CASE REPORT

Unilateral internuclear ophthalmoplegia, strabismus and transient torsional nystagmus in focal pontine infarction

Ali S Haider

John Hunter Hospital,
Newcastle, New South Wales,
Australia

Correspondence to
Dr Ali S Haider,
alishaider@live.com.au

Accepted 6 July 2016

SUMMARY

Vertebrobasilar stroke carries a high mortality rate and can have symptom patterns that are complex and difficult to diagnose. Isolated infarcts of the pons are uncommon and the neuro-ophthalmic presentation of pontine stroke can be quite variable. There is a paucity of cases in the literature documenting neuro-ophthalmic pathology as the sole or primary manifestation of pontine stroke. Here is presented the case of a unilateral internuclear ophthalmoplegia (INO) with concomitant skew deviation, contralesional exotropia and ipsiversive torsional nystagmus as the initial and only presenting feature of an isolated pontine stroke. This case illustrates the need to consider a cerebrovascular event early in the differential of a complex ocular motility disturbance not in keeping with specific cranial nerve palsy. It similarly highlights non-paralytic pontine exotropia and skew deviation as important causes of acute onset acquired strabismus, and transient torsional nystagmus as a rare but relevant localising feature in pontine strokes causing INO. Acute onset of this constellation of signs is highly suggestive of pontine infarction.

BACKGROUND

Pontine strokes account for only a small percentage of all ischaemic events.¹ They are most often part of larger infarcts involving multiple territories in the vertebrobasilar system. Seldom are eye movement disorders isolated findings in pontine stroke.²

Unilateral internuclear ophthalmoplegia (INO) as a predominant neuro-ophthalmic feature in brainstem stroke is very uncommon.^{3–4} The association of INO with pure torsional nystagmus is also rare, with only a few cases having been reported.^{5–9} Exotropia can occur in INO but likewise has rarely been documented.¹⁰ The constellation of these signs in the absence of other neurological findings is a rare occurrence.

Here is reported INO in association with contralesional exotropia, a pure ipsiversive torsional nystagmus and skew deviation as the only presenting manifestation of pontine infarction.

CASE PRESENTATION

History

A 56-year-old man with type 1 diabetes presented to the emergency department after noticing diplopia and a divergent squint on waking up that morning. The previous day he had noted the onset of blurred vision while at work. The patient came to the hospital most concerned about the inferolateral deviated

position of his right eye when looking in the mirror. “Why has my eye gone down and out doc?”

There was no associated vertigo, motor, speech or sensory symptoms. He denied any recent trauma, headache, nausea or vomiting. The diplopia was binocular, painless and noticed in horizontal more so than vertical gaze. His ocular history was significant for bilateral panretinal photocoagulation for diabetic retinopathy. There was no previous history of strabismus, eyelid or intraocular surgery. His medical history was remarkable for hypertension. Despite poorly controlled diabetes there was no prior history of ischaemic heart disease, cerebrovascular disease or renal impairment. Medications included a basal-bolus regime of insulin, an ACE inhibitor and a calcium channel blocker.

Examination

On physical examination, the patient was hypertensive at 160/93 mm Hg with all other vital signs being normal. Unaided visual acuity was 6/9 OD (right eye) and 6/7.5 OS (left eye). The pupils were equal but sluggishly reactive to light. There was no afferent pupillary defect. Neuro-ophthalmic assessment in primary gaze revealed a large right exotropia of ~45 prism dioptres ([figure 1](#)). The exotropic right eye was able to fixate during cover–uncover testing. On close inspection a moderate hypotropia of the right and hypertropia of the left eye (15 prism dioptres) was evident and constant in all positions of gaze. A prominent counter-clockwise (defined with respect to the patient) torsional nystagmus was present that increased on left gaze. Extraocular motility testing revealed the diplopia to be subjectively worse in right gaze. A horizontal abducting nystagmus and inability of the left eye to adduct beyond midline was noted on right lateral gaze. The patient was able to converge on presentation of a near target despite the absence of voluntary adduction in the left eye. Vertical movements were intact.

Confrontation visual fields testing and fundus examination were within normal limits.

