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Clinical Reasoning: Psychomotor regression in the young

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SECTION 1

A 38-year-old right-handed man was referred for investigation of a 20-year history of progressive behavior change and involuntary movements. Symptom onset was in his late teens. Up until that time he had achieved age-appropriate motor and cognitive milestones and had completed normal schooling. There was no family history of dementia or movement disorders.

Initially, family members noted deterioration in his gait, which became increasingly imbalanced and clumsy. By the age of 20, speech and cognitive difficulties emerged. His speech was dysarthric with reduced output. By 25 years of age, he was noted to be inattentive at work. A decline in short-term memory and safety awareness was also noted by coworkers. After several episodes of inappropriate behavior, he was referred to psychiatric services. By age 30, he was deemed unfit for work. Over the next 8 years, further symptoms emerged: involuntary movements of his upper limbs, dysphagia, and episodes of apparent collapse after raucous laughter. At age 38, he was admitted to the hospital after an episode of unwitnessed collapse, presumed to be a seizure. Head CT confirmed a subdural hematoma requiring evacuation. After recovery, his examination demonstrated generalized chorea, past-pointing and dysarthria, limb and gait ataxia, and impaired vertical gaze eye movements. His Mini-Mental State Examination score was 14/30, with 0/3 recall at 5 minutes.

Questions to consider:

1. What is the differential diagnosis?
2. What are the important examination findings?

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SECTION 2

The patient is a young man with a 20-year history of progressive decline in cognition, behavior, and motor function. An important initial step in the evaluation of this clinical scenario is to distinguish between a progressive psychomotor decline, as in this case, and a static encephalopathy.

Static encephalopathies can be broadly classified into antenatal insults (infections [cytomegalovirus, herpes simplex virus, rubella], toxins [alcohol, cocaine]) and perinatal (hypoxic-ischemic encephalopathy, hyperbilirubinemia). It is also important to determine the point at which regression began, and the evolution of the psychomotor symptomatology; were age-appropriate milestones achieved (figure)? In this case, the patient achieved age-appropriate motor and cognitive milestones and thereafter experienced psychomotor regression. The slowly progressive nature of symptoms suggests a degenerative condition. The age at onset in the second decade of life and apparent absence of family history might be consistent with an autosomal recessive condition, rather than an autosomal dominant condition.

When considering a differential diagnosis for early-onset cognitive impairment, it is useful to identify associated neurologic features (figure).

Many of the listed conditions may be deemed unlikely given the mode of inheritance (Huntington disease and similar disorders, spinocerebellar ataxia, dentatorubral pallidoluysian atrophy) whereas others may require specific investigation. A paraneoplastic or autoimmune disorder is most unlikely given the slow evolution of symptoms.

An important finding on clinical examination was the presence of a vertical supranuclear gaze palsy. This sign narrows the differential diagnosis considerably in a patient presenting with ataxia and chorea (figure).

Although not present in this patient, splenomegaly is an important clinical feature to exclude in a young patient presenting with a mixed movement disorder and a key finding in generating a differential diagnosis.

Question to consider:

1.What testing would you perform?

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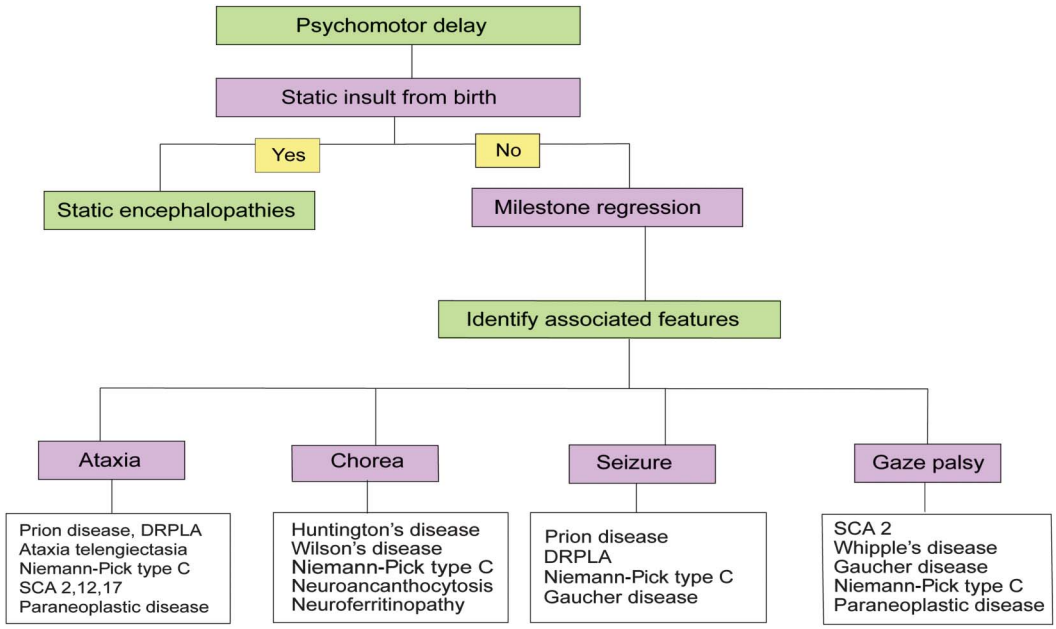
Figure **Psychomotor delay: Differential diagnosis**



DRPLA = dentatorubral pallidoluysian atrophy; SCA = spinocerebellar ataxia.

