be underdiagnosed because some disturbances can be ascribed to more common chronic diseases [3]. Some researches indicated that age was an independent risk factor for the mortality in MG patients.
Aims: We evaluated the incidence and the features of MG, presenting after the age of 75 years, among our MG population.
Patients and Methods. We identified 36 patients (17 females, 19 males) with a MG onset >75 years (age-range 75-89). All the patients were evaluated at onset with clinical examination, QMG score, SFEMG, RNS, thorax CT, routine blood examinations, anti-AChR and Anti MUSK assays.
Results: Among those 36 patients, 17 were females and 19 were males. According to Osserman criteria, the majority of patients at onset showed a type-2 MG (23/35), 7 patients type-1 MG, 2 patients type-3 and only one patient type-4, therefore with a prevalence of generalized MG. Anti-AChR antibody titers were elevated in 32 patients; 4 patients were negative for anti AChR and anti-MuSK antibodies. Thymoma was found in 3 patients. The average time before the diagnosis was 11 months. The most common regimen of therapy was prednisone at low doses (less than 12,5mg/day); Azathyoprine (50 to 100mg) was used as steroid sparing agent.
Discussion: In our population of very late onset MG patients (>75 years), we found a high prevalence of male gender, type-2 MG at onset and Ab AchR serum positivity. Few patients had thymoma or thymic hyperplasia. No patients had elevated titers of anti-Musk antibodies. The most common therapy used in this population was corticosteroids at low doses.
Conclusion: In conclusion, our findings show that the diagnosis and therapy of MG in the elderly can be difficult. The very late MG can be undiagnosed and the comorbidities associated (hypertension, diabetes, glaucoma, osteoporosis) in these patients may need a different therapeutic approach.

References: 1. Conti-Fine BM, Milani M, Kaminski HJ. Myasthenia gravis: past, present, and future. J Clin Invest. 2006 Nov;116(11):2843-54.
2. Somnier FE. Increasing incidence of late-onset anti-AChR antibody-seropositive myasthenia gravis. Neurology. 2005 Sep 27;65(6):928-30.
3. Vincent A, Clover L, Buckley C, Grimley Evans J, Rothwell PM; UK Myasthenia Gravis Survey. Evidence of underdiagnosis of myasthenia gravis in older people. J Neurol Neurosurg Psychiatry. 2003 Aug;74(8):1105-8

MITOCHONDRIAL ENCEPHALOMYOPATHIES: A SINGLE CENTRE EXPERIENCE

Alessia Pugliese, A. Toscano, O. Musumeci

Department of Clinical and Experimental Medicine - University of Messina – Messina

Background Mitochondrial diseases (MDs) are a heterogeneous group of disorders, caused by nuclear or mitochondrial DNA (nDNA or mtDNA) genes mutation. Clinical phenotypes range from less severe single-organ involvement to multisystemic syndromes, known as mitochondrial encephalomyopathies because of prominent brain and skeletal muscle involvement. MELAS and MERRF are the most common mitochondrial syndromes due to mtDNA mutations. MELAS is a mitochondrial encephalomyopathy characterized by lactic acidosis, stroke-like episodes, migraine, deafness, diabetes and muscle weakness [1]. MERRF is the acronym of myoclonic epilepsy with ragged-red fibers, characterized by myoclonus and generalized epilepsy, ataxia and ragged red fibers at muscle biopsy [2]. A rarer category of MDs is mtDNA multiple deletions syndromes, related to nDNA genes as C10orf2, also called Twinkle, or POLG1. Twinkle mutations are usually responsible of Chronic Progressive External Ophthalmoplegia (CPEO) or mitochondrial myopathy [1]. POLG1 mutations are associated with variable phenotypes, ranging from adult-onset CPEO to encephaloneuromyopathies [1]. An emerging MD is the form associated with dominant missense mutations in OPA1 gene, linked to autosomal dominant optic atrophy but also to PEO, peripheral neuropathy, ataxia and deafness [3].
Aims To report clinical, biochemical and histopathological features of a cohort of mitochondrial encephalomyophaties patients, evaluated in our Neuromuscular Centre. Patients and methods In the last 30 years about 167 MDs patients have been diagnosed in our Centre (89 male patients, 78 female patients; with an age from 1 st to 9th decade). All patients have undergone clinical examination, laboratory assessment including routinary laboratory exams, serum lactic acid dosage before and after muscular effort, muscle biopsy with mitochondrial respiratory chain enzymes evaluations and genetic study. Results In our cohort most patients have a cPEO phenotype (79%), associated with single or multiple mtDNA deletions (MDel). Among patients with MDel, 4 are affected by Twinkle mutation, 9 by POLG1 and 9 by OPA1 mutation. We also count 2 patients affected by MERRF and 11 by MELAS. MERRFs present a particular phenotype, featured by multiple lipomatosis in association with muscle involvement. In MERRFs and MELASs muscle biopsies, ragged red fibers are observed with cytochrome c oxidase reduction. At genetic analysis, MERRFs have A8344G mutation and MELASs A3243G mutation.
Conclusion Our cohort reflects the heterogeneity of MDs, both phenotypically and genetically. New therapeutic perspectives are been considered and some trials are in progress. Consequently, a correct diagnostic approach has to be followed in order to recognize early patients and to ensure them an efficient and timely treatment.