On formal neurological assessment the patient was alert, coherent and exhibited no pronator drift. Detailed examination of the other cranial nerves was normal. There was no facial or limb weakness. Diminished sensation and proprioception in the lower limbs was attributable to a long-standing diabetic peripheral neuropathy. Mobility was otherwise independent. The remainder of the neurological examination including testing of limb coordination and plantar reflexes was unremarkable.

CrossMark

To cite: Haider AS. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2016-216503

Figure 1 Manifest heterotropia in primary gaze. Note the hypertropia as evidenced by scleral show OS. A mild hypotropia and exotropia OD were also present.

INVESTIGATIONS

An initial brain MRI with gadolinium demonstrated two small areas of infarction adjacent to one another, and confined to the pontine region ([figure 2](#)). Two foci of restricted diffusion were seen in the pons; a larger one anteriorly near the midline in the upper pons and a smaller one posteriorly just anterior to the fourth ventricle in the central pons. These foci were best seen on the axial diffusion-weighted images ([figure 2A](#)). Two corresponding small hyperintense signals were also seen on the T2-weighted fluid-attenuated inversion recovery (FLAIR) images consistent with foci of acute infarction within the pons ([figure 2B](#)). Coronal slices better revealed these foci to be just left of the midline causing ischaemic injury to the left medial longitudinal fasciculus (MLF; [figure 2C](#)).

Multiple white matter T2/FLAIR hyperintense foci were present bilaterally in both the cerebral hemispheres in the absence of restricted diffusion. These were consistent with small vessel ischaemic change.

An MR angiogram demonstrated no aneurysm, but mild narrowing and an irregular outline of both intracranial internal carotid arteries likely reflective of atherosclerotic change.

The cerebellum was normal.

OUTCOME AND FOLLOW-UP

The diplopia was subjectively better the following day, with an objective improvement in the INO and strabismus. The torsional nystagmus had resolved in primary position but persisted in left gaze ([video 1](#)). The exotropia had completely resolved by day 3. Review at 3 months indicated complete resolution of the diplopia, strabismus and nystagmus.

DISCUSSION

This patient presented with a complex oculomotility disorder in the absence of other neurological findings. He demonstrated a manifest heterotropia in primary position, an INO with an otherwise full range of ductions in conjunction with an ipsiversive torsional nystagmus. Both the contralesional exotropia and ipsiversive torsional nystagmus were transient findings that had markedly improved within 48 hours of presentation.

In unilateral INO the lesion is ipsilateral to the eye that fails (or lags) in adduction. Unilateral INO is uncommon and

generally related to brainstem infarction in the older population.^{3 5} Non-paralytic pontine exotropia (NPPE) is defined as unilateral INO with contralateral exotropia. It is a syndrome of horizontal dysconjugate gaze without gaze palsy as described by Bogousslavsky and Regli¹¹ in 1983. Possibly because the signs tend to be short-lived, it has rarely been reported since then, mainly in the French and Japanese literature.¹⁰ Previous authors have postulated a secondary deviation of the contralateral eye through overexcitation of the contralateral paramedian pontine reticular formation (PPRF) on attempts to fixate with the ipsilateral parietic eye.^{10 12}

Demyelinating lesions typically cause bilateral INO in the younger demographic. Features arguing against multiple sclerosis in this case include the patient's age, gender and presence of significant cardiovascular risk factors. Other less common causes of INO include neurosyphilis, Arnold-Chiari malformation, head trauma, hydrocephalus, drug intoxication and nutritional disorders such as Wernicke encephalopathy and pernicious anaemia.¹³

The PPRF at the level of the abducens nucleus is considered the primary horizontal gaze centre for conjugate eye movements within the pons. Its major efferent projections for horizontal gaze are towards the ipsilateral abducens nucleus. The abducens nerve nuclei lie just beneath the floor of the upper part of the fourth ventricle. In addition to ipsilateral projections to the lateral rectus muscle, the abducens nucleus contains interneurons that cross the midline to extend up the MLF to the contralateral medial rectus subnucleus within the midbrain. The end result is activation of the contralateral medial rectus to produce version eye movements for horizontal gaze. Contralateral innervation signals for vertical movement and graviception also travel in the MLF, with the bulk of fibres in fact having their origins in the vestibular nuclei. Structures critical for vertical and torsional eye movements in the midbrain include the rostral interstitial nucleus of the MLF (riMLF), the interstitial nucleus of Cajal (INC) as well as the posterior commissure.¹³ The INC, situated between the red nucleus and superior colliculus, is known to function as the neural integrator for gaze holding whereas the riMLF contains burst neurons for saccadic movement in these directions.¹³⁻¹⁵ The MLF is considered the final pathway for all classes of conjugate eye movements.

