UNIVERSITA' degli STUDI di ROMA
TOR VERGATA

PTV
FONDAZIONE PTV
POLICLINICO TOR VERGATA

«DIAGNOSTIC CHALLENGE IN RAPIDLY PROGRESSIVE DEMENTIA: A CASE REPORT»

UOC Neurologia: M.R. Bagnato, A. Castelli, C.G. Bonomi, M. Conti, A. Bruno, L. Boffa, M. Pierantozzi, N. B. Mercuri.

MEDICAL HISTORY

- A **45 old woman** from **Ukraine**
- In Italy **since 2003**
- Comes to the ER because of two **tonic-clonic generalized seizures in 24 hours**
- Previously affected by an ***ischemic stroke***
- **Cognitive impairment**, postural instability, mood swings since May 2018
- No home drug therapy

N.E. AT ADMISSION

- Non fluent aphasia
- Dysmetria in left arm > right arm
- Ataxia, with positive Romberg sign
- Intentional tremor in left arm
- Marked hyperreflexia
- Non-reactive mydriatic pupils

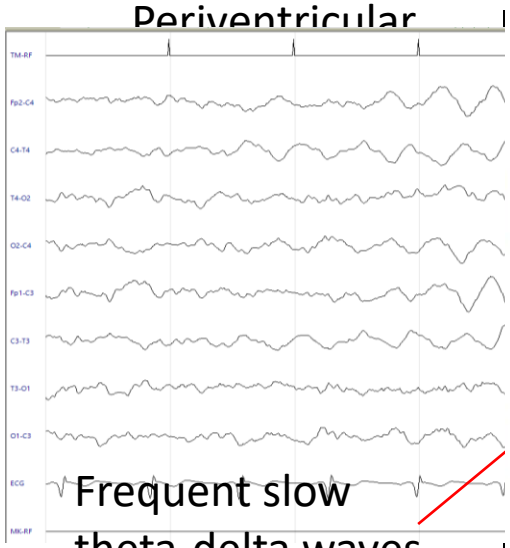
DIAGNOSTIC INVESTIGATION

4) CSF AND SIEROLOGY TESTS

3) EEG

2)LUMBAR PUNCTURE

PREVIOU



Periventricular

Frequent slow theta-delta waves with **bi-triphasic sharp morphology**

Dipartimento dei Processi Assistenziali Integrati
Area Funzionale Diagnostica di Laboratorio

TSH
Anticorpi Anti-Tireoperossidasi
Anticorpi Anti-Tireoglobulina (Anti TG)
Acido Folico
Vitamina B12
25 OH -Vitamina D

ES COLTURALE (LIQUOR)

Materiale: Liquor
Isolati:

R:Resistente - I:Sensibile, aumentata
Antibiogramma interpretato secondo i

CONTA MICROBICA

Materiale: Liquidi Biolog
Isolati:

R:Resistente - I:Sensibile, aumentata
Antibiogramma interpretato secondo i

EMATOLOGIA
Resp.: Prof. Renato Massoud

EMOCROMO

Globuli Rossi	4.61		milioni/µL
Emoglobina	12.30		g/dL
Ematocrito	40.20		%
Volume Globulare Medio	87.2		fL
MCH	26.7		pg
MCHC	**30.6**	**	g/dl
RDW-CV	14.6		%
Piastrine	348		mila/µL
Globuli Bianchi	**11.38**	**	mila/µL
Neutrofili #	8.10		mila/µL
Linfociti #	1.78		mila/µL
Monociti #	1.05		mila/µL
Eosinofili #	0.41		mila/µL
Basofili #	0.04		mila/µL

ERIOLOGIA SIEROLOGICA

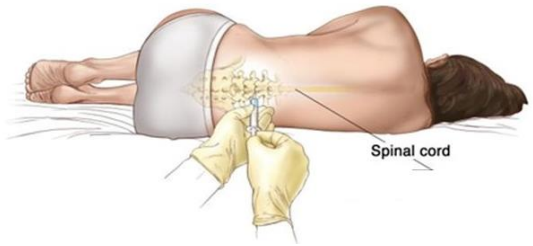
(qual)	PEND
(quant)	PEND
	PEND
rpi	PEND
rpi (FTA-ABS quant)	PEND

