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Case Report

Facial-onset sensory-motor neuronopathy, a rare variant of Huntington's disease or chance association?

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Abstract

Objectives: To describe a patient with facial-onset sensory-motor neuronopathy (FOSMN) that later developed Huntington's disease (HD).

Case report: A 62-year-old woman complained of progressive dysphagia 8 years before referral. At initial evaluation, there was excessive salivation, dysphagia, and sensory-motor trigeminal impairment. Denervation was noted on the upper limbs and the tongue. Blink reflexes were abolished. Genetic study of amyotrophic lateral sclerosis (ALS)-related genes was normal. She was diagnosed with FOSMN syndrome. Her clinical state progressively worsened with corneal anesthesia, severe denutrition, right arm and axial weakness. Seven years after referral, she was unable walk and developed generalized chorea. Abnormal huntingtin gene repeat expansion confirmed the diagnosis of HD. She died 16 years after onset of dysphagia.

Conclusion: Cases with both HD and ALS have already been reported but not FOSMN and HD, to our knowledge. Some FOSMN cases have been linked to ALS-related gene mutations and HD phenocopies have been associated with C9ORF72 repeat expansions. Recently, huntingtin repeat expansions were described in the ALS population. Although a chance association cannot be excluded, data from the literature are in favor of a pathogenic relationship between FOSMN and HD in this particular case. We suggest that huntingtin gene be more systematically studied in patients with FOSMN.

More Information

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Introduction

Facial-onset sensory and motor neuronopathy (FOSMN) is a rare clinical syndrome characterized by trigeminal involvement and bulbar palsy that may progress to the limbs [1]. Onset of FOSMN is usually after the fourth decade, and the prognosis is variable, from months to decades. Some authors have suggested that FOSMN syndrome is an amyotrophic lateral sclerosis (ALS) variant as, first, most patients have a similar evolution and prognosis to ALS patients and, secondly, because a number of ALS-related gene mutations have been described in FOSMN cases [2-6]. We now present the case of a woman with typical FOSMN syndrome who developed generalized chorea and cognitive impairment 15 years after FOSMN onset. Genetic analysis revealed Huntington's disease (HD) with a Huntingtin (*HTT)* gene expansion.

Case report

A 62-year-old woman was first referred to our tertiary ALS center for dysphagia. She had been complaining of progressive difficulties eating and swallowing solid food and liquids for 8 years, and in the last 2 years her problems particularly worsened. She had no medical antecedents; her parents had died without any neurological disorder. Her usual weight was 56 kgs, and she weighed 53 at entry. Medical inquiry noted excess of saliva, difficulties for chewing and swallowing, dysgeusia and numbness of the right face accompanied by pain of the right face. First neurological examination in January 2010, found bilateral amyotrophy of temporal and masseter muscles, bilateral hypoesthesia of the face, including the lips, and bilateral corneal hypoesthesia. Examination

of the limbs was completely normal as was cognition. Electroneuromyography showed chronic denervation on the upper limbs and the tongue. Sensory and motor nerve conductions were normal. Blink reflex was bilaterally abolished. Somatosensory and auditory evoked potentials were normal, as were extensive biological investigations (blood, urine and cerebrospinal fluid). She gave written informed consent for genetic analysis including *C9ORF72* gene and a panel of 40 genes implicated in adult motor neuron diseases studied by new gene sequencing. Genetic analysis was normal as were magnetic resonance imaging of the brain and sublingual salivary gland biopsy. Spirometry gave normal results with, particularly, 99% slow vital capacity.

A diagnosis of FOSMN was made and she was proposed monthly infusions of intravenous immunoglobulin and amitriptyline for facial pain. In the 3 months following treatment initiation, facial pain disappeared and swallowing improved significantly as shown by nasofibroscopic exam. She gained 2 kgs.

Twelve months later, no more improvement could be noted, but facial pain did not resume. Conversely, excess of saliva increased, she developed bilateral corneal anesthesia, a dropped head and a right arm weakness. Fasciculations of the tongue were also present. The 2nd year after referral, dysphonia and dysphagia increased and she developed a right corneal ulcer that required a graft during the 3rd year, July 2013. Intravenous immunoglobulins were then stopped. On the 4th year, denutrition was present, she weighed 45 kgs, corresponding to a 16% loss from baseline weight, and corneal ulcer resumed despite the graft. Because of major excessive saliva despite local medication, a radiotherapy of the salivary glands was decided but was not efficient. Electroneuromyography, in January 2015, was unchanged as was spirometry.

