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AU1) Refs. 15 through 25 have been renumbered to appear in chronologic order in text, including citations in figure legends.

AU2) Please confirm spelling of Visuo200. Could not find on an Internet search.

AU3) “Lastly” changed to “Third” as this item is followed by another item introduced by “Finally,” which implies that it is the last item in the series. It the series is not meant to have four items, please reword appropriately.
Upbeat Nystagmus From a Demyelinating Lesion in the Caudal Pons

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Abstract: A 51-year-old man developed positional vertigo, ataxia, dysgeusia, diplopia, and oscillopsia. Eye movement examination and video-oculographic recording disclosed primary position upbeat nystagmus (PPUN) and a right internuclear ophthalmoplegia. Brain MRI showed a small focal lesion in the right dorsal tegmentum of the caudal pons with signal characteristics consistent with a primary demyelinating central nervous system disease. PPUN has not been described previously with a lesion in such a location. Clinicoanatomic correlation in this patient suggests that a lesion of the superior vestibular nucleus and its efferent crossing ventral tegmental tract could be responsible for the PPUN. This case report contributes to a better understanding of the role of this pathway in humans.

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Primary position upbeat nystagmus (PPUN) has been reported in patients with focal brainstem lesions of different locations, usually involving either the rostral pons bilaterally (1-4) or the paramedian dorsal part of the caudal medulla (1,5-13). The pathophysiology of the caudal medullary lesions is not clear (14).

We report a patient in whom PPUN was due to a small unilateral lesion in the dorsal tegmentum in the caudal pons, a location not previously reported for PPUN. This case report highlights the brainstem pathways involved in vertical vestibular eye movements in humans.

CASE REPORT

A 51-year-old man without a prior medical history experienced the subacute onset of vertigo, ataxia, dysgeusia, vertical diplopia, and oscillopsia. Examination disclosed that his walking was moderately ataxic. He showed a slight right lower motor neuron facial weakness and reduced taste on the right anterior two thirds of the tongue. Neuro-ophthalmologic examination revealed findings consistent with a left skew deviation (right hypertropia), a mild right internuclear ophthalmoplegia (INO) manifested by decreased velocity of the adducting right eye during left ward saccades, and PPUN. Results of cardiovascular and general physical examinations were normal.

T2 MRI showed a single area of high signal in the brainstem in the right caudal part of the pontine tegmentum, extending longitudinally 7 mm from the caudal pons just above (maximum 3 mm above) the sixth nucleus and terminating just before the mid-pons (Fig. 1). The lesion extended laterally 7 mm from midline to the trigeminal nuclei. There were two other high signal areas around the lateral ventricles. The lesions were hypointense on T1 MRI and did not enhance. Lumbar puncture showed a normal cell count, a protein level of 0.53 g/L, and oligoclonal bands. Results of serology tests for lyme disease, HIV, and syphilis were negative.

A first manifestation of multiple sclerosis was diagnosed, and the patient was given cortisone (1 g/day for 3 days) intravenously. One month later, the patient had no more complaints, and results of clinical examination were normal. Fluid-attenuated inversion recovery image (FLAIR) MRI performed at that time showed a persisting hypersignal of the right posterior part of the caudal pontine tegmentum without any new lesions.

Eye movements were recorded using infrared video-oculography (200 Hz frequency; Visuo200; Synapsys, Marseille, France). Nystagmus was upbeat in the primary position of gaze, with mean amplitude of 10° and a mean velocity of 7°/s (Fig. 2). The nystagmus slow phase was linear in the primary position of gaze. Nystagmus velocity was increased in upgaze (12°/s) with an exponentially decreasing velocity waveform. In right gaze, the velocity also increased (10°/s), and the nystagmus...
showed a torsional clockwise (from the patient’s viewpoint) beating component. In left gaze, from about 20° eccentricity, the nystagmus changed to left-beating. The velocity of the upbeating nystagmus decreased in downgaze and during convergence. The relationship of the nystagmus to head position was not tested.

Horizontal pursuit (amplitude: 34°, frequency: 0.15 Hz) was smooth except for beats of leftward nystagmus in left gaze. Vertical upward pursuit (amplitude: 24°, frequency: 0.15 Hz) was interrupted by catch-up saccades or quick phases; downward pursuit was normal. The vestibulo-ocular reflex was not recorded.

Saccades were tested in the direction of 15 and 30° to the right and left and in the direction of 10° up and down. Saccades were of normal gain except for the leftward eye movement made by the right eye. In this case, eye movement recording showed saccades of decreased gain (mean accuracy 76%) with appropriate velocity (mean peak velocity 257°/s) compared with the left eye (accuracy: 97%; velocity: 312°/s), consistent with a mild right INO.

**DISCUSSION**

Vertical nystagmus in the primary position of gaze is thought to be the consequence of asymmetries in the cerebello-brainstem network involved either in the vertical “neural integrator” or the vestibulo-ocular reflex (14,17). Pursuit disorders are also usually associated, particularly in the direction of the vertical quick phase, but such abnormalities could be the consequence rather than the cause of most of the jerk nystagmus.

