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CASE REPORT

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CASE REPORT

Facial Dystonia with Facial Grimacing and Vertical Gaze Palsy with "Round the Houses" Sign in a 29-Year-Old Woman

J. Crespi[a,b], G. Bråthen[a,b], P. Quist-Paulsen[b,c], J. Pagonabarraga[d], and C. Roig-Arnall[d]

[a]Department of Neurology, St Olav's Hospital, Trondheim, Norway; [b]Department of Neuroscience, Norwegian University of Science and Technology (NTNU), Trondheim, Norway; [c]Department of Hematology, St Olav's Hospital, Trondheim, Norway; [d]Department of Neurology, St Paus Hospital, Barcelona, Spain

ABSTRACT

A 29-year-old woman developed progressive dysarthria and balance and coordination problems from the age of 15. Examination showed dysarthria, facial dystonia, bibrachial dystonia, hyperreflexia, ataxia, and emotional incontinence. Downward supranuclear gaze palsy was prominent with a "Round the Houses" sign. Magnetic resonance imaging (MRI) of the brain and medulla, electroneurography, and cerebrospinal fluid were normal. A computed tomography (CT) scan showed hepatosplenomegaly. This combination of progressive neurological symptoms together with hepatosplenomegaly was suggestive of inborn error of metabolism. A bone marrow biopsy showed an increased number of macrophages with foamy content, which was highly suggestive of lysosomal storage disorder. Plasmatic chitotriosidase activity was increased (60 nkat/L). CCL18 (C-C motif ligand 18) was 172 µg/L (reference: <100 µg/L). Genetic testing showed heterozygosis for the variation c.1070C→T (p.Ser357Leu) and c.1843→T (Arg615Cys), confirming the diagnosis of Niemann-Pick type C (NPC). The disease prevalence is around 1 in 150,000. The "Round the Houses" sign has only been described in patients with progressive supranuclear palsy (PSP). This sign is described as an inability to produce pure vertical saccades along the midline and instead moving the eyes in a lateral arc to accomplish the movement. The observation of this sign in a patient with NPC indicates that this interesting bedside finding is not specific for PSP, but a sign of medial longitudinal fasciculus (riMLF) dysfunction. The presence of facial dystonia with facial grimacing together with a supranuclear gaze palsy is highly characteristic and useful for the diagnosis of NPC. NPC is an important differential diagnose given the availability of treatment and that the mean diagnostic delay is around 6 years.

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CONTACT J. Crespi, MD joan.crespi@ntnu.no Department of Neurology, St Olav's Hospital, Prinsesse Kristinas gate 3, 7030 Trondheim, Norway.

Introduction

Niemann-Pick type C (NPC) is thought to be an underdiagnosed condition (the disease prevalence is around 1 in 150,000, but the real prevalence is probably higher, around 1 in 120,000 live births).[1] Its diagnosis is often a challenge, since the clinical presentation is heterogeneous and most patients have normal routine examinations (magnetic resonance imaging [MRI], cerebrospinal fluid [CSF], electrophysiology, etc.), thus delaying the start of treatment several years.[2] We present the case of a 29-year-old woman where the neuro-ophthalmological findings were the key to confirm the diagnosis. We also describe a new neuro-ophthalmological finding in NPC.

Case report

A 29-year-old woman developed slowly progressing dysarthria from the age of 15. Around the age of 20, she began to experience problems with balance. After 5 years from disease onset, the dysarthria caused social withdrawal and she limited contact to her closest relatives. She had a normal childhood, reached normal developmental milestones, managed to finish high school, and started vocational studies in graphic design. However, she could not finish her studies because of low performance and never managed to work, currently receiving social security benefits. Since the age of 20, cognitive and behavioural symptoms developed slowly. She became more introverted. Approximately 10 years after the onset of dysarthria, she complained of coordination problems with her hands. She had a normal pregnancy at the age of 26. The last year before being examined in our department she managed to perform most daily activities but needed additional help from her family to take care of her child.

She did not have a significant family history.

Clinical examination found a patient with a body mass index of 16.37 kg/m^2. She was well oriented and gave a slightly childish contact. There was pronounced dysarthria and facial dystonia with facial grimacing. Postural and action bibrachial dystonia was noticed, with left-sided predominance and major involvement of distal muscle groups. She had hyperreflexia and Hoffmann's sign was positive bilaterally. Truncal ataxia was evidenced during normal and tandem gait. During the examination, the patient appeared emotionally incontinent.

Following a closer examination of eye movements, even though smooth pursuit was normal, there was a clear limitation to trigger saccades in the vertical plane. Specifically, downward supranuclear gaze palsy was prominent, and corrective horizontal saccades were needed to accomplish upward voluntary saccadic movements ("Round the Houses" sign; Video 1).[3] The rest of the cranial nerves appeared normal. Muscle balance, coordination, and all

modalities of sensation were not affected. Neuropsychological tests showed a diffuse dysfunction of multiple cognitive domains, pronounced dysexecutive syndrome, and hypoprosexia.

MRI of the brain and medulla performed in the referring centre and in our hospital were normal. Electroneurography and electromyography did not show any pathological findings. The cerebrospinal fluid was normal. The blood tests showed a slight thrombopenia (110×10^9/L). An abdominal computed tomography (CT) scan showed mild hepatomegaly and splenomegaly, not evidenced during abdominal examination. Electroencephalography (EEG) showed unspecific slowing that was most prominent in the frontotemporal lobes.

This clinical findings combined with hepatosplenomegaly were suggestive of inborn error of metabolism. A bone marrow biopsy was then performed, which showed an increased number of macrophages with a foamy content (Figure 1).

No Gaucher cells were observed. This finding was suggestive of a lysosomal storage disorder. Combining the clinical picture with the pathology, Niemann-Pick type C (NPC) was suspected. Plasmatic chitotriosidase activity was increased (60 nkat/L; reference: 40 nkat/L). The chemokin CCL18 (C-C motif ligand 18) was 172 µg/L in our patient (reference: <100 g/L). Both biomarkers have been described to be increased in NPC.[1,4]

Genetic testing showed that the patient is heterozygote for the variation c.1070C→T (p.Ser357Leu) and c.1843→T (Arg615Cys), confirming the diagnosis of NPC. The variant p.Ser357Leu has been described by Saito et al.,[5] and the variant Arg615Cys has also been described on several occasions.[6]

The patient was prescribed miglustat (*N*-butyldeoxynojirimycin), which is a glucosylceramidase synthase inhibitor.[7]

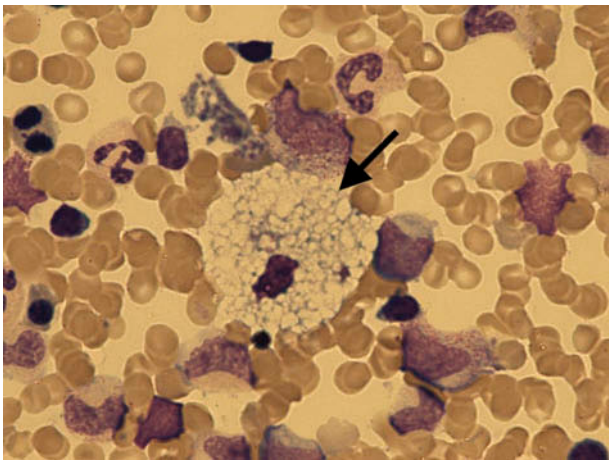

Figure 1. Bone marrow biopsy showing increased amount of macrophages, some of them with foamy cytoplasm (arrow). May-Grunwald-Giemsa staining; magnification: 1000×.

Discussion

NPC is an autosomal recessive lysosomal storage disease. Most of the patients have a mutation in NPC1 (95%) or NPC2 gene.[1] The disease prevalence is around 1 in 150,000, but the real prevalence is probably higher, around 1 in 120,000 live births.[1]

Eye movement disturbances in NPC are highly characteristic. The mechanism is due to damage of the nuclei in the brainstem responsible to generate saccades, but also due to affection of the prefrontal areas, which control these nuclei.[8] NPC can also affect horizontal saccades, but this is much less frequent. This suggests that the cell loss or dysfunction is more severe in the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), which contains neurons responsible for triggering saccades in the vertical plan, than in the paramedian pontine reticular formation, which is responsible for saccades in the horizontal plane. As far as we know, the "Round the Houses" sign has only been described in patients with progressive supranuclear palsy (PSP). Rottach et al. described a hypometria in saccades that was considerably more pronounced in the vertical plane in patients with pure akinesia and PSP, producing a curved course of oblique saccades. Shortly after, Quin described the "Round the Houses" sign as an inability to produce pure vertical saccades along the midline and instead moving the eyes in a lateral arc to accomplish the movement.[3] This sign uses the plural form "Houses" as an analogy to each eye making a round excursion in its own "house" (each orbit). The observation of this sign in a patient with NPC indicates that this interesting bedside finding is not specific for PSP, but a sign of riMLF dysfunction.

The presence of facial dystonia with facial grimacing together with a supranuclear gaze palsy is highly characteristic and useful for the diagnosis of NPC. NPC is an important differential diagnose when confronted with the symptomatology described here, especially given the availability of promising treatment and that the mean diagnostic delay is around 6 years.[2] There are several clinical trials currently recruiting patients with NPC for intrathecal cyclodextrin and oral heat shock protein 70, bringing new hope for the treatment of lysosomal disorders.

Learning points

- In a patient with neurological impairment and hepatosplenomegaly, an inborn error of metabolism should always be ruled out.
- Eye movement examination should always include saccades. In the patient we present, *smooth pursuit* was normal and the finding of supranuclear gaze palsy was solely based on the observation that she could not trigger normal saccades in the vertical plane.

- The finding of vertical gaze palsy is highly characteristic and extremely helpful to limit the differential diagnoses.
- Common causes of vertical gaze palsy include NPC, Wilson's disease, some spinocerebellar ataxias, neuroacanthocytosis, Huntington's disease, mitochondrial disease, and Whipple's disease. Supranuclear gaze palsy with parkinsonism is a key feature in progressive supranuclear palsy, but can also be seen in corticobasal degeneration, dementia with Lewy bodies and multiple system atrophy.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

Note

Video 1 is available online at

References

[1] Wraith JE, Baumgartner MR, Bembi B, Covanis A, Levade T, Mengel E, Pineda M, Sedel F, Topcu M,Vanier MT, Widner H, Wijburg FA, Patterson M. Recommendations on the diagnosis and management of Niemann-Pick disease type C. *Mol Genet Metab* 2009;98:152–165.

[2] Wijburg FA, Sedel F, Pineda M. Development of a Suspicion Index to aid diagnosis of Niemann-Pick disease type C. *Neurology* 2012;78:1560–1567.

[3] Quinn N. The "Round the Houses" sign in progressive supranuclear palsy. *Ann Neurol* 1996;40:xx–xx.

[4] Chang KL, Hwu WL, Yeh HY, Lee NC, Chien YH. CCL18 as an alternative marker in Gaucher and Niemann-Pick disease with chitotriosidase deficiency. *Blood Cells Mol Dis* 2010;44:38–40.

[5] Saito Y, Suzuki K, Nanba E, Yamamoto T, Ohno K, Murayama S. Niemann-Pick type C disease: accelerated neurofibrillary tangle formation and amyloid beta deposition associated with apolipoprotein E epsilon 4 homozygosity. *Ann Neurol* 2002;52:351–355.

[6] Park WD, O`Brien JF, Lundquist PA, Kraft DL, Vockley CW, Karnes PS, Patterson MC, Snow K. Identification of 58 novel mutations in Niemann-Pick disease type C: correlation with biochemical phenotype and importance of PTC1-like domains in NPC1. *Hum Mutat* 2003;22:313–325.

[7] Patterson M, Vecchio D, Prady H, Abel L, Wraith JE. Miglustat for treatment of Niemann-Pick C disease: a randomised controlled study. *Lancet Neurol* 2007;6:765–772.

[8] Abel LA, Walterfang M, Fietz. Saccades in adult Niemann-Pick disease type C reflect frontal brainstem, and biochemical deficits. *Neurology* 2009;72;1083–1086.