The 5th year after referral, she developed gait difficulties in relation to axial weakness, and right visual acuity was less than 2/10e. As dysphagia and weight loss increased, she underwent gastrostomy. The 6th year she needed a rollator to walk. In June 2018, during the 7th year, she developed major anxiety, she frequently cried and also had sudden bursts of aggressive behavior. A new corneal graft was done but was unsuccessful, right visual acuity decreased to 0/10e. She could no longer walk and in November 2018 she developed chorea on the four limbs. Tetrabenazine treatment significantly reduced chorea. She had behavioural troubles as well as marked memory impairment. After verbal agreement by the patient and written consent by her husband, in February 2019, genetic analysis of the *HTT* gene was done and showed one abnormal allele with 38 repeats (normal < 36), confirming HD diagnosis. She died in October 2019.

Discussion

We present a case of FOSMN in a woman who later developed genetically proven HD, and discuss the relationships between those disorders. The co-occurrence of those rare disorders as well as the variabiliy of the phenotypes of HD, seemed in favor of a direct relationship. In the last 30 years, several cases associating ALS and HD have been reported, including in familial ALS cases [7,8]. However, to our knowledge, a co-occurrence of FOSMN syndrome and HD has never been described. This patient had almost all the features described in the FOSMN syndrome, including the recently described taste disturbance [9]. Her slow evolution is also classical both for FOSMN and HD, but the severity of corneal ulcer leading to blindness is unusual. Conversely, the clinical progression of the FOSMN syndrome in this patient well correspond to what is described in the literature, with progressive paralysis of the upper and then lower limb [1-4]. Psychiatric and cognitive involvement was late and preceded of a few months the occurrence of Chorea. Pathogenesis of the FOSMN syndrome remains unclear, but in several cases, gene mutations undoubtedly implicated in hereditary ALS pathogenesis, have been reported [4-6]. Almost all FOSMN cases have weakness, amyotrophy and fasciculations, and the analogy with ALS led to suggest that this rare syndrome is an ALS variant [2,3]. To date, none of the reported FOSMN cases carried a *C9ORF72* repeat expansion. Conversely, patients with HD phenocopies, e.g., no *HTT* repeat expansion, have been shown to carry an abnormal repeat expansion on the *C9ORF72* gene, expanding the phenotypes related to this hexanucleotide repeat which represents the most frequent genetic cause of familial and apparently sporadic ALS [10].

Once chorea appeared in our patient, the clinical presentation of HD was rather classic, with behavioral disorder and cognitive impairment. However, she had late-onset HD, which is known to be related to the limited *HTT* CAG expansion [11]. In patients with limited *HTT* repeat expansions and late HD, familial history is frequently lacking, leading to diagnostic errors or delays. Such errors or delays are also facilitated by the variability of symptoms at onset of HD, and even more when they are atypical [7,8,12]. Interestingly, ALS patients with *HTT* gene expansions have been recently described and had not only pathological features of HD, including neostriatal atrophy, but they also had TDP-43 pathology, a hallmark of ALS with or without frontotemporal lobe dementia [13]. TDP-43 has been implicated in various disorders linked to CAG repeats, including HD, but this RNA-binding protein is also implicated in typical FOSMN syndrome [14,15]. Taken together, although a chance association cannot be excluded, we believe that these arguments are in favor of a pathogenic relationship between FOSMN and HD in this particular case. The description of other HD cases with initial symptoms of ALS or ALS variants are warranted to support this hypothesis. To this aim, we also suggest that *HTT* gene be more systematically studied in patients with FOSMN.

Contributors

Clinical data: RJM, WC.

Writing of the manuscript: WC, ED, RJM.

Critical revision of the manuscript: ED, FE, NP, RJM, GT, WC.

Ethics: This work was approved by the Institutional Review Board of the CHU of Montpellier, number: IRB-MTP_2021_03_202100798.

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