A family with late onset and predominant choreic Niemann Pick type C: a treatable piece in the etiological puzzle of choreas.

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A family with late onset and predominat choreic Niemann Pick type C: a treatable piece in the etiological puzzle of choreas.

Niemman Pick type C (NPC) is a treatable neurodegenerative lysosomal disorder characterized by a widespread age of onset and clinical presentation. The adult NPC phenotype frequently includes ataxia, supranuclear gaze palsy, cognitive and behavioral problems [1]. Movement disorders are often observed in these patients too. Among them, chorea has been rarely described as a dominant sign [1, 2]. On the other hand, a phenotype dominated by chorea, cognitive and behavioral manifestations is suggestive of Huntington's disease [3, 4]. The rare cases, that showing this phenotype, proved to be negative for the CAG expansion in HTT are categorized as Huntington like disorders (HDL) [5]. Although the list of HDL genetic etiologies has grown considerably during the last years, the diagnostic yield for these conditions is still limited [3, 5]. Noteworthy, NPC is neither routinely considered in the differential diagnosis of chorea nor among the HDL disorders. We present here two siblings presenting

with a late onset and predominat choreic phenotype, where the final diagnosis was NPC.

CASE REPORT

Case I: A 58-year-old man was referred to our center for evaluation of an HDL disorder due to the presence of chorea, cognitive impairment, psychiatric symptoms and a normal molecular study for HD. He was healthy until the age of 40, when started a progressive complex neuropsychiatric disorder. Depressive mood and apathy were present at the beginning, whereas cognitive decline and visual hallucinations became evident during the first five years of disease. Neurological examination at our first consultation was remarkable for the presence of generalized chorea, inability to sustain tongue protrusion, slowed horizontal saccades and vertical supranuclear gaze palsy (VSGP) (Video 1). An abridged evaluation evidenced severe cognitive impairment as well. Magnetic resonance imaging (MRI) of the brain showed no abnormalities. Initial routine laboratory testing was uninformative. In a first instance, we ruled out HD finding a normal number of repeat expansions in both alleles (17 and 19 CAG repeats) of the HTT gene. Following our molecular diagnostic algorithm for HDL cases, we ruled out mutations in the *TBP* and C9*orf*72 genes as well.

Case II: The sister of case I was a 42-year-old woman with a previous diagnosis of schizophrenia at the age of 17 when she presented visual and auditory hallucinations. She was chronically treated with neuroleptics

with control of her psychiatric symptoms. She was free of other significant impairments until the age of 40, when she started with involuntary choreic movements in upper and lower limbs. Cognitive decline became evident a few months later. At the time of our first consultation, we found signs of severe cognitive impairment, slurred speech, slowed horizontal saccades, severe VSGP along a manifest impairment in maintaining motor postures and positions. Choreic movements were present in upper and lower limbs affecting also her gait (Video 2). MRI of the brain and initial laboratory testing were unremarkable.

The presence of VSGP in both patients, despite a predominat choreic phenotype, led us to rule out NPC. Accordingly, we assessed in the proband the concentration of the lyso-SM-509 biomarker in blood using HPLC-MS/MS (CentoGene). We found a marked increment in its levels. NPC was thereafter confirmed by Sanger sequencing of NPC1 gene, where we identified compound heterozygosity for two novel likely pathogenic variants (***c.1672G>A;p.Ala558Thr and c.3249_3250delGT;p.Phe1084Leufs*12***). Treatment with Miglustat (600mg/day) was started in case I.

DISCUSSION

We described here two siblings presenting a choreic and late onset NPC phenotype that were initially categorized as HD phenocopies. Chorea has been described in about 19% of NPC patients [1], however all previous reports have

described this involuntary movement as part of complex phenotypes that invariably include more typical features of NPC as predominant clinical manifestations, such as visceral compromise, dystonia or ataxia [1]. Furthermore, none of these cases were mentioned as an HDL. The prevalence of HD phenocopies is probably larger than previously thought [5]. Moreover, the list of its etiologies is heterogeneous and expanding. Even comprehensive approaches, investigating abnormalities in 63 genes in a cohort of patients presenting with HD phenotypes, have not included NPC1 and NPC2 as etiologic candidates [6]. Nevertheless, the majority of patients presenting initially as HDL progress to include clinical features that often are characteristic of the condition finally identified. We think that our patients showed this evolution too, where the appearance of VSGP was the key for suspecting and investigating NPC. It is present in about 75% of the adult form of NPC patients [1]. However, other neurodegenerative conditions show impairments in eye movements as well [7] Abnormalities in ocular motility and saccades are frequent in HD too [8]. The evaluation of HD patients typically show increased saccade latency and saccade slowing affecting both the vertical and horizontal planes [9].

NPC may be under-diagnosed due to its wide spectrum of clinical manifestations. Our cases highlight that NPC can mimic and should be considered in the diagnostic approach of patients of any age with a predominant choreic phenotype. Its recognition is of paramount importance for an early and correct diagnosis with a therapeutic relevance.

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Ethical Compliance Statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines. The authors confirm that the patient provided verbal and written consent. for this work but because this article is a case report no IRB approval was necessary.

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Legends for Supplemental files

Video 1. This video shows relevant finding in the neurological examination of both patients. Here, we could see the presence of distal chorea in upper limbs, motor impersistence that was clearly present when we asked them to protrude and sustain in that position their tongues and abnormal gaits where we could observe ataxia and chorea.

Video 2. This video shows main findings found during eye movement testing in case 1. Segment 1 shows the presence of abnormal horizontal and vertical smooth pursuit. Segment 2 shows the presence of abnormal saccade movements, whereas conjugate eye movements are preserved, defining supranuclear gaze palsy predominantly on the vertical plane.

Video 3. This video shows main findings found during eye movement testing in case 2. Segment 1 shows abnormal horizontal and vertical smooth pursuit. Segment 2 shows abnormal saccade movements, whereas vestibule ocular reflex was normal, defining supranuclear gaze palsy predominantly on the vertical plane.