Sistema Socio Sanitario
Ospedale Papa Giovanni XXIII
Regione Lombardia
ASST Papa Giovanni XXIII

AN ATYPICAL CASE OF RAPIDLY EVOLVING UPPER MOTOR NEURON DISEASE, WITH TWO VARIANTS OF UNCERTAIN SIGNIFICANCE FOUND IN THE SENATAXIN GENE.

Marcella Vedovello [1], Valentina Dell'Era [1], Armanda Negroni [2], Dario Alimonti [1]
[1] Neurology Unit, Papa Giovanni XXIII Hospital, Bergamo
[2] NeurorehabilitationUnit , Papa Giovanni XXIII Hospital, Bergamo

BACKGROUND

Primary lateral sclerosis (PLS) is a rare variant of motor neuron disease (MND) with at least ten years life expectancy. The onset is typically spinal to the lower limbs, but corticobulbar involvement and extrapiramidal features are not uncommon. The need for artificial mechanical ventilation is exceptional. Differential diagnosis between PLS, early-stage amyotrophic lateral sclerosis and hereditary spastic paraplegia is challenging.

CASE REPORT

We describe the case of 50 year old woman who insidiously presented with spasticity and progressive clumsiness involving the left upper limb, with ipsilateral pyramidal features on neurological examination. Electroneurography and electromyography were normal. Transcranial Magnetic Stimulation revealed impaired central motor conduction at the left upper limb; brain MRI disclosed focal atrophy in the right frontal girus (fig.1). Brain positron emission tomography with FDG and electroencephalogram were unremarkable. Standard CSF analisys was normal. Markers of neurodegeneration, as well a a broad panel of onconeural antigens and anti-glutamic acid decarboxylase (GAD) antibodies were negative. Molecular analysis of the senataxin gene (SETX) revelead the presence in heterozygous form of two nucleotide variants of uncertain pathogenetic significance (VUS) (Box1).

During the following year, the condition affected the right limbs and the bulbar region with progressive dysphagia and dysarthria. At this point the patient also presented insomnia, emotional lability, attention disorder, stress incontinence, ocular apraxia and parkinsonian signs. One years after the patient lost the ability to walk and a few months later was bedridden, with tetraplegia, almost unintellegible speech, severe dysphagia. Clinical or neurophysiological signs of lower motor neuron involvement never appeared. In the end sleep apnea and daytime sleepiness appeared. The respiratory function tests which have been normal so far except for a reduction in cough flow, detected multiple episodes of nocturnal desaturation. An attempt with non-invasive mechanical ventilation was then made, which, however, led to a worsening of the hypoventilation. After a carefull planning, the patient underwent tracheostomy and gastrostomy placement.

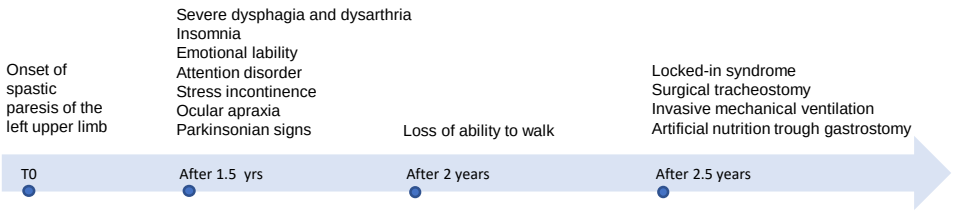
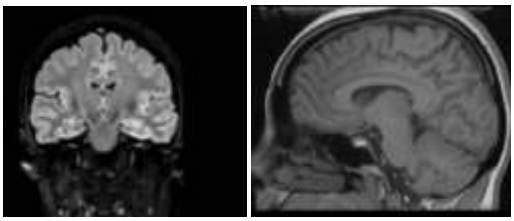


Figure 1



Coronal T2 flair sequences Sagittall T1 sequences

Box 1

VUS in the SENATAXIN gene

- In exon 15 presence of the nuclotidic variant in heterozygosis c.6085G>C (NM_015046), that results into the amino acid substitution p.Lys2029Glu (chr9:g.135171280T>C, GRCh37/hg19)
- In exon 10 presence of the nuclotidic variant in heterozygosis c.2038G>C (NM_015046), that results into the amino acid substitution p.Glu680Gln (Chr9:g.135204947C>G, GRCh37/hg19)

CONCLUSION

We report an aggressive case of Upper MND, which led to the use of invasive life-support maneuvers.
Advance care planning was particularly complex also due to the severe impairment of communication, to configure a picture of almost totally locked-in syndrome.
Even the mutations found in the SETX gen are classified as VUS, other dominant and recessive mutations in the same gene have been described in a juvenile form of amyotrophic lateral sclerosis (ALS4) and ataxia with oculomotor apraxia type 2.

References:
- *Michio Hirano et al. Senataxin mutations and amyotrophic lateral sclerosis. Amyotroph Lateral Scler . 2011 - 12(3) - 223-7*
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mail: mvedovello@asst-pg23.it