8ª GIORNATA DELLO SPECIALIZZANDO IN NEUROLOGIA

UNIVERSITÀ DI SIENA 1240

# Gait ataxia, pyramidal involvement and leukoencephalopathy: what's underneath?

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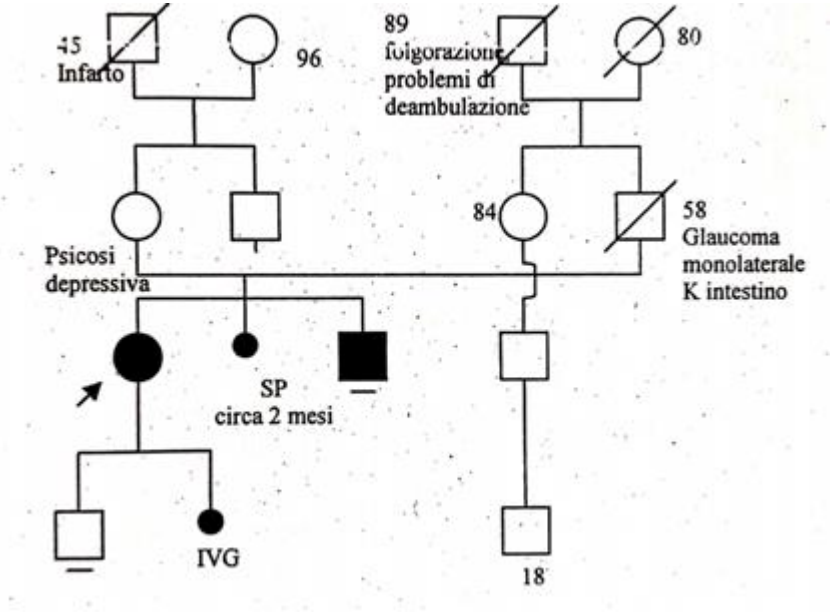
# AMP, ♀ 65 y.o.

Adolescent-onset (11 y.o.) writing disorder (“trembling handwriting”)

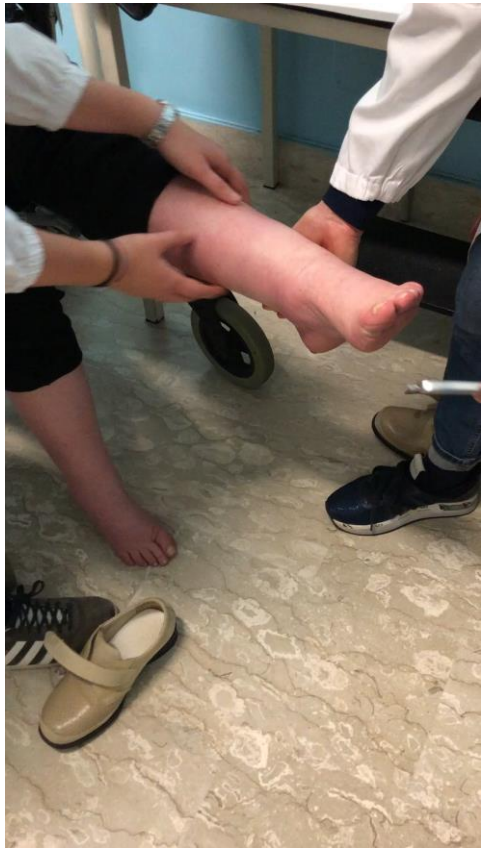
Severe intention tremor, dysmetria, dysarthria