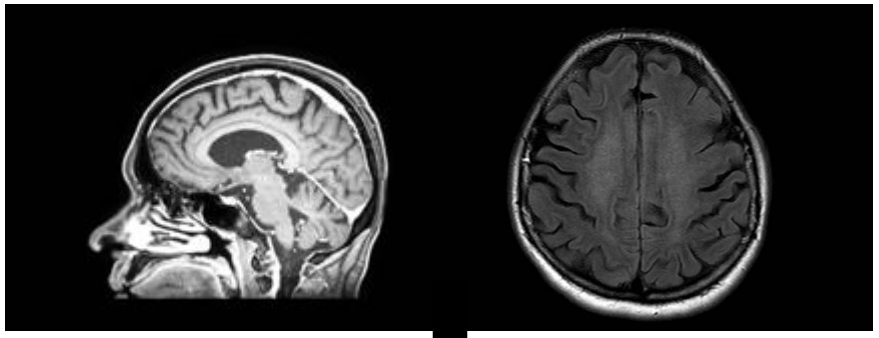
Quoziente Albumina	6.68			0.00 - 9.00
LCR-Albumina	27.60		mg/dl	0.00 - 35.00
IgG Liquor	**14.50**	**	mg/dL	0.00 - 4.00
Indice di Link	1.78			< 0.7

CEFTRIAXONE 2g

CEREBELLUM ATROPHY

DIFFERENTIAL DIAGNOSIS:





AUTOIMMUNE ENCEPHALOPATHY?

- Negative anti-neuronal antibodies
- clinical suggestive
- PET-CT not showing increased uptake areas
- Absence of suggestive MR signs
- Not typical clinical features

Because of alcoholism we empirically start Thiamine therapy

B9 Deficiency

Alcoholism

BUT

NEUROLOGICAL EXAMINATION 10 DAYS AFTER

… after 10 days of treatment with Valproate, Ceftriaxone, Thiamine…

1. The woman can understand and answer to easy questions: **MMSE 25/30**
2. **Improvement in DYSMETRIA**
3. **Improvement in AMBULATION** still ataxic but possible without any support**,** and swinging at Romberg test.
4. **Reduction of tremor**
5. Hyperreflexia
6. **Not reagent, mydriatic pupils**

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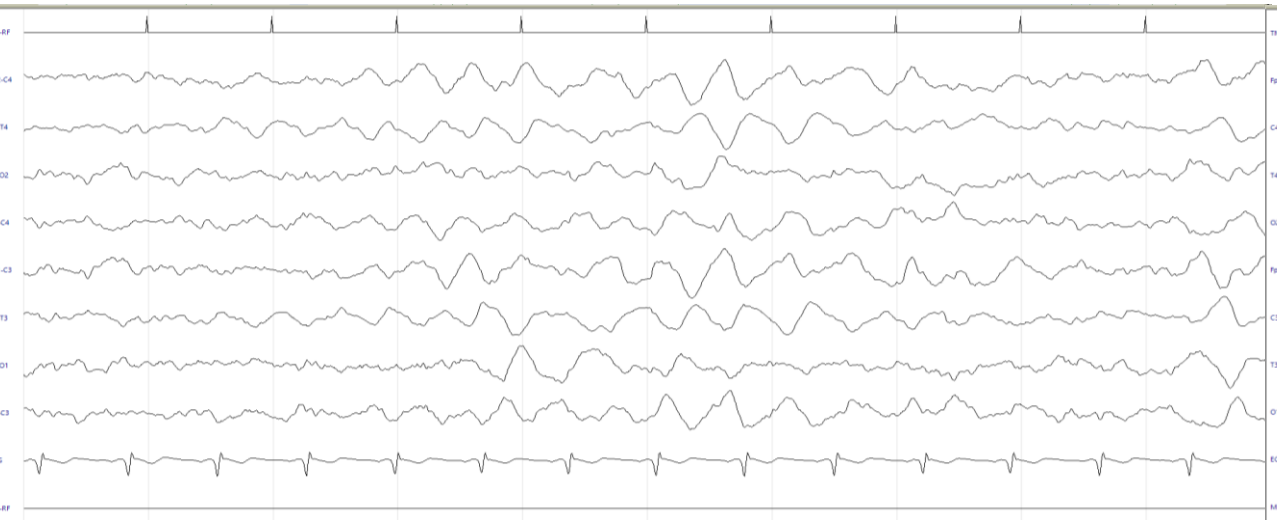
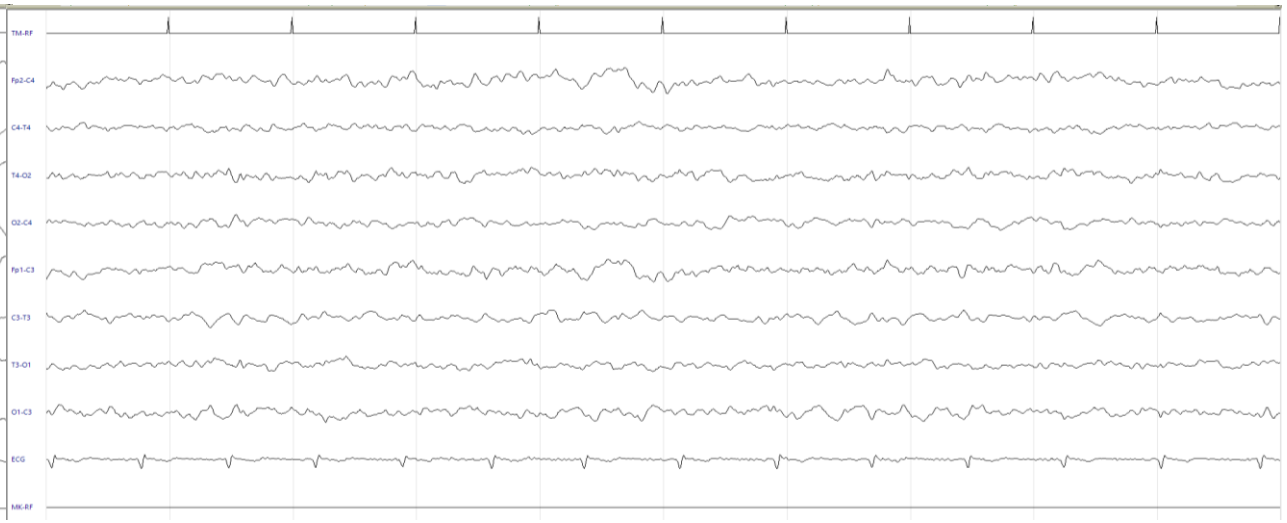
WE PERFORM ANOTHER EEG:





14/01: Alpha background activity at 9-10 c / s characterized by poor stability and regularity, mixed with frequent slow theta-delta waves with sharp morphology and bi-triphasic waves, expressed on bilateral fronto-center-temporal sites tending to bi-hemispheric diffusion and to **gather in short bouffèes lasting about 2-3 seconds**

21/01: Slow-sharp anomalies on bilateral fronto-center-temporal sites with alternating side prevalence. Compared to the previous exam carried out on 14.1.19, we note a **greater stability of the background rhythm and a reduction of the slow components.**

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MEANWHILE, WE RECEIVE THE RESULTS OF LABORATORY TESTS

MICROBIOLOGIA E VIROLOGIA

BIOLOGIA MOL

CITOFLUORIMETRIA E BATTERIOLOGIA SIEROLOGICA

BIOLOGIA MOLECOLARE CLINICA

Pol. genetici (F. V Leiden-G1691A)	Assenza della M	Treponema Pallidum (TPHA qual)	**Reattivo**	**
Pol. genetici (MTHFR C677T)	Presenza della			
Pol. genetici (Protrombina G20210A)	Assenza della M	Treponema Pallidum (TPHA quant)	Positivo (1:2560)	
AUTOIMMUNITA'				
Ab anti Beta2-Glicoproteina IgG (CLIA)	<6.40	Treponema Pallidum (VDRL)	Positiva	
Ab anti Beta2-Glicoproteina IgM (CLIA)	<1.10	Treponema Pallidum anticorpi	**Positivo**	**
Ab anti cardiolipina IgM (CLIA)	1.50	Treponema Pallidum anticorpi (FTA-ABS quant)	Positiva (1:20)	
Ab anti cardiolipina IgG (CLIA)	<2.60			

30

1.25

1.20

> 2.2

124

145.00

Laboratory findings reveale the serological and CSF positivity of Treponema Pallidum, and so **NEUROSYPHILIS IS DIAGNOSED.**

NEUROSYPHILIS

- Known as **GREAT IMPOSTOR**
- onset after about 11 years from the primitive
- Variability of clinical features

DIAGNOSIS:

- ***SIEROLOGICAL FINDINGS*** *(VDRL + / TPHA +/ FTA- ab +)*
- ***CSF FINDINGS***: VDRL+ and *increase in LCR-proteins or lymphomonocytes*
- ***SYMPTOMS*** *(cognitive impairment, aphasia, stroke, tabe…)*

NEUROSYPHILIS

CLASSIFICATION:

- **ASYMPTOMATIC NEUROSYPHILIS**
- **MENINGEAL NEUROSYPHILIS:** nausea, vomiting headache, loss of hearing and vision
- **MENINGOVASCULAR NEUROSYPHILIS:** stroke
- ***TABE DORSALIS:*** trouble balancing, a loss of coordination, incontinence , an altered walk, vision problems, pains in the abdomen, arms, and legs
- ***GENERAL PARESIS:*** mood swings, emotional troubles, personality changes, weakened muscles, a loss of the ability to utilize language, cognitive impairment
- ***GUMMATOUS DISEASE:*** destructive inflammation and space-occupying lesions, most often involving the frontal and parietal lobes of the brain.

THIS SEPARATION IS NOW ARCAIC: CLINICAL FEATURES OF DIFFERENT TYPES OF NS CAN BE PRESENT

THE GREAT IMPOSTOR

REVIEW ARTICLE

Changes in neurosyphilis presentation: a survey on 286 patients

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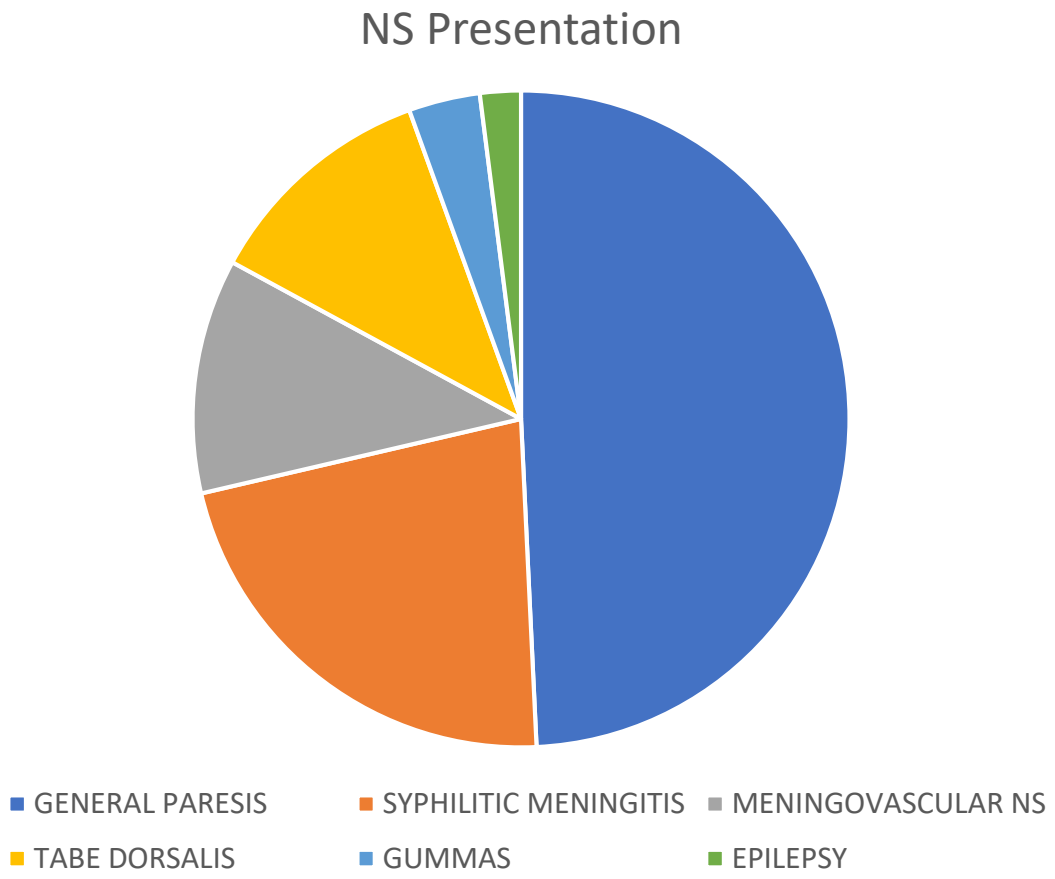
11% have presentation sympthoms of **2 different NS types**

