A 30-year old female presented with a five-day history of vertical diplopia. Clinical examination revealed bilateral restriction of adduction and nystagmus of the abducting eye, diagnosed as a bilateral internuclear ophthalmoplegia. A three-day course of intravenous methylprednisolone was prescribed and her signs and symptoms soon resolved. Later, magnetic resonance imaging revealed no signs of demyelination.

**Keywords:** internuclear ophthalmoplegia, multiple sclerosis, medial longitudinal fasciculus, nystagmus, methylprednisolone

**INTRODUCTION**

Internuclear ophthalmoplegia (INO) is a disorder of conjugate horizontal gaze. Typically it is elicited as an abduction paresis of one eye and nystagmus of the abducting eye on lateral gaze.\(^1\) It can be either unilateral or bilateral, and is caused by a lesion of the medial longitudinal fasciculus (MLF) between the third and sixth cranial nerve nuclei in the brainstem, with or without involvement of the vergence midbrain control mechanisms.\(^1,2\)

As the MLF is a highly myelinated tract within the brainstem, the most common cause of INO in young people is demyelinating disease secondary to multiple sclerosis (MS) (41%-54%). Other aetiologies can include cerebral/brainstem vascular accidents (23-27%), infection (5-14%), head trauma (6%), brainstem tumour (4-5%), systemic lupus erythematosus (<5%), nutritional and metabolic disorders, or degenerative disorders.\(^3,6\)

Patients are unlikely to experience diplopia in primary position with most being orthophoric. In fact bilateral INO may be asymptomatic.\(^1\) Horizontal diplopia on lateral gaze is the most common complaint, with or without the presence of oscillopsia due to the lateral gaze nystagmus.\(^1\)

**CASE STUDY**

Ms Z, a 30-year old female legal assistant, presented with a five-day history of vertical diplopia in left gaze with no loss of vision. Ms Z also reported that on the second day of her symptoms she noticed a transient decrease in her "mental acuity". There had been no history of head trauma. Aside from slight asthma and being clinically overweight, her general health was good and she took no medications. Ms Z did, however, report that she had recently been under a lot of stress at work.

Ms Z’s past ocular history was uneventful and revealed only a slight myopic refractive error. Her mother has a history of diabetic eye related problems.

On examination, visual acuity was 6/5 and N5 both eyes. Cover testing revealed orthophoria at near and a small exophoria with rapid recovery at distance fixation. Ocular motility assessment revealed slight bilateral limitation of adduction on horizontal gaze. Nystagmus was noted on both right and left abduction, left worse than right, with no oscillopsia. Small amplitude downbeat nystagmus was also noted on down gaze. The patient reported vertical diplopia on left gaze, although no vertical muscle anomaly was noted. There was no pain on eye movements. Colour vision testing with Ishihara showed no defect. Brightness saturation was estimated at 90-95% right, and 100% left. Red saturation was estimated at 80-85% right and 100% left. Pupils showed no sign of relative afferent pupil defect. Upon ophthalmic examination, anterior chamber, lens, peripheral retina and macula were all found to be healthy in either eye, with the optic nerve showing no signs of papilloedema. Routine testing of blood pressure recorded 150/80.

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The patient was subsequently diagnosed with bilateral INO. Possible aetiology was suspected to be MS due to her young age. She was therefore immediately admitted to the Royal Victorian Eye & Ear Hospital (RVEEH) for treatment. Upon arrival, the patient was re-assessed, confirming mild bilateral limitation of adduction on contralateral gaze, clinically observed slow saccades and abducting nystagmus of either eye. Convergence was intact and no propotosis was observed. Diagnosis of bilateral INO was verified and the patient was admitted as an inpatient for intravenous (IV) pulse methylprednisolone for three days. Urgent magnetic resonance imaging (MRI) was also ordered.

The following day her fasting blood glucose levels, HbA1c, measured 9.0% (normal ≤7%). The patient was unwell and complaining of a headache. She was also tachycardic, although this was attributed to her anxiety. Intermittent horizontal diplopia on extreme dextroversion and levoversion was present, now with no vertical component. A Humphrey Visual Field was performed and showed no defects. A second dose of methylprednisolone was commenced.

On the third day, the last dose of IV steroids was commenced and blood sugar levels via the finger prick test were measured at 9.8mmol/L (normal 4-8mmol/L). The patient’s general health had improved, the headache resolved and a reduction of the nystagmus amplitude was observed. The patient was discharged later that day and was due for follow-up with a neuro-ophthalmologist.

Two months later, the MRI scan revealed two non-specific supratentorial T2 hyperintense white matter foci, which of themselves were not diagnostic of demyelination. Cerebral, brainstem and cerebellar parenchymal signals were normal, in particular there were no callosal septal interface, corpus callosum, midbrain, middle cerebellar peduncle or temporal lobe lesions. There was no evidence of atrophy. The optic nerves had a symmetrical size and signal.

DISCUSSION

Optic neuritis and internuclear ophthalmoplegia are the most common ocular presenting signs in MS, with optic neuritis present in 50% to 90% of MS patients and INO in 17% to 53%. MS is said to be the most common cause of bilateral INO in young adults.