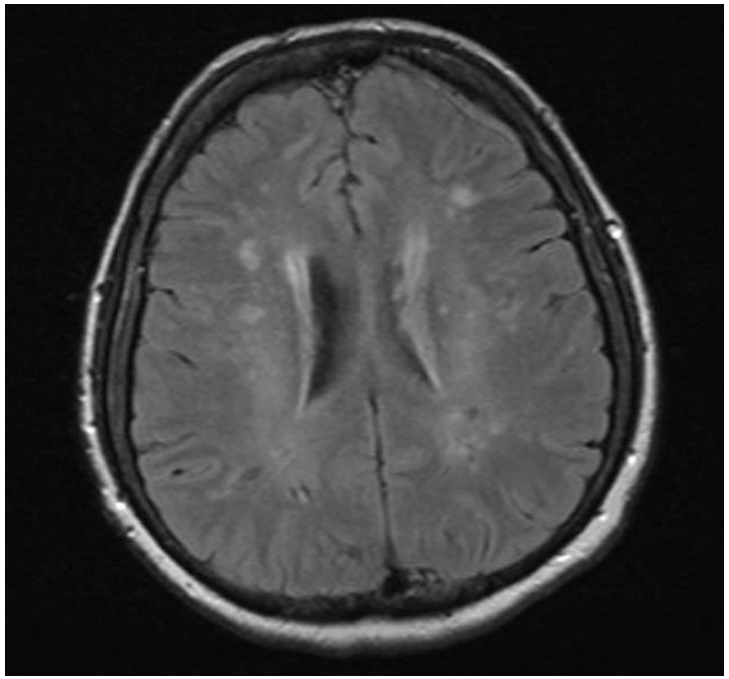
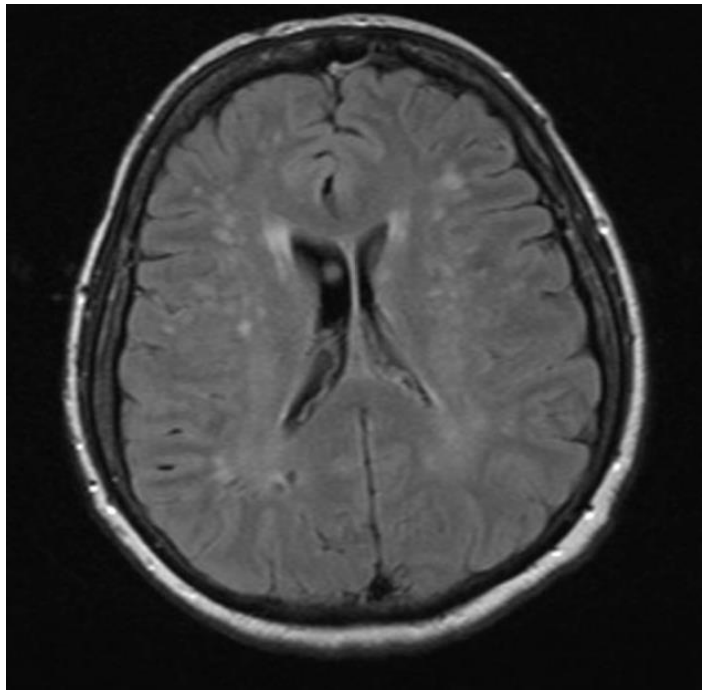
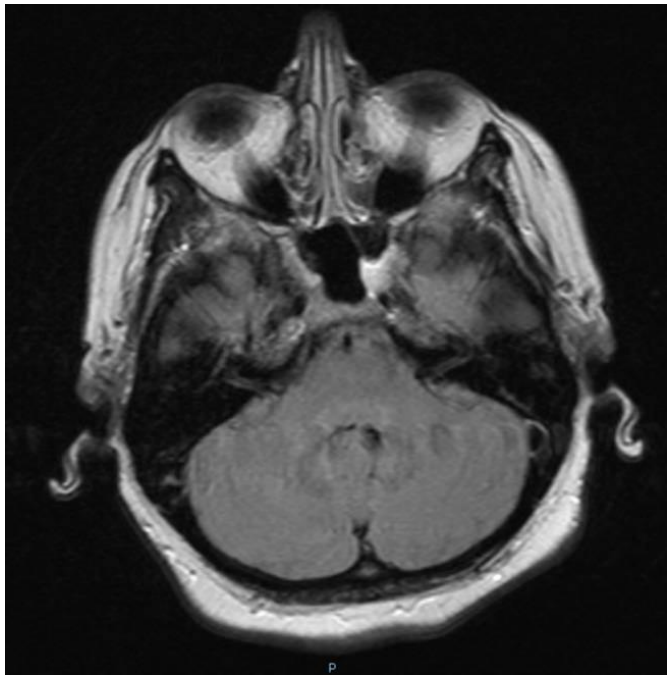
Inability to walk. Areflexia and bilateral extensor plantar response.

No cognitive impairment. No family history of neurological diseases.