The human brainstem pathways involved in vertical vestibular eye movements are not yet well known, and previously reported cases of PPUN owing to brainstem damage are relatively rare and involve the caudal medulla or less frequently the central part of the mid-pons and rostral pons (1-13) but not so far the lateral part of caudal pons as reported here.

Damage to one of the three excitatory vestibulo-oculomotor tracts involved in upward eye movements (17) could theoretically account for the pathophysiology of PPUN. The first excitatory tract originates in the medial vestibular nucleus (MVN), decussates at this level, and runs in the contralateral medial longitudinal fasciculus (MLF) before connecting with the third cranial nerve nuclei (17). The second excitatory tract is the crossing ventral tegmental tract (CVTT), described only in the cat (16) but probably also existing in humans, as suggested 20 years ago (18). The CVTT originates in the superior vestibular nucleus.
(SVN), first courses rostrally in the paramedian posterior tegmentum of the caudal pons, and then arches ventrally and medially at the mid-pons level and decusses just above this level in the ventral tegmentum or the dorsal part of the basis pontis (4) before reaching the third cranial nerve nuclei via the ventral tegmentum of the rostral pons and caudal midbrain (Fig. 1C). The third excitatory tract could be within the brachium conjunctivum (BC), also known as the superior cerebellar peduncle, receiving afferent input from the SVN region, coursing rostrally in the caudal tegmentum, and decussating in the caudal midbrain before projecting to the third cranial nerve nuclei.

In our patient, the lesion was in the vicinity of these three tracts, either in the caudal pons (Fig. 1A) or in the mid-pons (Fig. 1B). First, the lesion probably damaged the right MLF because a slight right INO and left skew deviation existed in our patient (15,19). The lesion appeared to involve this fascicle at the caudal pontine level (Fig. 1A). However, we believe that MLF damage was not mainly responsible the PPUN here, given that the impairment was unilateral and the INO was moderate and the previously reported cases of unilateral INO, even those with adduction saccade paralysis, were not associated with a PPUN and at most comprised a gaze-evoked upbeat nystagmus.

FIG. 2. Plot of vertical eye position (in degrees) versus time, in upgaze, primary eye position, and downgaze. The slow phase of the vertical nystagmus was linear in the primary position of gaze. Velocity nystagmus was increased in upgaze with exponentially decreasing velocity waveform and was slightly decreased in downgaze.
nystagmus in the extreme upgaze position. In our patient, only the decelerating slow phase as seen in upgaze might reflect a lesion of the MLF. Absence of a PPUN with an MLF lesion is probably due to the fact that impairment affecting the excitatory tracts involved in upward and downward vestibular eye movements is relatively balanced.

Second, even though the lesion was located very close to the BC, this tract appeared to be spared here. However, the role of the BC in upward vestibular eye movements is currently uncertain. Although a few cases of PPUN have previously been attributed to possible BC damage, such cases are not convincing because lesions were hemorrhagic or tumorous, very large, and bilateral in the brainstem. Another fascicle in the caudal tegmentum that may be involved is the putative CVTT, which is very close to the BC in the caudal pons. Furthermore, the only reported patients with small lesions that were restricted to the BC and located more dorsally compared with the lesion in our patient had isolated positional downbeat nystagmus, not PPUN. Third, experimental data on the role of the BC in the upward vestibulo-ocular reflex seem to be much less documented than those concerning the other two tracts (MLF and CVTT). Therefore, we believe that the PPUN of our patient was not due to extension, which was not visible by imaging, of the lesion to the BC. Finally, the PPUN in our patient could perhaps have resulted from a SVN-CVTT impairment. Indeed, the upper pole of the SVN was clearly damaged by the lesion and the CVTT is supposed to leave this nucleus rostrally in the posterior tegmentum of the caudal pons, also damaged here (Fig. 1C). The right peripheral facial paresis observed in our patient probably resulted from such caudal pontine damage. More rostrally, at the mid-pons level, the CVTT is supposed to be located in the ventral tegmentum, apparently spared in our patient (Fig. 1B).

Thus, a lesion of the SVN-CVTT pathway in the caudal pons appears to be principally responsible for the PPUN of our patient. This case report emphasizes for the first time in humans the critical role of damage to the origin of this pathway in the genesis of upbeat nystagmus. The clearly unilateral feature of brainstem damage could also explain the asymmetrical torsional component of nystagmus in lateral gaze. It should be noted that the slow phase of this upbeat nystagmus was linear in the primary position of gaze, suggesting vestibular imbalance, and decelerating in upgaze, consistent with integrator failure. These two aspects of the upbeat nystagmus slow phase, which have previously been observed in patients with either pontine or medullary lesions and even in the same patient, may coexist as the vestibular system and its circuitry could contribute to eye movement integration.

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REFERENCES