References: Filosto M. et Mancuso M., Mitochondrial diseases: a nosological update. Acta Neurol Scand 2007; 115: 211-221
Musumeci O. et al., Lipomatosis Incidence and Characteristics in an Italian Cohort of Mitochondrial Patients. Front Neurol. 2019 Feb 27;10:160
Carelli V. et al., Syndromic Parkinsonism and dementia associated with OPA1 missense mutations. Ann Neurol. 2015 Jul;78(1):21-38

HOMEOSTATIC-LIKE PLASTICITY IS IMPAIRED IN MULTIPLE SCLEROSIS

Vanessa Ziccone[1], C. Terranova[1], M. Buccafusca[1], A. Quartarone[2], P. Girlanda[1], V. Rizzo[1]

[1] Department of Clinical and Experimental Medicine - University of Messina – Messina
[2] IRCCS Centro Neurolesi, Department of Biomedical, Dental Sciences, and Morphological and Functional Images - Messina, University of Messina – Messina

Background: Acute and chronic brain damage disrupts brain connectivity producing neurological signs and/or symptoms. In several neurological diseases, particularly in Multiple Sclerosis (MS), structural imaging studies cannot always demonstrate a clear association between lesion site and clinical disability, originating the "clinico-radiological paradox." The discrepancy between structural damage and disability can be explained by a complex network perspective. Both brain networks architecture and synaptic plasticity may play important roles in modulating brain networks efficiency after brain damage.
Aims: In this study, we evaluate homeostatic plasticity mechanism in naïve patients with Multiple Sclerosis (MS)
Patients and Methods: We enrolled 10 naïve MS patients. We explored the effect of transcranial direct current stimulation (TDCS) priming on the conditioning effect of 1 Hz repetitive transcranial magnetic stimulation (rTMS) on motor cortex excitability. All participants received 15 min of subthreshold 1 Hz rTMS to the left primary motor cortex (M1), this was preceded either by a 10 min period of effective TDCS to the left motor cortex using anodal (excitatory) or cathodal (inhibitory) polarity.
Results: Our data showed that homeostatic plasticity mechanism are impaired. Discussion: Homeostatic mechanisms that stabilize excitability levels within a useful dynamic range are impaired in naïve patients with MS.
Conclusions: Modulation of plasticity with different non-invasive brain stimulation (NIBS) techniques has been used to promote recovery of MS symptoms. Better knowledge of features inducing brain disconnection in MS is crucial to design specific strategies to promote recovery and use NIBS with an increasingly tailored approach.