4% have presentation sympthoms of >**2 different NS types**

10 % HIV +

62% **Misdiagnosed**



INCREASING TREND IN SYPHILIS

ECDC epidemiological data 2012- 2016:

increasing trend in Europe (21269 vs 29365)
increasing trend in Italy (1138 vs 1420)

Table 1. Distribution of confirmed cases of syphilis, EU/EEA, 2012–2016

Country	2012		2013		2014		2015		2016				
	Confirmed cases		Confirmed cases		Confirmed cases		Confirmed cases		National coverage	Reported cases	Confirmed cases		
	Number	Rate	Number	Rate	Number	Rate	Number	Rate			Number	Rate	ASR
Austria	78	-	538	-	.	.	.	.	.	.	.	.	.
Belgium	658	-	867	-	872	-	892	-	N	1531	1531	-	-
Bulgaria	309	4.2	354	4.9	460	6.3	465	6.5	Y	367	367	5.1	-
Croatia	28	0.7	80	1.9	51	1.2	25	0.6	Y	29	27	0.6	0.7
Cyprus	6	0.7	12	1.4	18	2.1	31	3.7	Y	16	16	1.9	1.8
Czech Republic	329	3.1	402	3.8	408	3.9	554	5.3	Y	538	538	5.1	5.1
Denmark	343	6.1	317	5.7	361	6.4	777	13.7	Y	365	365	6.4	6.9
Estonia	40	3.0	39	3.0	35	2.7	25	1.9	Y	25	25	1.9	2.0
Finland	201	3.7	153	2.8	196	3.6	243	4.4	Y	230	211	3.8	4.1
France	865	-	1014	-	1405	-	1755	-	N	1742	1742	-	-
Germany	4414	5.5	5324	6.6	5821	7.2	6688	8.2	Y	7175	7175	8.7	9.2
Greece	363	-	300	-	247	-	320	-	.	.	.	.	.
Hungary	621	-	627	-	622	-	617	-	N	712	712	-	-
Iceland	5	1.6	3	0.9	25	7.7	23	7.0	Y	30	30	9.0	9.7
Ireland	110	2.4	163	3.6	204	4.4	276	6.0	Y	291	291	6.2	6.3
Italy	1138	1.9	1170	2.0	1151	1.9	1060	1.7	Y	1424	1420	2.3	2.3
Latvia	148	7.2	127	6.3	139	6.9	141	7.1	Y	159	159	8.1	8.3
Liechtenstein	.	.	.	.	.	.	.	.	.	.	.	.	.
Lithuania	227	7.6	269	9.1	257	8.7	130	4.5	Y	151	151	5.2	5.4
Luxembourg	20	3.8	27	5.0	27	4.9	21	3.7	Y	27	27	4.7	4.8
Malta	35	8.4	45	10.7	49	11.5	41	9.5	Y	40	40	9.2	8.9
Netherlands	649	-	743	-	975	-	1221	-	N	1515	1515	-	-
Norway	109	2.2	185	3.7	189	3.7	172	3.3	Y	188	188	3.6	3.8
Poland	961	2.5	1324	3.5	1147	3.0	1239	3.3	Y	1291	1291	3.4	-
Portugal	235	2.2	155	1.5	101	1.0	43	0.4	Y	705	60	0.6	0.6
Romania	1717	8.5	1393	7.0	1267	6.4	969	4.9	Y	928	928	4.7	4.7
Slovakia	412	7.6	337	6.2	369	6.8	295	5.4	Y	349	349	6.4	6.3
Slovenia	63	3.1	35	1.7	23	1.1	43	2.1	Y	35	35	1.7	1.6
Spain	3641	7.8	3723	8.0	3568	7.7	3756	8.1	Y	3356	3356	7.2	-
Sweden	197	2.1	275	2.9	244	2.5	325	3.3	Y	346	346	3.5	3.9
United Kingdom	3347	5.3	3631	5.7	4740	7.4	5768	8.9	Y	6470	6470	9.9	10.2
EU/EEA	**21269**	**4.7**	**23632**	**5.0**	**24971**	**5.4**	**27915**	**5.9**	.	**30035**	**29365**	**6.1**	**6.5**

ASR: age-standardised rate; - = rate not calculated because country has a sentinel surveillance system

NEUROSYPHILIS

TABLE 10-3 Treatment of Neurosyphilis

▶ **Recommended Regimens**[a]

Aqueous crystalline penicillin G 18–24 million units/d IV, given as 3–4 million units IV every 4 hours or as a continuous IV infusion for 10–14 days

OR

Procaine penicillin G 2.4 million units IM once per day, plus probenecid[b] 500 mg orally 4 times/d, both for 10–14 days

▶ **Nonstandard Regimens**[a]

Ceftriaxone 2 g IV once per day for 10–14 days

Doxycycline 200 mg orally 2 times/d for 28 days

IM = intramuscular; IV = intravenous.

