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A case of ataxia with oculomotor apraxia type 2 due to a novel mutation of SETX gene: a deep clinical-instrumental phenotyping

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Introduction: Ataxia with oculomotor apraxia type 2 (AOA2) is an autosomal recessive disorder presenting with cerebellar ataxia, sensory-motor axonal neuropathy, occasional oculomotor apraxia, cerebellar atrophy on imaging and high alpha-fetoprotein (AFP) serum level. AOA2 is genetically defined by a variety of SETX coding mutations mapped to chromosome 9q34. Seldom noncoding mutations affecting RNA processing have been reported too. AOA2 diagnosis is established in patients with clinical, laboratory, and radiographic hallmarks and confirmed by identification of biallelic pathogenic variants of *SETX*.

Case presentation: A 19 years-old man came to our attention for progressive gait ataxia debuted five years earlier. His past medical history was unremarkable, except for scoliosis, while his parents were consanguineous. On neurological examination, he had bilateral horizontal gaze-evoked nystagmus with hypometric saccades and saccadic horizontal smooth pursuit, appendicular ataxia, limbs and trunk myoclonic involuntary movements with hands' dystonic postures and dance of the tendons. Video-oculography confirmed oculomotor signs suggestive of cerebellar impairment. Blood tests detected an elevated AFP level. Brain MRI showed cerebellar atrophy, while electroneuromyography revealed an axonal sensory-motor polyneuropathy.
Instrumental gait analysis showed an initial alterations both during the stance and the swing phase of the gait cycle. The protocol for balance assessment detected an impairment in the tasks with eyes closed.
In the suspicion of a pathology belonging to the autosomal recessive cerebellar ataxias (ARCA) spectrum disorder, a direct search of point mutations by second-generation sequencing was performed revealing a novel biallelic variant in SETX gene (c.6208+2dupT), which probably led to an aberrant splicing of mRNA with intron retention. Considering patient's typical AOA2 features and parental consanguinity, it is likely that this variant played a pathogenic role in our case.

Conclusion: The present case highlights a possible novel pathogenic mutation causing aberrant splicing of SETX mRNA in a patient with AOA2.