The ability to converge despite the absence of voluntary adduction indicates a more caudal lesion, with preservation of the medial recti subnuclei in the midbrain. This is in keeping with the MRI finding of solely pontine infarction in our patient. Cogan's historical classification of unilateral INO into an anterior (midbrain) and posterior (pontine) subtype rested on the preservation or loss of ocular convergence.¹⁶ The fact that adduction paresis is overcome by convergence in close range is definitive evidence of INO, since this function is not related to the MLF.¹⁷ This finding similarly helps in distinguishing INO from a third (oculomotor) nerve palsy, which impairs convergence in addition to causing limited vertical eye movements, pupillary abnormalities and varying degrees of ptosis.

Skew deviation, a supranuclear disorder causing vertical strabismus of the eyes, is due to damage to prenuclear vestibular input to the ocular motor nuclei.¹⁸ The result is a vertical disparity in position of the eyes which move equally, but in opposite directions. The INC receives input from otolithic pathways, which, if damaged, results in skew. It is often the initial manifestation of disease affecting the brainstem, cerebellum or peripheral vestibular system and is commonly associated with other neurological signs that localise to the posterior fossa. Such signs may include gaze palsy, gaze-evoked nystagmus,

Figure 2 MRI with gadolinium demonstrating two small acute infarcts within the pons. (A) Diffusion-weighted images with areas of punctate hyperintensity close to the midline anteriorly (left) and posteriorly (right) in the central pons. (B) Fluid-attenuated inversion recovery images with hyperintensities in the same areas. (C) T2-weighted coronal images demonstrating the slightly rostral location of the larger lesion (left) in proximity to the pontomedullary junction; and the more caudal location of the smaller lesion (right) within the central pons. Both slices afford greater appreciation for an ischaemic injury to the left medial longitudinal fasciculus.

dysarthria, ataxia and hemiplegia.¹⁹ It can be associated with the 'ocular tilt reaction' (OTR) which is a clinical triad of skew deviation, ocular torsion and head tilt. By convention the direction of skew is given by the side of the hypotropic eye.^{13 20} Our patient had a right hypotropia contralateral to a left MLF lesion that was consistent with a skew deviation. He did not, however, present with an associated head tilt, or the complete OTR vestibular syndrome.

Skew deviation may be caused by any acute lesion within the posterior fossa and is thus considered a non-specific sign. Ischaemia of the posterior or dorsal paramedian pons is most

often implicated in cases of brainstem stroke.^{3 21} The supranuclear lesion causing skew deviation is thought to cause an imbalance of graviceptive (mainly otolithic) pathways from the inner ear to the INC in the rostral midbrain.^{19 22} This pathway is believed to cross the midline at the level of the pons, but localisation of the level of crossing is not precisely known. Zwergal *et al*²² however postulated graviceptive pathways to join the MLF after crossing between the vestibular and abducens nuclei within the pons. Since axons from the vestibular nuclei cross the midline at the level of the pons to ascend along the MLF, lesions in the rostral pons and midbrain cause

Video 1 Horizontal versions on day 2 of admission demonstrating: (1) torsional nystagmus on left gaze and (2) left internuclear ophthalmoplegia on right gaze. Both forms of nystagmus had improved considerably in amplitude in comparison with the initial assessment. Testing on left gaze revealed no weakness of ipsilateral (left) abduction to suggest involvement of the abducens nucleus or its fascicles in the pons.

contralesional hypotropia and head tilt.¹⁹ The clinical utility of a skew associated with INO is in lateralisation of the lesion. If the approximate level of brainstem damage is evident from the clinical syndrome (eg, INO), then skew deviation indicates the side of the lesion. The direction of skew is contraversive with rostral brainstem lesions and ipsiversive with caudal brainstem lesions. When it accompanies INO, the higher eye is usually on the affected side, suggesting a rostral lesion of the MLF after it crosses the pons.^{18 23} As in this case, patients with INO are more likely to show an ipsilateral hypertropia.

