The long way to diagnose a childhood-onset ophthalmoparesis: the discovery of a rare variant of HNRNPA2B1 gene

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Clinical Case

We report the case of a 40-year-old female patient who, from the age of 6, presented with ophthalmoparesis without diplopia, bilateral ptosis, global muscle hypotrophy, and fatigability. No family history of neuromuscular disorders was reported. Serum lactate was normal, while creatine kinase (CK) levels were elevated (2–5× upper limit of normal). Electromyography revealed myopathic changes in proximal muscles and the orbicularis oculi muscles.
A right quadriceps biopsy was performed at the age of 12, revealing a myogenic pattern with marked variability in fiber size and the presence of "rimmed vacuoles" in approximately 5% of fibers. *(Figure 1)* NADH staining showed moth-eaten fibers. The presence of autophagic vacuoles was confirmed by electron microscopy. In consideration of the clinical and histopathological presentation, an atypical form of oculopharyngeal myopathy (OPMD) was suspected mainly due to the early onset and lack of family history. Hence genetic testing for PABPN1 triplet expansion was performed and tested negative. At the age of 16 the patient reported swallowing difficulties. Following this, another quadriceps muscle biopsy was performed at the age of 18, which confirmed the previous findings, showing in addition mitochondrial changes (ragged-red-like fibers in Gomori's Trichrome staining).
In spite of a negative research for mtDNA rearrangements on muscle tissue, a diagnosis of possible mitocondrial myopathy was formulated.

Throughout the following years, the patient underwent comprehensive multidisciplinary follow-up, whose results are summarized in *Figure 2.*

After a recent revision of the clinical data, we decided to perform a mtDNA sequencing and an NGS panel of nuclear genes associated with myopathies - including congenital myasthenic syndromes (CMS) and nuclear genes related to primary mitochondrial disorders (PMD) - identified the heterozygous likely pathogenic variant c.1036_1037dup p.(Tyr347ValfsTer25) in the HNRNPA2B1 gene. Parental segregation analysis confirmed it is a de novo mutation.
This rare variant is consistent with the clinical manifestations and the histological results, thus proving its pathogenetic role. This gene according to the literature is associated with autosomal dominant OPMD but also with inclusion body myopathy with early-onset Paget disease, with or without frontotemporal dementia (autosomal dominant).

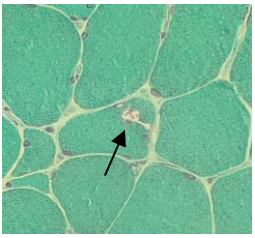

Figure 1 Gomori's Trichrome staining showing "rimmed vacuoles" (black arrows)

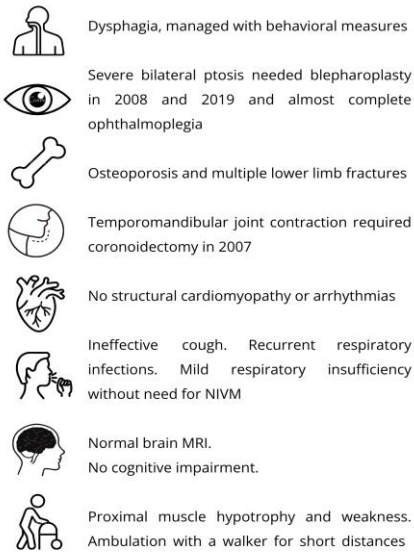

Figure 2 Multidisciplinary follow-up

Discussion

The differential diagnosis of childhood-onset ophthalmoparesis includes several conditions, such as CNS disorders, congenital myopathies, congenital myasthenic syndromes, and mitochondrial diseases. Oculopharyngeal muscular dystrophy (OPMD) is a rare, adult-onset inherited disorder primarily affecting ocular and pharyngeal muscles. The classic form is caused by an expansion of the (GCN)n repeat in the *PABPN1* gene and is characterized by rimmed vacuoles on muscle biopsy (1). Pathogenic variants in RNA-binding protein genes have been linked to a group of disorders known as multisystem proteinopathies. Kim et al. described ten families with a juvenile-onset form of OPMD associated with frameshift variants in *HNRNPA2B1*, in which the underlying mechanism involves cytoplasmic accumulation rather than fibrillization (2). Consistent with these reports (2;3), our *de novo* variant supports the phenotypic and pathological features of OPMD, enabling diagnosis of an atypical case, providing long-term multisystemic follow-up data and appropriate patient management.

Conclusion

The increasing availability of advanced genetic testing allows for the re-evaluation of unresolved rare cases, providing crucial information to improve and optimize multidisciplinary follow-up, genetic counselling in terms of inheritance, and inclusion in clinical trials.

References

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