Bilateral INO affects both sides of the MLF, producing bilateral adduction deficits, abducting nystagmus, as well as horizontal diplopia on lateral gazes. Horizontal gaze is mediated by the abducens nucleus, from which abducens motor neurons innervate the ipsilateral lateral rectus via the sixth nerve. Abducens interneurons cross to the contralateral MLF to the oculomotor nucleus, with motor neurons innervating the contralateral medial rectus. A bilateral MLF lesion results in disruption of adduction on horizontal gaze, with the abduction nystagmus thought to be a compensatory mechanism. Convergence is generally intact in INO, with only 10% of MS patients with eye movement problems having vergence affected. This indicates a more caudal lesion, sparing the vergence control centres in the rostral midbrain.

Vertical gaze-evoked nystagmus commonly occurs with bilateral INO, with one study reporting 55% of cases with bilateral INO having vertical nystagmus. This is due to a disruption of the vestibulo-ocular and cerebello-ocular pathways through the MLF to the vertical gaze integrator, the interstitial nucleus of Cajal. Skew deviation, a supranuclear vertical misalignment with hypertropia and incyclotorsion on the ipsilateral side to the INO may also occur in unilateral cases, with 20% demonstrating skew deviation. This is due to an interruption of the otolithic pathways ascending the MLF. It could be hypothesised that Ms Z originally had a unilateral INO with a skew deviation that progressed to a bilateral INO, hence explaining her change in diplopic symptoms from vertical to horizontal, as in a similar reported case. With hindsight, a more detailed examination of ocular motility with a prism cover test or Maddox Rod test would have elicited more information of the minor vertical muscle imbalance, and may have explained her initial complaint of vertical diplopia.

Although this patient had nystagmus on both lateral gazes, lateral recti defects were eliminated by the detection of full abduction and the presence of an adduction defect. A differential diagnosis of ocular myasthenia gravis was eliminated due to the patient’s reduced saccadic velocity on adduction. Patients with myasthenia gravis have normal saccades, despite their pseudo-INO appearance at times. The uncommon occurrence of INO is always reported in the context of previously diagnosed SLE, rather than as a presenting disorder, is rarely bilateral, and almost always resolves with corticosteroid treatment, which would eliminate SLE as a cause in this case.

Optic neuritis presents as a sudden unilateral loss of visual acuity, caeco-central scotoma on visual field testing, pain on eye movement, afferent pupil defect, colour vision impairment (predominantly red) and photopsia. Even though Ms Z reported subtle brightness and red desaturation on the right, she had no pupillary, visual acuity or visual field defects, and in particular, no signs of optic neuritis. A more appropriate colour vision test would have been the City University Colour Vision Test or the Farnsworth Munsell 100 Hue Test as these are more sensitive in detecting acquired defects. It has recently been demonstrated that subjective measurements of brightness intensity and red saturation are clinically significant tests able to detect optic neuropathy to a high degree of sensitivity and specificity. Optic neuritis is the most common ocular manifestation, and the initial presenting sign, in up to 20% of MS patients. The 10-year probability of developing MS after an acute episode of optic neuritis, for a female with no brain lesion found on MRI, is
25%.\textsuperscript{19} This risk may be applied to any isolated demyelinating episode, including optic nerve, brainstem or spinal cord.\textsuperscript{19-21} Despite an urgent MRI scan request, this was not available for two months, which caused the patient further distress and anxiety. This waiting time is of some concern, as in this case the opportunity to detect an early and transient aetiology has been missed. However, it is not unusual for MRI to be normal in the presence of an INO, with 31% reported by Bolanos.\textsuperscript{3} According to the 2005 McDonald Diagnostic Criteria for Multiple Sclerosis, the diagnosis of MS cannot be confirmed until deterioration over time is established by the collective data of repeat MRI, abnormal visual evoked potential test, lumbar puncture positive for oligoclonal bands or increased immunoglobulin G, or another neurological episode occurs.\textsuperscript{22}

Methylprednisolone is commonly used to treat inflammatory, haematological, neural and ophthalmic disorders. Its prescription is usually the first line of treatment for acute episodes in patients with MS, hence why it was prescribed to Ms Z. IV methylprednisolone reduces the duration and severity of attacks, and was found to reduce the 2-year risk of MS, 8% versus 18% placebo, however there was no difference in the longer term development of MS.\textsuperscript{23,24} There can however be collateral diabetic signs and symptoms as well as a manifestation of latent diabetes mellitus whilst on methylprednisolone, explaining the increase in blood glucose levels in this patient’s case.\textsuperscript{24,25} Despite this, with a family history of diabetes, Ms Z’s elevated blood glucose levels cannot solely be attributed to the treatment of methylprednisolone without further investigation.

CONCLUSION

There is no specific treatment for the eye signs of INO, as the diplopia in extreme lateral gaze precludes the use of prism therapy, orthoptic training or ocular surgery. The patient should be treated according to the underlying cause. In this patient’s case, given the diagnosis of bilateral INO and a possible right optic neuritis, MS was the tentative diagnosis, and high-dose IV pulse corticosteroids were prescribed. Given that only 25% of female patients will develop MS after 10 years, this natural history must be considered when deciding on prophylactic treatment at the time of the first acute demyelinating episode.\textsuperscript{26} For Ms Z, the tentative diagnosis of MS relies on the only sign being the bilateral INO. As this does not fit the McDonald Diagnostic Criteria as yet, it would be wise to repeat MRI testing in approximately six months with ongoing ophthalmic and neurologic review.

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