[a] Some experts recommend 3 weekly doses of 2.4 million units of benzathine penicillin G IM, which is the treatment for uncomplicated late latent syphilis, after completion of neurosyphilis treatment.

[b] Probenecid is contraindicated for patients with serious allergy to sulfa-containing medications.

We can observe the best clinical improvement in meningeal desease.
In tabe dorsalis and general paresis we observe a quick partial improvement of some symptoms and the **neurological degeneration interruption.**

Ceftriaxone 2g ev/die was added in treatment at the admission.

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AUTOIMMUNITA'

Beta 1-42 amiloide liquor (ELISA)	244.00		> 690 pg/mL
Proteina tau liquor (ELISA)	79.00	*pg/mL*	< 350
Proteina tau fosforilata liquor (ELISA)	<15.00	*pg/mL*	< 60

T. Pallidum can interfere with Ab42 both **directly** by neuronal invasion and **indirectly** by inflammation due to presence of spirochetes.

There is a **statitically significant difference** between Ab42 CSF between ANS and GP.
May we consider **Ab42 as a marker of NS progression?**

	(*n* = 17)	(*n* = 3)	2007.1 ± 419.4 (*n* = 30)	2363.3 ± 252.5 (*n* = 30)	0.053
p-tau181	34.3 ± 12.6	34.7 ± 7.7	75.1 ± 22.9	43.8 ± 14.5	<0.001
t-tau[a]	176.2 ± 72.4 (*n* = 17)	125.2 ± 28.1 (*n* = 3)	531.9 ± 189.3 (*n* = 53)	196.0 ± 59.4 (*n* = 36)	<0.001

AD, Alzheimer's disease; ANS, asymptomatic neurosyphilis; CSF, cerebrospinal fluid; GP, general paresis; NC, normal control.
Numbers are the mean ± standard deviations. Significance was set at $P < 0.05$ for analysis.

And what about Thiamine?

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Articles

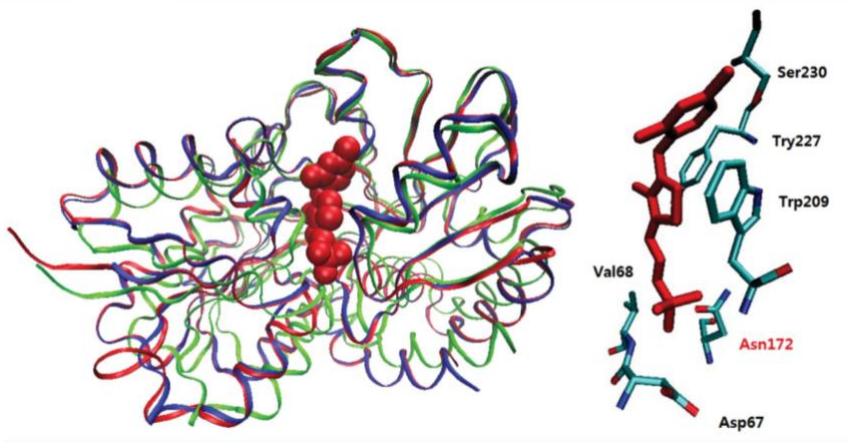
Evidence that TP_0144 of *Treponema pallidum* Is a Thiamine-Binding Protein

Jiang Bian, Youbin Tu, Song-Mei Wang, Xuan-Yi Wang, Chunhao Li

I. B. Zhulin, Editor

Genomics studies have shown **that T. Pallidum has not a Thiamine biosynthesis pathway.**

To get this vitamin, T. Pallidum is provided of many **ABC carrier proteins called TP0144.**



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CONCLUSIONS

- You should investigate T. Pallidum in **dementia differential diagnosis**, specially in young patients with seizures and stroke.
- You should consider **meningovascular NS** in case of ischemic strokes in young patients with no vascular risk factors known.
- Epidemiology suggests an increase of Syphilis in Europe: **screening test** in population at risk?


THANKS FOR YOUR ATTENTION!