Movement Disorders
CLINICAL PRACTICE

CASE REPORT

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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Niemman Pick type C (NPC) is a treatable neurodegenerative lysosomal disorder characterized by the widespread age of onset and clinical presentation. The adult NPC phenotype frequently includes ataxia, supranuclear gaze palsy, and cognitive and behavioral problems.[1] Movement disorders are also often observed in these patients. Among them, chorea has been rarely described as a dominant sign.[1,2] On the other hand, a phenotype dominated by chorea and cognitive and behavioral manifestations is suggestive of Huntington's disease (HD).[3,4] The rare cases showing this phenotype proved to be negative for the CAG expansion in *HTT* and are categorized as Huntington-like disorders (HDL).[5] Although the list of HDL genetic etiologies has grown considerably during the past few 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 2 siblings presenting with a late onset and predominate choreic phenotype, where the final diagnosis was NPC.

Case Report

Case 1

A 58-year-old man was referred to our center for evaluation of an HDL disorder as the result of the presence of chorea, cognitive impairment, psychiatric symptoms, and a normal molecular study for HD. He was healthy until the age of 40, when a progressive complex neuropsychiatric disorder started. Depressive mood and apathy were present at the beginning, whereas cognitive decline and visual hallucinations became evident during the first 5 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 S1). An abridged evaluation indicated severe cognitive impairment as well. Magnetic resonance imaging (MRI) of the brain showed no abnormalities. Initial routine laboratory testing was uninformative. 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 *C9orf72* genes as well.

Case 2

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 with visual and auditory hallucinations. She was chronically treated with neuroleptics for control of her psychiatric symptoms. She was free of other significant impairments until the age of 40, when involuntary choreic movements in the upper and lower limbs started. 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, and severe VSGP along a manifest impairment in maintaining motor postures and positions. Choreic movements were present in the upper and lower limbs also affecting her gait (Video S2). MRI of the brain and initial laboratory testing were unremarkable.

The presence of VSGP in both patients, despite a predominate choreic phenotype, led us to rule out NPC. Accordingly, we assessed in the proband the concentration of the lyso-SM-509

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Keywords: Niemann Pick type C, Huntington like, chorea, supranuclear gaze palsy.
Relevant disclosures and conflicts of interest are listed at the end of this article.
Received 25 November 2019; revised 22 January 2020; accepted 15 February 2020.
Published online 11 March 2020 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.12920

biomarker in blood using high-performance liquid chromatography/tandem mass spectrometry (CentoGene, AG (PB), Rostock, Germany). We found a marked increment in its levels. NPC was thereafter confirmed by Sanger sequencing of the *NPC1* gene, where we identified compound heterozygosity for 2 novel likely pathogenic variants *(c.1672G > A;p.Ala558Thr and c.3249_3250delGT;p.Phe1084Leufs*12)*. Treatment with miglustat (600 mg/day) was started in case 1.

Discussion

We described 2 siblings presenting with 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 as well, 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.[1] However, other neurodegenerative conditions show impairments in eye movements as well.[7] Abnormalities in ocular motility and saccades are frequent in HD as well.[8] The evaluation of HD patients typically shows increased saccade latency and saccade slowing affecting both the vertical and horizontal planes.[9]

NPC may be underdiagnosed because of 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.

Author Roles

(1) Manuscript Preparation: A. Writing of the First Draft, B. Review and Critique.

S.R.Q.: 1A, 1B
L.Z.: 1A, 1B
J.P.M.: 1A, 1B
D.G.-M.: 1B
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Disclosures

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 institutional review board approval was necessary.

Funding Sources and Conflict of Interest: No specific funding was received for this work. The authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for the Previous 12 Months: S.R.Q. has received scholarship support from Ministry of Health of Buenos Aires City. L.Z., D.G.-M., and N.G. declare that there are no additional disclosures to report. J.P.M. has received scholarship support from Argentinean National Science Council. M.A.K. has received grant support from Ministry of Health of Buenos Aires City, Argentinean National Science Council, and Argentinean Ministry of Science and Technology. He serves as associate editor of the journal *Neurologia Argentina*.

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Supporting Information

Supporting information may be found in the online version of this article.

Video S1. This video shows relevant finding in the neurological examination of both patients. Here, we 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 S2. This video shows the 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 S3. 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.