References: M. Stampanoni Bassi, F. Mori, F. Buttari, G.A. Marfia, A. Sancesario, D. Centonze, E. Iezzi.Neurophysiology of synaptic functioning in multiple sclerosis. Clinical Neurophysiology 128 (2017) 1148-1157. H.R. Siebner, N. Lang, V. Rizzo, M. A. Nitsche, W. Paulus, R. N. Lemon, and J. C. Rothwell. Preconditioning of Low-Frequency Repetitive Transcranial Magnetic Stimulation with Transcranial Direct Current Stimulation: Evidence for Homeostatic Plasticity in the Human Motor Cortex. The Journal of Neuroscience, March 31, 2004 â€¢ 24(13):3379-3385 Duffau H. Brain plasticity: from pathophysiological mechanisms to therapeutic applications. J Clin Neurosci. 2006 Nov; 13(9):885-97

LIMPHOCYTE SUBPOPULATION CHANGES IN CHIMERIC AND HUMANIZED B-CELL-DEPLETING ANTIBODIES FOR MULTIPLE SCLEROSIS

Nicola Capasso, N. Capasso, A. Nozzolillo, R. Lanzillo, A. Carotenuto, M. De Angelis, M. Petruzzo, F. Saccà, C. Russo, V. Brescia Morra, M. Moccia

Department of Neuroscience - Federico II – Naples

Background: CD20 B-cells are implicated in the pathogenesis of multiple sclerosis (MS). Chimeric (Rituximab) and humanized (Ocrelizumab) anti-CD20 monoclonal antibodies represent an important treatment option for patients with MS, depleting B-lymphocytes from the pre-B stage to the mature B stage. Anti-CD20 antibodies also affect T-lymphocytes either directly, on a subset of CD20 T-lymphocytes, or indirectly, as a consequence of changes in B-cell activity. Differences in the profile of action have been shown between chimeric and humanized antibodies in other fields of medicine. We aim to evaluate differences in lymphocyte subpopulations between Rituximab and Ocrelizumab-treated MS patients.
Methods: we included 88 patients with MS, treated with Rituximab (n=50) or Ocrelizumab (n=38). We used flow cytometry in the peripheral blood to count total lymphocytes and lymphocytes expressing different phenotypic markers (CD4, CD8, CD19, CD20, CD4/CD8 ratio), before treatment and after 1, 3 and 6 months. Differences between Rituximab and Ocrelizumab were evaluated with linear regression models including different follow-up laboratory measures and adjusting by baseline
laboratory measures, age, sex, disease duration, baseline EDSS, disease subtypes and comorbidities.
Results: patients treated with Ocrelizumab presented with less CD4 lymphocytes after 1 (Coeff=-249.91; 95%CI=-438.44, -61.38;p=0.01), 3 (Coeff=-212.19; 95%CI=-370.38, -54.00; p<0.01), and 6 months (Coeff=-200.77; 95%CI=-393.57, -7.98; p=0.04) compared with Rituximab. Also patients treated with Ocrelizumab presented with less CD8 lymphocytes after 1 (Coeff=-121.78; 95%CI=-198.38, -45.19; p<0.01), 3 (Coeff=-132.57; 95%CI=-230.72, -34.41; p<0.01) and 6 months (Coeff=-92.83; 95%CI=-177.10, -8.56; p=0.032). No differences were found for total lymphocyte count, CD4/CD8 ratio, CD19 and CD20 at different time points.
Conclusions: after Rituximab and Ocrelizumab administration, B-cell levels in the peripheral blood were equally decreased. On the contrary, CD4 and CD8 lymphocyte reduction was more pronounced in Ocrelizumab, when compared with Rituximab. CD20-depleting antibodies can also affect T cell levels, with greater effect for the humanized antibody.