Pure torsional nystagmus is a rare form of central vestibular nystagmus more commonly associated with conditions such as syringobulbia and the lateral medullary syndrome.⁶ Patients with unilateral INO have been described to exhibit a conjugate torsional nystagmus where the upper poles of the eyes rotate towards the side of the lesion—a so-called ipsiversive torsional nystagmus.^{5 6 18} Torsional nystagmus can be observed acutely in cases of skew deviation but it is an otherwise rare finding in association with INO.^{6 19} Noseworthy *et al*²⁴ reported a case of counter-clockwise (from point of view of the patient) torsional nystagmus ipsiversive to a left midpontine lesion in the absence of INO. There was an associated minor slowing of adduction as well as hypertropia of the left eye.^{6 24} The case, however, was attributed to a venous anomaly and not due to a pontine stroke

as described in our patient. Dehaene *et al*⁶ describe four cases of unilateral INO with ipsiversive torsional nystagmus in which skew deviation was present and associated with head tilt in two patients. Lin and Tsai⁹ reported transient torsional nystagmus associated with unilateral INO but without an associated skew. Komiyama *et al*¹² described one case of unilateral INO with NPPE associated with torsional nystagmus and skew deviation. Details on this case were limited, vertigo was associated and intact convergence could not be confirmed due to aggravation of the contralesional exotropia.

As highlighted previously, both vertical and torsional eye movements originate in the midbrain. Eye-head coordination in the roll plane is mediated by the INC which acts as the neural integrator for torsional gaze, receiving inputs from the riMLF and vestibular nuclei. Burst neurons in the riMLF are responsible for conjugate ipsilateral torsional saccades, such that conjugate counter-clockwise saccades are the result of left riMLF activation. It has been suggested that unilateral INC inactivation produces contralesional torsional deviation and ipsilesional torsional nystagmus.^{5 25} The clinical findings in this patient were consistent with loss of left INC activation combined with intact adjacent riMLF function, permitting a corrective ipsiversive torsional nystagmus. Partial injury with rapid compensation, or transient ischaemia to the INC might explain the quick resolution of torsional nystagmus in small MLF lesions. Contralesional exotropia in the setting of unilateral INO is likely due to a secondary deviation mechanism from excitation of the contralateral PPRF when fixating with the paretic eye. Covering the paretic eye in this patient prevented excitation of the contralateral PPRF and consequently allowed the exotropic eye to move medially.

CONCLUSION

This is the first description, to the best of my knowledge, of the quartet of acute onset unilateral INO, skew deviation, NPPE and ipsiversive torsional nystagmus as the only manifestation of pontine stroke. Acute onset of this constellation of signs in isolation is highly suggestive of pontine infarction.

Both skew deviation and torsional nystagmus can aid in localisation and lateralisation of a unilateral brainstem lesion. These two ocular signs should never be overlooked by the examining clinician when faced with cases of acute diplopia in the outpatient or emergency room setting.

Learning points

- ▶ Double vision is an important symptom with a vast differential that requires a comprehensive neuro-ophthalmic examination.
- ▶ Skew deviation, often with ipsilesional hypertropia, exotropia of the contralateral eye in primary gaze and transient torsional nystagmus may all be associated neuro-ophthalmic findings in unilateral internuclear ophthalmoplegia (INO) due to pontine infarction.
- ▶ Both skew deviation and non-paralytic pontine exotropia are important causes of acute onset acquired strabismus.
- ▶ Pure torsional nystagmus and/or exotropia may occur in small medial longitudinal fasciculus lesions. These signs are often transient, under-reported and mandate prompt imaging of the posterior fossa in the acute setting, especially if the presence of INO is in doubt.