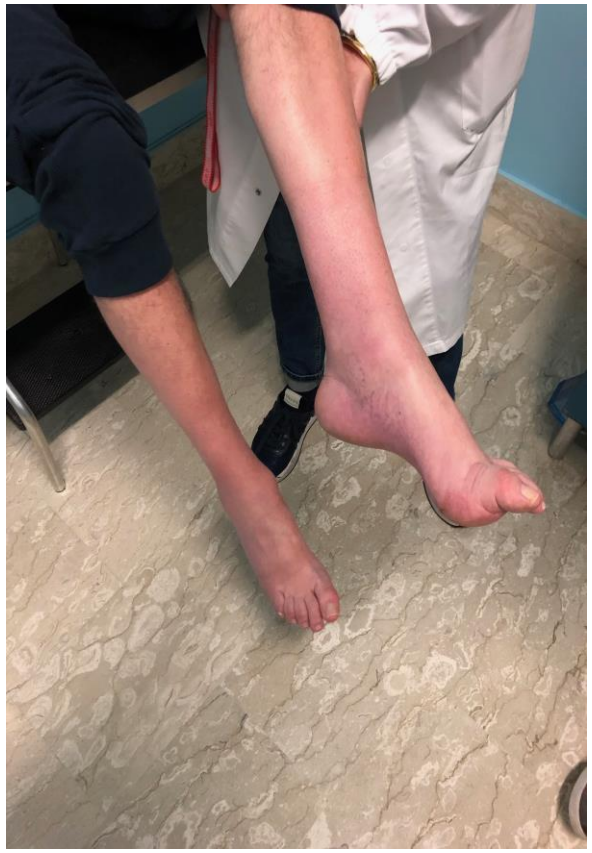
# Neurological examination:



# Neuroimaging

# SP, ♂ 59 y.o



# Diagnostic Work-up:

MRI

Nerve conduction studies and EMG

Muscolar Biopsy

Lactic and Piruvic Acid

Vit. E

Lysosomal enzyme activity

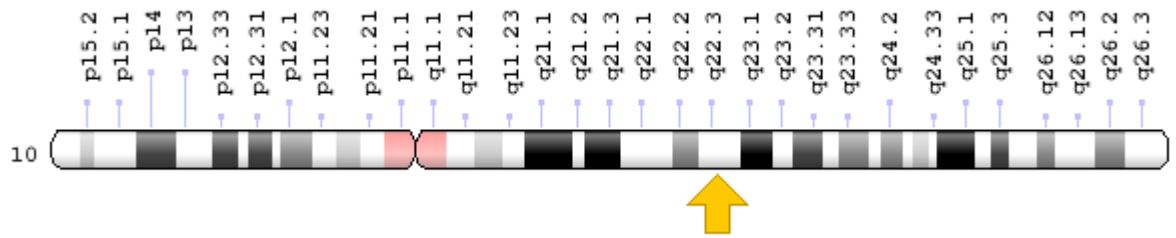
Genetic tests:

FRDA, SCA (1,2,3,6,7,8), DRPLA, SPG.

Extensive laboratory and metabolic investigations were performed and resulted negative.

# Target re-sequencing (ataxia related genes)

| Gene | Trascritto | Mutazione | Genotipo | Polyphen/SIFT | Frequenza GNOMAD | Conferma Sanger |
|---|---|---|---|---|---|---|
| *POLR3A* | NM_007055.3 | c.4073G>A (p.G1358E) | Het | Probably Damaging/Damaging | - | Si |
| *POLR3A* | NM_007055.3 | c.1909+22G>A | Het | - | - | Si |




**POL III-Related Adolescent Onset Spastic Ataxia**

# «POL III - Related conditions»

Inherited in an autosomal recessive manner and result from mutations in POLR3A gene (chromosome 10q22) or the POLR3B gene (chromosome 12q23) which are responsible for encoding the two largest subunits of RNA polymerase III. It has been hypothesized that Pol III is crucial for tRNA synthesis and these mutations lead to abnormality in tRNA levels in the brain.

## Suggestive Findings

POLR3-related leukodystrophy **should be suspected** in individuals with the following major/shared **clinical features**, which may or may not be present:

- Neurologic dysfunction: progressive cerebellar features, including:
  - Gait ataxia, dysarthria, dysmetria, tremor, eye movement abnormalities; and
  - To a lesser extent, extrapyramidal (typically dystonia), pyramidal, and cognitive features
- Abnormal dentition (e.g., hypodontia, oligodontia, delayed teeth eruption) [Wolff et al 2010]
- Endocrine abnormalities such as short stature (in ~50% of individuals) with or without growth hormone deficiency, and more commonly, hypogonadotropic hypogonadism manifesting as delayed, arrested, or absent puberty
- Ocular abnormality in the form of myopia, typically progressing over several years and becoming severe

Note: Although this tetrad is highly suggestive of the diagnosis, not all features are present in all individuals who have POLR3-related leukodystrophy.


Patients carrying the c.1909 + 22G>A variant in combination with a second POLR3A mutation share a homogenous phenotype, characterized by adolescent onset and slowly progressive ataxia combined with pyramidal involvement.

# Conclusions

- 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 ataxias.
- The expanding phenotypic spectrum of POLR3A-related syndromes, now including leukodystrophies, a disease of premature ageing and hereditary ataxia/HSP, calls for future disease classification which includes both clinical and genetic information.