ELUCIDATION OF A NOVEL TRIGGERING MECHANISM OF MULTIPLE SCLEROSIS MEDIATED BY NON-TYPEABLE HAEMOPHILUS INFLUENZAE

Martina Petruzzo[1], R. Lanzillo[1], C. Criscuolo[1], A. Lamberti[1], M. Cavaliere[2], P. Salvatore[3], R. Colicchio[3], C. Pagliuca[3], E. Scaglione[3], G. Mantova[3], F. Real-Fernandez[4], P. Rovero[4], F. Lolli[5], H. Rusche[6], R. Berisio[7], F. Nuti[4], M. Mancini[7], A. Papini[4], V. Brescia Morra[1]

[1] Multiple Sclerosis Clinical Care and Research Centre, Department of Neuroscience, Reproductive Sciences and Odontostomatology - Federico II University – Naples
[2] Department of Neuroscience, Reproductive and Odontostomatologic Science, Ear, Nose and Throat Section - Federico II University – Naples
[3] Department of Molecular Medicine and Medical Biotechnology - Federico II University – Naples
[4] French-Italian Interdepartmental Laboratory of Peptide and Protein Chemistry and Biology, - University of Florence - Sesto Fiorentino
[5] Department of Biomedical, Experimental and Clinical Sciences - University of Florence – Florence
[6] PeptLab@UCP and Laboratory of Chemical Biology - Université Paris-Seine - Cergy-Pontoise
[7] Institute of Biostructure and Bioimaging - Italian National Research Council – Naples

Introduction and aim of the study The defined cause of MS is still unknown, but it is established that complex interactions between environmental factors and multiple gene products are involved. Emerging hypotheses consider that the progression of MS is linked to exogenous infectious agents expressing antigenic molecules, which mimic the structure and/or conformation of endogenous mammalian surface glycoproteins and/or glycolipids (myelin). We have recently shown that a prokaryotic adhesin carrying an aberrant asparagine-glucosylation (N-Glc), was preferentially recognized by antibodies from MS patients. This is the High Molecular Weight 1 (HMW1) adhesin in non-typeable Haemophilus influenzae (NTHi). In this study we aim to correlate the presence of anti-HMW1A antibodies in the sera of the study population with the possible colonization by H. influenzae evaluated through microbiological analysis conducted on nasopharyngeal swab.
Methods The pilot project has a duration of 1 year, and subgroup of 50 patients will undergo a nose / oropharyngeal swab in order to confirm the presence of H.influenzae infection. SP-ELISA for antibody titer determination Specific anti-HMW1ct(Glc) IgG and IgM antibodies were evaluated in SP-ELISA following a previously validated protocol. In order to identify native candidate antigen(s) of anti-hyperglucosylated Adhesin antibodies, immunoprecipitation experiments utilizing purified serum antibodies and mouse brain homogenate as model are to be carried out. We included 9 MS patients and 9 healthy controls that underwent nose / oropharyngeal swab to study the the presence of H.influenzae and SP-ELISA for titer determination of Specific anti-HMW1ct(Glc) IgG and IgM antibodies. Oropharyngeal and rinopharyngeal swabs were spread on Chocolate agar supplemented with bacitracin, vancomycin and clindamycin to maximise culture of Non Typable Haemophilus influenzae (NTHi). Matrix Assisted Laser Desorption/Ionization (MALDI) mass spectrometer was used to differentiate

H. influenzae from other Hemophilus spp(NTHi). NTHi was confirmed by X- and V-factor dependence and capsule absence by DifcoTM Haemophilus influenzae Antiserum Poly.
Results No differences were found in H influenzae subtypes at nasal and oropharingeal swab, when compared with healthy controls. Ms patients presented with higher Specific anti-HMW1ct(Glc) IgG (p= 0.003), but not IgM, when compared with healthy controls.
Conclusion Our preliminary data suggest that there is a statistically significant difference in HMW1A glc IgG levels between MS patients and healthy controls. We are currently completing enrolment and analysis in order to verify if a previous contact with HMW1A might be a trigger of MS and if its adhesion might persist in nasal mucosa.

References: Walvoort MT, et al. Antibodies from multiple sclerosis patients preferentially recognize hyperglucosylated adhesin of non-typeable Haemophilus influenzae Lolli F, Mazzanti B, Pazzagli M, et al. The glycopeptide CSF114(Glc) detects serum antibodies in multiple sclerosis. J Neuroimmunol. Epub 2005 4. Harris TM, et al. Culture of non-typeable Haemophilus influenzae from the nasopharynx: Not all media are equal. J Microbiol Methods. 2017 Jun; 137:3-5.

DEFAULT MODE NETWORKS ABNORMALITIES PREDICT THE CUTANEOUS ALLODYNIA IN PATIENTS WITH EPISODIC MIGRAINE WITHOUT AURA

Fabrizio Scotto di Clemente

Neurology – University of Campania L. Vanvitelli – Naples

Background: Approximately two-thirds of patients with migraine without aura (MwoA) complain of cephalic or even extracephalic cutaneous allodynia (CA) during migraine attacks. CA is a clinical sign of central nociceptive pathway sensitization and independent predictor for migraine chronification. This article aims to investigate if abnormalities of default mode network (DMN) functional connectivity could predict the development of cutaneous allodynia in patients with MwoA.
Methods: 37 patients with MwoA were recruited between 2009 and 2015 and underwent whole-brain blood oxygen levelâ€“dependent (BOLD) fMRI. All these patients have been followed over a three years period and then divided into 2 groups based on whether or not cutaneous allodynia was developed. Then, we compared functional connectivity within the DMN in 20 patients with MwoA who have developed CA versus 17 patients with MwoA who have not developed CA and 19 sexand age-matched healthy controls (HC). Furthermore, we assessed the correlation between functional connectivity within DMN and all clinical parameters of disease severity.
Results: We observed a significantly lower functional connectivity within posterior cingulate cortex (PPC)/precuneus in patients with MwoA who have developed CA when compared to patients with MwoA who have not developed CA and HC.
Discussion: PCC is known as a key hub of DMN with a prominent antinociceptive functions, deactivated by experimental pain in HC but not in patients with chronic pain condition which show a reduced brain posterior cingulate cortex volume. Interestingly, an increased functional connectivity between the precuneus and the posterior cingulate cortex regions of the DMN has been observed in patients with MwoA.
Conclusions: We suggest that DMN abnormal functional connectivity could represent a prognostic imaging biomarker for the incipient development of CA in patients with episodic MwoA.

ONABOTULINUMTOXINA AFFECTS VISUAL CORTICAL EXCITABILITY IN CHRONIC MIGRAINEURS: PRELIMINARY RESULTS OF A STUDY WITH SOUND INDUCED FLASH ILLUSIONS

Salvatore Ferlisi, S. Di Marco, L. Pilati, A. Torrente, S. Scardina, E. Di Marco, F. Ferraro, G. La Bianca, G. Cosentino, M. Gangitano, F. Brighina

Department of Biomedicine, Neurosciences and Diagnostic (Bi.N.D.) - University of Palermo – Palermo

Background: perception of the surrounding environment results from the interaction of multiple sensory stimuli. The modulation of perception can be explored by sound-induced flash illusions (SIFI): when a single flash is presented with two or more beeps, it is often perceived as multiple flashes (fission illusion); such illusory perception is associated to changes in visual cortical excitability. It is known that migraineurs show an abnormal visual cortical excitability, even interictally, so, here, we aim to evaluate whether there are SIFI changes in chronic patients treated with onabotulinumtoxinA.
Methods: we enrolled 15 chronic migraine patients without aura (mean age 53yo +- 13; 14 females) candidated to onabotulinumtoxinA therapy (195 UI in 39 sites) and 12 control subjects (10 females) in the same age range. We used a software able to show a transient single flash presented together with concurrent beeps. Subjects had to count aloud flashes seen each time (5 tests randomly presented several times: 1FxB, where x goes from 0 to 4; F=flash, B=beep). We compared such scores using repeated measures ANOVAs: a first time comparing healthy controls and baseline migraineurs, then baseline migraineurs VS the ones three months after first treatment. Moreover, we performed a post-hoc Duncan's test analysis.
Results: first rmANOVA showed that healthy controls refer a higher number of flashes compared to chronic migraineurs (p=0.011), while the second analysis did not show significant changes in such scores before and after 3 months from the treatment (p=0.194), but post-hoc analysis showed a significant augmentation of scores between 1F4B tests (p=0.010).
Discussion: data obtained suggest that chronic migraineurs manifest more fission illusions than healthy controls, consistently with previous studies. Furthermore, onabotulinumtoxinA restores, though partially, fission illusions and, consecutively, normalizes visual cortical excitability.

