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Tremor and Other Hyperkinetic Movements

Video Abstracts

Abnormal Vertical Eye Movements as a Clue for Diagnosis of Niemann–Pick Type C

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Abstract

Background: Adult-onset Niemann–Pick Type C is a rare neurogenetic lysosomal disorder, whose diagnosis is often delayed and missed because of its heterogeneous clinical presentations and rarity as well as the lack of awareness of characteristic eye findings among neurologists.

Phenomenology Shown: Impaired smooth pursuits, saccades, and optokinetic nystagmus in the vertical direction, with relatively normal eye movements in the horizontal direction, and ataxia features on finger chase testing, tandem walking, and gait ataxia.

Educational Value: Impairment of vertical eye movements in combination with ataxia, cognitive impairment, and/or psychiatric symptoms in an adult patient should always raise clinical suspicion of Niemann–Pick Type C.

Keywords: Niemann–Pick type C, cerebellar ataxia, eye movements

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Ethics Statement: All patients that appear on video have provided written informed consent; authorization for the videotaping and for publication of the videotape was provided.

A 30-year-old male with unremarkable birth history had poor coordination since childhood and below-average school performance. He developed delusions at the age of 21, for which he was treated with bupropion and aripiprazole. At the age of 23, he developed memory difficulty, hand tremor, loss of hand dexterity, and imbalance with occasional falls. He also developed slurred speech at the age of 28. His neurological examination showed impaired smooth pursuit, saccades, and optokinetic nystagmus in the vertical direction with relatively preserved horizontal eye movements (Video 1). The impaired eye movements were even more prominent in the downward direction than the upward direction. He also had cognitive impairment (Montreal Cognitive Assessment score of 19: he lost 2 points in visuospatial/executive, 2 points in attention, 5 points in delayed recall, and 2 points in orientation), mild dysarthria, and features of cerebellar ataxia.

Routine laboratory testing revealed a reduced platelet count of 122,000 per μL, and an ultrasound showed splenomegaly. A brain magnetic resonance imaging (MRI) scan showed cerebellar atrophy with pontine and medullary atrophy. Targeted genetic testing showed bi-allelic mutations in the *NPC1* gene: c.3265 G>A, (E1089K) and c.2903 A>G, (N968S); both mutations have been reported in patients with a classical biochemical phenotype of Niemann–Pick type C (NPC).[1,2] No mutations were detected in the *NPC2* gene. Subsequently, his brother, who also reportedly exhibited cognitive symptoms and lack of coordination, was also found to carry these two mutations in *NPC1*.

Impaired vertical eye movements, in combination with cerebellar ataxia, cognitive impairment, and/or psychiatric symptoms, are pathognomonic for NPC.[3] Other considerations for vertical eye movements include progressive supranuclear palsy and Whipple's disease. NPC is a rare lysosomal storage disorder caused by mutations in either *NPC1* (~95% of cases) or *NPC2* (~5% of cases), which lead to abnormal intracellular lipid trafficking and accumulation. NPC most commonly manifests in middle to late childhood after normal development; however, neonatal and adult onset may also occur. In addition to the above-mentioned symptoms, NPC patients may exhibit dystonia, myoclonus, parkinsonism, and gelastic cataplexia, which are not present in our patient.

Video 1. **Vertical eye movements and ataxia features in Niemann-Pick Type C**. The patient had relatively intact horizontal smooth pursuit, saccades, and optokinetic nystagmus. However, these eye movements in the vertical direction were impaired. In addition, the downward smooth pursuit was slower than the upward smooth pursuit. The patient also exhibited features of cerebellar ataxia as characterized by abnormal finger chase test, tandem walking, and gait ataxia.

Although no curative therapies are currently available for treatment of NPC, early detection is important as patients can be offered treatments with potential disease-modifying agents. These include miglustat,[4] which reduces the synthesis of glycolipids by inhibiting glucosylceramide synthase and possibly slows disease progression, and arimoclomol,[5] which is a co-inducer of heat shock protein and was recently granted rare pediatric disease designation by the US Food and Drug Administration for the treatment of NPC.

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