Acknowledgements The review and advice of Professor David B Williams (Professor of Neurology, The University of Newcastle and John Hunter Hospital) in preparing this manuscript is gratefully acknowledged.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Varsou O, Stringer MS, Fernandes CD, *et al.* Stroke recovery and lesion reduction following acute isolated bilateral ischaemic pontine infarction: a case report. *BMC Res Notes* 2014;7:728.
- Moncayo J, Bogousslavsky J. Oculomotor disorders in vertebrobasilar stroke. *Expert Rev Ophthalmol* 2009;4:1–23.
- Kim JS. Internuclear ophthalmoplegia as an isolated or predominant symptom of brainstem infarction. *Neurology* 2004;62:1491–6.
- Deleu D, Sokrab T, Salim K, *et al.* Pure isolated unilateral internuclear ophthalmoplegia from ischemic origin: report of a case and literature review. *Acta Neurol Belg* 2005;105:214–17.
- Srivastava AK, Tripathi M, Gaikwad SB, *et al.* Internuclear ophthalmoplegia and torsional nystagmus: an MRI correlate. *Neurol India* 2003;51:271–2.
- Dehaene I, Casselman JW, D'Hooghe M, *et al.* Unilateral internuclear ophthalmoplegia and ipsiversive torsional nystagmus. *J Neurol* 1996;243:461–4.
- Marshall RS, Sacco RL, Kreuger R, *et al.* Dissociated vertical nystagmus and internuclear ophthalmoplegia from a midbrain infarction. *Arch Neurol* 1991;48:1304–5.
- Nozaki S, Mukuno K, Ishikawa S. Internuclear ophthalmoplegia associated with ipsilateral downbeat nystagmus and contralateral incyclorotatory nystagmus. *Ophthalmologica* 1983;187:210–16.
- Lin HY, Tsai RK. Internuclear ophthalmoplegia associated with transient torsional nystagmus. *J Formos Med Assoc* 2002;101:446–8.
- Johkura K, Kudo Y, Amano Y, *et al.* Gaze palsy and exotropia in internuclear ophthalmoplegia. *J Neurol Sci* 2015;353:158–60.
- Bogousslavsky J, Regli F. Paralytic and non-paralytic pontine exotropia. *Rev Neurol (Paris)* 1983;139:219–23.
- Komiyama A, Takamatsu K, Johkura K, *et al.* Internuclear ophthalmoplegia and contralateral exotropia nonparalytic pontine exotropia and WEBINO syndrome. *Neuroophthalmol* 1998;19:33–44.
- Wong AM. *Eye movement disorders*. New York: Oxford University Press, 2008.
- Shaikh AG, Ghasia FF, Rasouli G, *et al.* Acute onset of upbeat nystagmus, exotropia, and internuclear ophthalmoplegia—a tell-tale of ponto-mesencephalic infarct. *J Neurol Sci* 2013;332:56–8.
- Strupp M, Kremmyda O, Adamczyk N, *et al.* Central ocular motor disorders, including gaze palsy and nystagmus. *J Neurol* 2014;261:S542–S58.
- Hoyt WF, Daroff RB. Supranuclear disorders of ocular control systems in man: clinical, anatomical and physiological correlations. In: Bach-y-Rita P, Collins C, Hyde JE, eds. *The control of eye movements*. US: Academic Press Inc., 1971:175–236.
- Strupp M, Hufner K, Sandmann R, *et al.* Central oculomotor disturbances and nystagmus: a window into the brainstem and cerebellum. *Dtsch Arztebl Int* 2011;108:197–204.
- Brodsky MC, Donahue SP, Vaphiades M, *et al.* Skew deviation revisited. *Surv Ophthalmol* 2006;51:105–28.
- Wong AM. Understanding skew deviation and a new clinical test to differentiate it from trochlear nerve palsy. *J AAPOS* 2010;14:61–7.
- Tilikete C, Vighetto A. When is diplopia strongly suggestive of a vascular event? *Expert Rev Ophthalmol* 2009;4:357–61.
- Hernowo A, Eggenberger E. Skew deviation: clinical updates for ophthalmologists. *Curr Opin Ophthalmol* 2014;25:485–7.
- Zwergal A, Cnyrim C, Arbusow V, *et al.* Unilateral INO is associated with ocular tilt reaction in pontomesencephalic lesions: INO plus. *Neurology* 2008;71:590–3.
- Brandt T, Dieterich M. Skew deviation with ocular torsion: a vestibular brainstem sign of topographic diagnostic value. *Ann Neurol* 1993;33:528–34.
- Noseworthy JH, Ebers GC, Leigh RJ, *et al.* Torsional nystagmus: quantitative features and possible pathogenesis. *Neurology* 1988;38:992–4.
- Halmagyi GM, Aw ST, Dehaene I, *et al.* Jerk-waveform see-saw nystagmus due to unilateral meso-diencephalic lesion. *Brain* 1994;117:789–803.

Copyright 2016 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow