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The mind's eye: A neuro-ophthalmological perspective on Niemann-Pick type C disease

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Niemann-Pick disease type C (NPC) is a rare autosomal recessive genetic disease caused by mutations in the NPC1 and NPC2 genes with an estimated incidence of 1:120 000 live births. The clinical presentations vary across the ages. Children present with visceral symptoms related to cholesterol accumulation in the liver and adults have predominantly neuropsychiatric features such as dementia. However, vertical supranuclear gaze palsy can be present from the first year of life and is a strong feature in the diagnosis of NPC, which can be confirmed by a skin biopsy. A 36-year-old female with long-standing depression was referred for an evaluation of dystonia. She had progressive cognitive decline, dysarthria, dysphonia, dystonia of the trunk and limbs, ataxia and supranuclear gaze palsy. A similar course of illness affected her brother. Her parents were first cousins. She had positive Filipin stain of fibroblasts cultured from her skin biopsy, confirming the diagnosis of NPC. Miglustat, the approved drug for treatment, was not accessible. She had been on simvastatin since diagnosis, with a poor response, and had ongoing severe cognitive and physical disability. There are few conditions that present with neuropsychiatric symptoms and supranuclear gaze palsy. This patient had been managed as chronic depression with psychosis since her teenage years and her diagnosis was reviewed only when she had developed dystonia. Supranuclear gaze palsy is an early diagnostic clinical clue that could be present from infancy and should be sought in patients with neurocognitive presentations.

Keywords: Niemann-Pick disease type C; vertical supranuclear gaze palsy; miglustat; psychosis; ocular motility.

Introduction

The origin of the famous phrase 'The eyes are a window to your soul' is unknown. Much credit needs to be given to the originator, for little did he or she realise how true that sentiment would be to practitioners of the neurosciences. At the risk of being too humanistic, perhaps that reference to the soul would be better substituted for the mind or brain – much safer ground for the clinician. In fact, the beauty of examining the eyes transcends the beholder. It is unfortunate, nonetheless, that current practitioners deny their skills and focus rather on the patient's immediate needs. We are governed by time and time is money. A full neuro-ophthalmological examination is relegated to our distant past when time was a luxury, for some in training, and when the full examination was compulsory. The secret, however, lies in the eyes, where a thorough assessment is most revealing in some patients. A brief but focused assessment saves nine …

Case report

Miss A is a 36-year-old female who has been treated for depression since she was 16 years old, when her mood and behaviour had changed soon after the death of her older brother who drowned while on a family holiday. For 20 years, she has been treated with various antidepressant regimens and risperidone for psychotic features, to which her mood responded poorly. In the last 5 years, she developed clumsiness and weakness of both upper limbs and needed assistance with all the activities of daily living. She began having frequent falls owing to poor balance. A cognitive decline was evidenced by increasing forgetfulness and problems in decision-making. She had word-finding difficulty and her speech became slurred and indistinct. There was general slowness to her psychomotor functioning, which was always attributed to her low mood. Of equal concern was the occurrence of a generalised tonic clonic seizure prior to her admission. From the fall that ensued, she fractured her nasal bone.

Communication with her caregiver was declining. She would close her eyes frequently when attempting to change her direction of gaze. Visual acuity seemed relatively preserved. She had no

difficulty with hearing or sphincter control. Dysphagia to solids and liquids was present, complicated frequently by aspiration pneumonia. Her appetite declined and weight loss was inevitable. She had performed satisfactorily at school prior to the onset of depression, because of which she quit school at the age of 16 years.

The patient's parents are first cousins. Her younger brother had also suffered a neurodegenerative condition, suspected to be Huntington's disease, manifesting with cognitive decline and a movement disorder. His demise, 5 years ago, precipitated the worsening of Miss A's depression with psychotic features. She had no other medical disorders and had normal developmental milestones.

On examination, she had a childlike demeanour and depressed affect but was not psychotic. She was emaciated. The examination of the chest, spine, cardiovascular system and abdomen was normal. She had severe dementia with a mini-mental score of 12/30. She was inattentive and easily distracted. Her insight and judgement were poor. Immediate recall, short-term and remote memory were poor. Her speech was slow and slurred with content that was mostly inappropriate and irrelevant.

A formal assessment of visual testing was unreliable because of her reduced attention span. A corneal examination did not reveal Kaiser–Fleischer (KF) rings. Her pupils and funduscopy were normal. An assessment of ocular movements revealed a marked limitation of vertical gaze on saccadic and pursuit testing (Figure 1). The vestibulo-ocular reflex (VOR), however, was preserved, suggesting vertical supranuclear gaze palsy. On attempted vertical gaze, she would close her eyes and swing her head to allow the VOR to move her eyes.