SECTION 3

The combination of progressive cognitive decline, ataxia, chorea, and vertical gaze impairment all suggest a diagnosis of Niemann-Pick disease, type C (NP-C). Therefore, genetic testing for NP-C and a skin biopsy should be performed. We identified our patient as having a compound heterozygote mutation for the *NPC1* gene. A skin biopsy demonstrated polymorphic cytoplasmic bodies on electron microscopy, pathognomonic of NP-C.

Vertical supranuclear gaze palsy is an important clinical sign and invariably present in this disorder when there are neurologic manifestations beyond infancy. It is also the first neurologic sign to develop in individuals who present with organomegaly. The history also provides a useful clue of gelastic cataplexy (muscle atonia after episodes of heightened emotion).

NP-C is an autosomal recessive, inherited, lysosomal storage disorder. The condition results from a defect in intracellular lipid trafficking. Mutations have been identified in 2 genes: *NPC1* (chromosome 18q11-q12) (94%) and *NPC2* (chromosome 14q24.3) (5%).[1]

Impaired function of *NPC1* and *NPC2* is associated with excess accumulation of free cholesterol and glycosphingolipid in endosomal intracellular compartments, including the brain.[2] There is no difference in clinical presentation between *NPC1* and *NPC2*.

Clinical presentation, disease progression, and severity are strongly influenced by age at onset of neurologic symptoms. Presentation in early infancy is marked by delayed developmental motor milestones. Juvenile onset, as in our case, presents with gait problems, falls, clumsiness, cataplexy, and cognitive problems. Adult onset presents predominantly with neuropsychiatric disease manifestations.[2,3]

Question to consider:

1. How would you treat this patient?

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SECTION 4

Until recently, the treatment for NP-C was supportive, addressing symptomatology including seizures, dystonia, tremor, behavioral problems, and gelastic cataplexy. Our patient was treated with levetiracetam for control of seizures and haloperidol to manage choreiform movements.

Miglustat, an iminosugar successfully used in other lysosomal storage disorders, namely Gaucher type 1, has recently been approved for use in NP-C.[4] Iminosugars are small molecules that mimic monosaccharides but contain a nitrogen atom in place of the endocyclic oxygen. Miglustat acts by reversibly inhibiting glucosylceramide synthase, which catalyzes the first step of glycosphingolipid synthesis.[4,5] Miglustat crosses the blood-brain barrier, reduces glucosylceramide synthase, and has demonstrated efficacy in delaying the onset of neurologic symptoms, stabilizing neurologic manifestations of the disease, and prolonging survival.[5] Our patient has since commenced miglustat and his neurologic symptoms were stable at his last clinical review.

Of note, miglustat is approved for use in NP-C in 42 countries, but not in the United States.

DISCUSSION This case reminds us that when assessing young patients with cognitive decline, we must first distinguish static encephalopathies from progressive encephalopathies, and second, differentiate psychomotor delay from regression. Clues from the history provide valuable information regarding the underlying process, e.g., young onset and absence of family history are more consistent with autosomal recessive inheritance (or X-linked in males), and a progressive evolution of symptoms is consistent with neurodegeneration. Careful attention to seemingly bizarre phenomena, such as gelastic cataplexy, can inform the diagnosis. Finally, the pattern of neurologic system involvement (chorea, seizure, vertical gaze, palsy) narrows the differential diagnosis further.

Early-onset cognitive and motor impairment, especially with movement disorders such as ataxia, chorea, or dystonia, in the presence of vertical gaze impairment suggests NP-C.

AUTHOR CONTRIBUTIONS

Dr. Eavan Mc Govern: acquisition of case history information, composition of case history and discussion. Dr. Timothy Counihan: critical revision of the manuscript, supervision of the case history and discussion.

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DISCLOSURE

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REFERENCES

1. Patterson MC, Hendriksz CJ, Walterfang M, Sedel F, Vanier MT, Wijburg F; NP-C Guidelines Working Group. Recommendations for the diagnosis and management of Niemann-Pick disease type C: an update. Mol Genet Metab 2012;106:330–344.
2. Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis 2010;5:16.
3. Wijburg FA, Sedel F, Pineda M, et al. Development of a suspicion index to aid diagnosis of Niemann-Pick disease type C. Neurology 2012;78:1560–1567.
4. Patterson MC, 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.
5. Wraith JE, Vecchio D, Jacklin E, et al. Miglustat in adult and juvenile patients with Niemann-Pick disease type C: long-term data from a clinical trial. Mol Genet Metab 2010;99:351–357.

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