References: Shams L, Kamitani Y, Shimoyo S. Illusions: what you see is what you hear. Nature 2000;408:788.
Aurora SK, Cao Y, Bowyer SM, Welch KM. The occipital cortex is hyperexcitable in migraine: experimental evidence. Headache 1999;39:469-476.
F.Brighina, N.Bolognini, G.Cosentino, S.Maccora, P.Paladino, R.Bas chi, G.Vallar,
B.Fierro. Visual cortex hyperexcitability in migraine in response to sound-induced flash illusions. Neurology, May 2015, 84 (20) 2057-2061

EFFECTS OF ONABOTULINUMTOXINA ON HEADACHE DISABILITY AND COMORBID DEPRESSION IN CHRONIC MIGRAINE PATIENTS

Serena Scardina[1], A. Torrente[1], S. Ferlisi[1], F. Ferraro[1], S. Di Marco[1], L. Pilati[1], E. Di Marco[1], G. La Bianca[1], M. Gangitano[1], G. Cosentino[2], F. Brighina[1]

[1] Department of Biomedicine, Neurosciences and Diagnostic (Bi.N.D.) - Policlinico Giaccone – Palermo
[2] National Neurological Institute - Mondino – Pavia

Background: chronic migraine (CM) results in a serious limitation of life activities and it is frequently associated (more often than episodic migraine) to psychiatric comorbidity, particularly to depression.
OnabotulinumtoxinA is an approved treatment for CM patients, so we aim to evaluate positive effects of such therapy on migraine disability and concomitant depressive symptoms.
Methods: we enrolled 12 women (mean age 49.91 years old +11.00) suffering from chronic refractory migraine who started treatment with OnabotulinumtoxinA (195 UI divided among 39 sites each 90 days). We asked patients to fill in a headache diary and two questionnaires: Migraine Disability Assessment (MIDAS) and Beck Depression Inventory II (BDI-II). The evaluations were administered at baseline, at three and six months after OnabotulinumtoxinA injections.
Results: the headache days number reduced significantly during the six months since first administration of therapy (p=0.00493). Similar reductions, even if slightly less statistically significative, were observed on MIDAS (p=0.01177) and BDI-II scores (p=0.3196). Moreover, it is worth to note that significant therapeutic effects were already observed at three months after first drug administration.
Conclusion: OnabotulinumtoxinA is an effective treatment for patients suffering from chronic migraine and such effect is not only important for a reduction of headache days (as already showed by literature), but even for an improvement of disability, as well as depressive symptoms associated to migraine.

References: Bekir Enes Demiryurek, Devrimsei Harika Ertem et al. Effects of onabotulinumtoxinA treatment on efficacy, depression, anxiety, and disability in Turkish patients with chronic migraine; Neurol Sci; 2016; 37:1779-1784
A Santoro, A Fontana et al. Quarterly repeat cycles of onabotulinumtoxinA in chronic migraine patients: the benefits of the prolonged treatment on the continuous responders and quality-of-life conversion rate in a real-life setting; Neurolol Sci; 2017; 38: 1779-1789

VISUAL CORTICAL EXCITABILITY IN FIBROMYALGIC PATIENTS: A STUDY WITH SOUND INDUCED FLASH ILLUSIONS

Angelo Torrente[1], G. Damerino[1], R. Aronica[1], S. Ferlisi[1], S. Scardina[1], S. Di Marco[1], L. Pilati[1], G. La Bianca[1], N. Bolognini[2], G. Guggino[3], F. Brighina[1]

[1] Department of Biomedicine, Neurosciences and advanced Diagnostic (Bi.N.D.) - University of Palermo – Palermo
[2] Department of Psychology - University of Milano-Bicocca - Milano
[3] Biomedical Department of Internal and Specialistic Medicine (DIBIMIS) - University of Palermo – Palermo