Marked dystonia of her tongue and both hands at rest were noted (Figure 2). She had right head tilt and hyper-extension of her trunk when walking. Her strength and reflexes were normal. There were no primitive reflexes, and plantar responses were flexor bilaterally. She had no axial or appendicular rigidity or cogwheeling to suggest Parkinsonism. Sensation to pain and light touch was normal, but the other modalities, including cortical sensory modalities, could not be assessed reliably. Her co-ordination was poor and gait was ataxic.

In summary, a 36-year-old female presented with chronic depression with psychotic features, progressive cognitive decline, dystonia of the upper limbs, tongue and trunk and, most significantly, profound vertical supranuclear gaze palsy. Her parents are consanguineously related and there is a possible history of Huntington's disease in her late brother, but no genetic testing results could be traced.

Vertical supranuclear gaze palsy is a leading clinical sign that points to specific diagnoses, namely, progressive supranuclear palsy (PSP), Parinaud's syndrome and inherited neurodegenerative disorders such as Niemann-Pick disease type C (NPC).

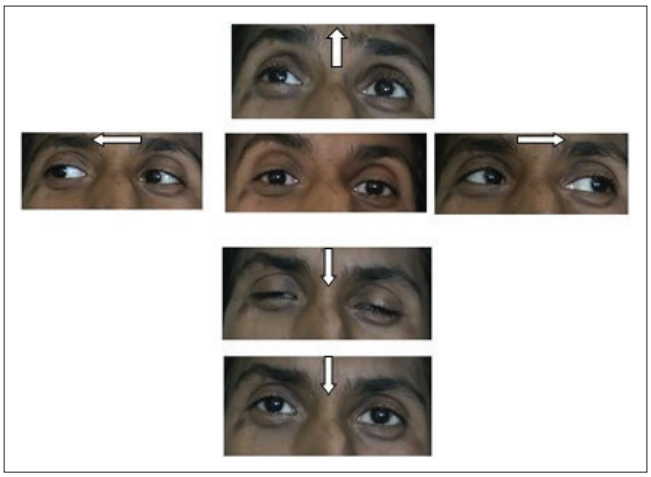


FIGURE 1: Testing of ocular movements showing full range of horizontal gaze but limited vertical gaze. Downgaze is affected more than upgaze. The arrows show the direction of gaze instructed by the examiner. Downward gaze is shown in the bottom two pictures: the first shows her attempting downgaze and the second shows the limitation.

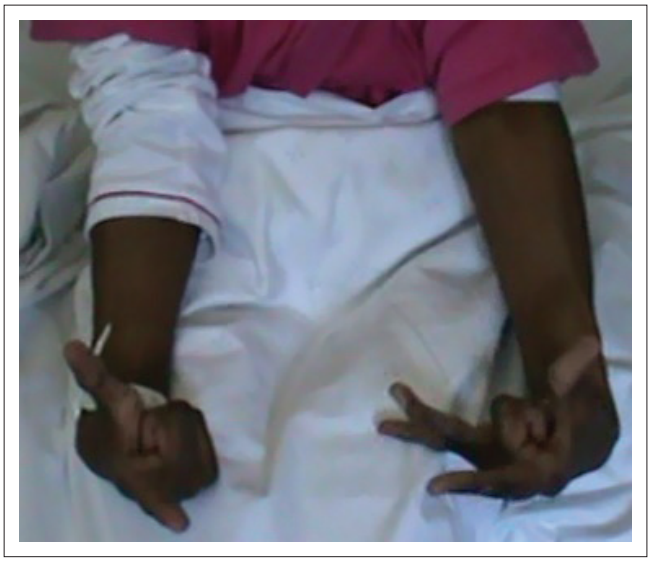


FIGURE 2: Marked dystonia of both hands.

Magnetic resonance imaging of the brain showed generalised, non-specific cerebral and cerebellar atrophy. There were no midbrain features to support PSP or Parinaud's syndrome. Serum copper and caeruloplasmin were normal. A slit lamp examination of the cornea did not show KF rings, and genetic testing for Huntington's disease was negative. A skin biopsy taken from her forearm was positive on Filipin staining of cholesterol-laden fibroblasts, consistent with the diagnosis of NPC. Miglustat, the treatment drug, was not affordable for the patient, was not provided by the healthcare service and sponsorship could not be found. Simvastatin was available, but the advanced nature of her disease probably resulted in a poor response and she continues to have severe cognitive and physical disability.

Discussion

Niemann-Pick disease type C is a rare autosomal recessive lysosomal storage disorder that can present at any age, including adulthood.[1,2] Niemann-Pick disease type C is

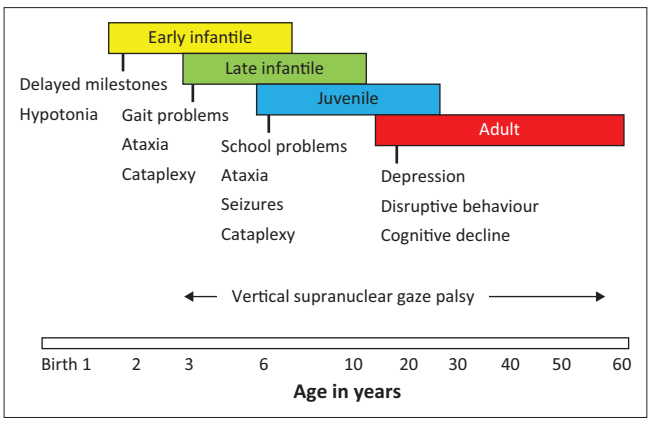
because of mutations in the NPC 1 (95%) and NPC 2 (5%) genes. There is an intracellular lipid transportation defect leading to an accumulation of cholesterol that cannot exit the lysosome, followed by disturbances of sphingolipids, phospholipids and sphingomyelin in the spleen, liver and central nervous system. Niemann-Pick disease types A and B present early in life with spleen and liver involvement. Type C tends to have a neuropsychiatric presentation in adults with vertical supranuclear gaze palsy, ataxia, bulbar dysfunction, dystonia, seizures, cognitive decline, psychosis, disruptive behaviour and depression. In younger patients, hypotonia and delayed developmental milestones have been noted.[2] An early diagnostic clue to NPC is the presence of vertical gaze palsy which is evident to varying degrees, even from infancy (Figure 3)[1].

The diagnosis of NPC can be confirmed by gene sequencing, Filipin staining of cultured skin fibroblasts to show cholesterol accumulation,[3] the detection of cholestanetriol by gas chromatography with mass spectrometry[4] and even the measurement of bile acid biomarkers in newborn dried blood spots.[5] In South Africa, molecular gene sequencing for NPC is not available, and Filipin staining of cultured skin fibroblasts was done for this patient.

Early diagnosis is vital as miglustat, a glucosylceramide synthase inhibitor approved in Europe since 2009 for the treatment of NPC, is beneficial.[6] This prevents the synthesis and accumulation of intracellular glycosphingolipids and has been shown to slow or prevent the neurological progression of the disease. Statins can also provide some benefit but only in early and mild disease.

The clinical clues to the disorder therefore cannot be overemphasised. A quick evaluation of horizontal and vertical eye movements is important. The supranuclear vertical gaze palsy is detected on saccadic testing initially, with slowed vertical saccades and preserved VORs. However, in the late stages, saccades, pursuit and VOR are significantly impaired.

Few disorders present with gaze palsies. Vertical gaze palsy is seen in dorsal midbrain lesions, PSP and NPC, whereas isolated horizontal gaze palsy is common in pontine lesions such as pontine glioma, brainstem haemorrhage and Gaucher's type 3. An impairment of both vertical and horizontal gaze is seen in the late stages of PSP, NPC and Gaucher's type 3.[7]



Source: Adapted from Vanier MT. Niemann-Pick disease type C. Orphanet J Rare Dis. 2010;5:16.

FIGURE 3: Neurological involvement in Niemann-Pick disease type C, with emphasis on type and age of onset of neuropsychiatric signs and symptoms.

Eye movement abnormalities in psychiatric disease are common but under-detected primarily because of their lack of specificity. Nonetheless, impaired smooth pursuit, slow saccades, saccadic dysmetria and vergence tracking deficits have been described in schizophrenia and major depression. Saccadic (or interrupted) pursuit is a common accompaniment of HIV-associated neurocognitive disorder. In Huntington's disease, slow saccades in the presence of chorea and dementia are an important clue to the diagnosis. Tricyclic antidepressants, benzodiazepines and anticonvulsants can induce ocular motility disorders such as nystagmus, saccadic pursuit and overt external ophthalmoplegia.

An examination of the full range of eye movements, cursory or otherwise, is routinely performed during a neurological examination to exclude third, fourth or sixth nerve palsies. However, examining the supranuclear control of eye movements, which is more relevant to the functioning of the brain, is often omitted owing to a lack of appreciation of their importance or a lack of knowledge of the pathways and mode of testing. In essence, the performance of supranuclear examination is not as time-consuming as one would fear, but is rapidly assessed with simple manoeuvres.

An examination of fixation, saccades, smooth pursuit and the vestibulo-ocular reflex provides valuable information about the functioning of the frontal lobes, the parieto-occipital-temporal (POT) junction, the brainstem, the cerebellum and the vestibular apparatus (Table 1). The optokinetic nystagmus and vergence testing are also systems of supranuclear gaze control, but are of less localising or functional value.[8] An assessment of the supranuclear control of eye movements should include the following:

- *Fixation*, as the name implies, is tested by maintaining a steady gaze on a stationary target. Poor fixation has been described in schizophrenia and interrupting square wave jerks are seen in PSP.
- *Saccadic eye movement* testing involves an assessment of rapid fixation between two targets held 20 cm – 30 cm apart in both the horizontal and vertical directions (Figure 4a and 4b). The latency, speed and accuracy of saccadic eye movement can be simply evaluated.