Abstract: Fibromyalgia (FM) is a disease characterized by chronic pain, so we decided to evaluate whether FM patients show cortical excitability changes using sound-induced flash illusions (SIFI). We analysed SIFI in 28 patients and results show that they were significantly low (compared to controls), so we can conclude that cortical excitability is increased FM patients.
Background: Perception of the environment results from multiple sensory stimuli interaction. Perception modulation can be explored using SIFI[1]: when a single flash is presented with two or more beeps, it is often perceived as multiple flashes (fission illusion). Such illusory perception varies in relation to changes of visual cortical excitability; particularly, the number of SIFI is reduced when visual cortical excitability is increased. Cortical excitability is altered in conditions associated to chronic pain, such as migraine, as explored in previous studies[2]. FM is a disabling disease characterized by widespread muscle pain, fatigue, cognitive impairment and other physic and psychopathological symptoms and, unfortunately, treatment options are few. There is evidence that excitability of pain-processing areas is abnormally enhanced in FM.
Aims: We aimed to explore whether such facilitation represents a general sensorial activation, instead of one strictly related to pain processing areas. To do so, we evaluated excitability of the visual cortex, an area not directly involved in pain processing.
Matherials and Methods: We enrolled 28 FM patients (mean age 45yo +8.53; 26F) and 24 healthy controls (HC “mean age 44yo +9.68; 22F). We used a software able to show a transient single flash presented together with concurrent beeps. Subjects had to count aloud flashes seen each time (5 tests randomly presented several times: 1FxB, where x goes from 0 to 4; F=flash, B=beep). We compared FM patients scores to HC ones using a rmANOVA, then we performed a post-hoc Duncan’s analysis.
Results: Data showed that FM patients SIFI scores were significantly lower than HC ones ($p=0.00001$) and post Hoc analysis revealed the highest significance was for 1F2B, 1F3B and 1F4B tests ($p<0.005$).
Discussion and Conclusion: SIFI study represents a cheap, very well tolerated and effective tool to explore cross-modal audio-visual perception and, indirectly, visual cortical excitability, even in FM patients. Our results suggest that the increased visual excitability showed by FM

patients could favor the hypothesis of a general sensorial activation, not strictly linked to pain. This could shed more light on the disease pathophysiological mechanisms, as well as provide new ways for treatments research.

References: Shams L, Kamitani Y, Shimoyo S. Illusions: what you see is what you hear. Nature 2000;408:788 F.Brighina, N.Bolognini, G.Cosentino, S.Maccora, P.Paladino, R.Baschi, G.Vallar, B.Fierro. Visual cortex hyperexcitability in migraine in response to sound-induced flash illusions. Neurology, May 2015, 84 (20) 2057-2061

DOES ACUTE PERIPHERAL TRAUMA CONTRIBUTE TO IDIOPATHIC ADULT-ONSET DYSTONIA?

Tommaso Ercoli, M. Mascia, G. Defazio

Institute of Neurology, Department of Public Health and Medical Sciences - Cagliari – Cagliari

Background and aims: to explore the controversial association between acute extracranial trauma and focal adult-onset dystonia [1]. Materials and Methods: we analyzed information by the Italian Dystonia Registry about the occurrence of acute peripheral trauma severe enough to require medical attention in 1392 patients with adult-onset idiopathic dystonia and 200 patients with adult-onset dystonia secondary to well established causes other than trauma. Although the retrospective assessment prevented us from rating the severity of trauma, we checked for sequelae that seemed potentially important in the development of idiopathic dystonia (contusion, wounds, fractures, dislocation/subluxation and sprain).
Results: by this approach we observed that patients with idiopathic and secondary dystonia showed a similar burden of peripheral injury in terms of number of patients reporting peripheral injury (115 vs 12, p = 0.3) and overall number of injuries (145 vs. 14). Although, most trauma occurred before the onset of idiopathic or secondary dystonia, only a minority of injuries (14 in the idiopathic group, 2 in the secondary group, p = 0.6) affected the dystonic body part. However, the time elapsing between injury and development of dystonia was consistent with Jankovic criteria [2] for causation (one year or less) only for 6/145 trauma (4.1%) from 5/1392 idiopathic patients (0.36%).
Discussion and conclusion: our data would suggest that the contribution of peripheral acute trauma to idiopathic dystonia is negligible and, if any, probably involves only a small subset of patients.