TABLE 1: Overview of the ocular motor examination.

Type of examination	Question
Eye position in primary gaze	Vertical or horizontal misalignment. Fixation on a target; square wave jerks; nystagmus
Ocular motility	Range of motility in eight positions. Gaze evoked nystagmus
Saccades	Horizontal and vertical saccades. Latency, speed and accuracy
Pursuit	Smooth or saccadic interruptions
VOR	Unilateral or bilateral vestibular deficit

VOR, vestibulo-ocular reflex.

Note: This is a demonstration of how testing is done with a test subject, Dr C.D Wells, as mentioned in the Acknowledgements' section.

FIGURE 4: (a and b) Quick saccadic movements between two horizontal targets. (c and d) The vestibulo-ocular reflex in both directions. (e) Anti-saccadic movements made opposite to the finger wiggled.

At speeds of over 700 degrees per second, saccades are too quick to follow and are therefore seen at the start and end when targets are reached. If there is a delay at onset, slowness of movement or overshooting and undershooting and abnormal saccades are immediately appreciated. Saccadic re-fixation from inaccuracy is a telltale sign of cerebellar dysfunction, whereas slowed saccades are seen in neurodegenerative and storage diseases as well as neuromuscular disorders of the external ocular motor system. An increased latency of saccades is appreciated in ocular motor apraxia, where there is a delay in the onset of saccadic movement. This is overcome by the patient swinging their head to the opposite side to employ the VOR instead. Anti-saccades are tested by asking a patient to fixate on the examiner's nose and then, while wiggling one of two targets held in front, the subject is asked to look at the non-moving one (Figure 4e). This involves some frontal processing by the subject (and clinician) to suppress a reflexive saccade and is therefore impaired in frontal lobe disorders. It is the commonest saccade abnormality in schizophrenia[9] and is a common finding in HIV-associated neurocognitive disorder.

- *Pursuit* is tested by following a moving target not faster than 30 degrees per second. An interrupted pursuit of the target, so-called saccadic intrusions, is indicative of dysfunction of the POT junction, pons or cerebellum. The pursuit system allows one to maintain the image of a slow-moving target on the retina. When pursuit is impaired and there is a lag in tracking the target, a rapid eye movement or saccade allows 'catch-up'. A double crossover of the pursuit pathway ensures that the right POT junction and dorsolateral pontine nucleus are responsible for pursuit towards the right side. The cerebellar flocculus, however, is responsible for pursuit towards the opposite side. A right homonymous hemianopia with impaired left-sided pursuit suggests a left POT junction lesion, but if pursuit is spared, then the lesion localises to the left occiput. The benefit of pursuit testing is invaluable in such a situation.
- *Vestibulo-ocular reflex* is mediated by the vestibular apparatus, the vestibular nuclei, and the final common pathway of the third, fourth and sixth nuclei; their nerves and muscles supplied. Accordingly, in supranuclear gaze palsies, the VOR is spared, unlike in nuclear or extra-ocular muscle disorders. Vestibulo-ocular reflex is tested by the head impulse test (Figure 4c and 4d). By asking the patient to fixate on the examiner's nose and then rapidly turning the patient's head by 20–30 degrees towards either side from the midline, a corrective re-fixation of the eyes towards the examiner's nose indicates dysfunction of the apparatus on the side towards which the head was moved.

In this case report, an assessment of the supranuclear control of gaze, in addition to testing the nuclear and infra-nuclear control of eye movements, has led to the diagnosis of NPC, a condition for which treatment is available and useful, especially if the condition is diagnosed early. Regular testing at the bedside will ensure that these tests become automatic and second nature and certainly be less time-consuming.

With funduscopy, the clinician gets a bird's eye view of the neuro-retina (ganglion cell layer) and optic nerve head (white matter tract). With eye movement testing, that perspective is enhanced by the appreciation of the electrical functioning of the frontal, parietal and occipital lobes of the brain, the brainstem and the cerebellum. With such amazing tools at hand at the bedside, it is no wonder that the eye is the window to the brain, a glimpse of the mind and a 'mirror of the soul'.

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Competing interests

The authors have no financial or personal relationships in the case report that may have influenced them.

Authors' contributions

P.B. and A.M. co-wrote the article. A.D.M. contributed to making the tissue diagnosis (the skin biopsy Filipin staining).

Ethical considerations

Confirmed as a case report with protected patient identity.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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