References: Frei K. Posttraumatic dystonia. J Neurol Sci. 2017 Aug 15;379:183-191. Jankovic J. Can peripheral trauma induce dystonia and other movement disorders? Yes! Mov Disord. 2001 Jan;16(1):7-12.

PREVALENCE OF HUNTINGTON'S DISEASE IN SARDINIA, ITALY

Maria Margherita Sechi[1], M. Murru[2], A. Muroni[1], G. Defazio[1]

[1] Institute of Neurology, Department of Public Health and Medical Sciences - Cagliari – Cagliari
[2] Multiple Sclerosis Center - Cagliari – Cagliari

Background and aims: the prevalence of Huntington disease (HD) may vary considerably, depending on the population and geographic area under study. In Italy, only two epidemiological estimation were reported after the genetic diagnostic test became available in1993. The prevalence estimates from the two studies (one published in abstract form alone) referred to restricted geographic areas from continental Italy and ranged between 2.48/100000 [1] and 10.85/100000 [2].
Materials and Methods: we have performed a service-based epidemiological analysis extended to the population residing in Sardinia. The socio-cultural isolation of this large Mediterranean island makes genetic structure of Sardinians more homogeneous than the Italian population (and also of many European populations). On the prevalence date, December 31st, 2017, there were 1.648.176 inhabitants. To identify HD patients we referred to multiple sources, including 10 local neurological services, other major neurological services in Italy, and the only one Sardinian reference point for genetic testing.
Results: a total of 51 symptomatic HD patients, aged 21 years or more, were identified. The correspondent prevalence rate was 3.1 per 100,000 inhabitants. The median CAG repeat lengths in normal alleles from both affected and unaffected individuals was 18 (range, 15 to 24).
Discussion and Conclusion: crude prevalence rates were remarkably higher in the inner part of Sardinia (Nuoro county: 4.3/100.000 inhabitants; and South Sardinia county: 4.8/100.000) than in the other counties (Cagliari county: 2.1/100.000 inhabitants; Sassari county: 3.04/100.000 inhabitants; Oristano county: 0.62/100.000), thus suggesting a founder effect.

References: Reverberi L, Contardi S, Fioravanti V, Cavallieri F, Codeluppi L, Valzania F. Epidemiological study on Huntington's disease in the districts of Modena and Reggio Emilia (Italy). [Abstract]. Mov. Disord. 2014; 29, Suppl 1: 582.
Squitieri F, Griguoli A, Capelli G, Porcellini A, D'Alessio B. Epidemiology of Huntington disease: first post-HTT gene analysis of prevalence in Italy. Clin Genet. 2016 Mar;89(3):367-70.

Badge

I badge dovranno essere ritirati presso il desk di segreteria. Raccomandiamo ai partecipanti di indossare il proprio badge durante tutto il convegno.

Attestato di partecipazione

L'attestato di partecipazione sarà rilasciato, al termine dei lavori, presso il desk di segreteria a tutti i partecipanti regolarmente presenti.

Lunch

Il lunch verrà servito in un'area dedicata dell'Università.

Assicurazione

La partecipazione al convegno non implica alcuna responsabilità da parte della segreteria scientifica e organizzativa per qualsivoglia incidente, danni personali o materiali o furti subiti dal partecipante durante la manifestazione. Invitiamo quindi tutti i delegati ad attivare un'assicurazione personale prima di partecipare al convegno.

Vietato fumare

I partecipanti sono gentilmente pregati di non fumare nell'area congressuale.

Disattivare la suoneria dei cellulari

I partecipanti sono gentilmente pregati a tenere i cellulari in modalità silenziosa nelle aule dove si svolgono i lavori.

Note personali