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Paraneoplastic disorders of eye movements

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Abstract

Paraneoplastic syndromes affecting the brainstem and cerebellum are reported to cause a variety of abnormalities of eye movements. Recent studies have begun to account for the mechanisms underlying several syndromes, characterized by opsoclonus, slow, or dysmetric saccades, as well as downbeat nystagmus. We provide evidence that upbeat nystagmus in a patient with pancreatic cancer reflected a cerebellar-induced imbalance of otolithic pathways: she showed marked retropulsion, and her nystagmus was dependent on head position, being absent when supine, and suppressed with convergence. In addition to anti-Hu antibodies, we demonstrated antibodies to a novel neuronal cell surface antigen. Taken with other recent studies, our findings suggest that paraneoplastic syndromes arise due to antibodies against surface neuronal antigens, including receptors and channels. Abnormal eye movements in paraneoplastic syndromes offer insights into the pathogenesis of these disorders and the opportunity to test potential therapies, such as new drugs with effects on neuronal channels.

Keywords

upbeat nystagmus; oscillopsia; pancreatic endocrine; neoplasm

Introduction

Abnormal eye movements may be prominent features of a range of paraneoplastic syndromes, especially those involving the brainstem and cerebellum.^{1–3} Disordered eye movements include opsoclonus, slow or inaccurate saccades, impaired smooth pursuit, and both gaze-evoked and downbeat nystagmus. A suggested mechanism for the pathogenesis of these paraneoplastic disorders is that immunological responses to neuronal antigens expressed by the underlying cancer are also active against receptors or channels on neurons.⁴

At the neuromuscular junction, Lambert–Eaton myasthenic syndrome is due to antibodies against P/Q voltage-gated calcium channel (VGCC), and myasthenia gravis is due to antibodies against acetylcholine receptors.^{2,4} Both these disorders may affect eye movements. Clinical disorders of ocular motility may not be prominent in Lambert–Eaton myasthenic syndrome, but measurements have demonstrated characteristic, closely spaced

saccades.⁵ Involvement of eye movements in myasthenia gravis is often prominent and eventually present in as many as 80% of patients, causing a range of disorders including strabismus, fatigue-induced gaze nystagmus, limited range of movements with preserved fast, small saccades (quiver movements), and involvement of muscles in a manner that mimics nerve palsies and central disorders, such as internuclear ophthalmoplegia (see Serra *et al.*, this volume).³

Within the central nervous system, some cases of paraneoplastic cerebellar degeneration have been associated with antibodies against VGCC;^{2–4} affected patients often show downbeat and gaze-evoked nystagmus,⁶ both of which also occur with structural lesions affecting the flocculus and paraflocculus.⁷ Other patients may show saccadic intrusions and dysmetria. Slow saccades are also reported as a feature of paraneoplastic disorders: they have been associated with prostate cancer in the horizontal plane⁸ and with the syndrome of anti-Ma2 antineuronal antibodies and testicular carcinoma in the vertical plane.⁹ Paraneoplastic opsoclonus and flutter (saccadic oscillations without intersaccadic intervals) occur in association with a range of tumors, but especially neuroblastoma in children¹⁰ and small-cell lung or ovarian cancer in adults.¹¹ It has been postulated that paraneoplastic opsoclonus could be caused by an immune attack on glycine¹² or NMDA glutamate receptors.¹³ Recently, the combination of Lambert–Eaton myasthenic syndrome and opsoclonus–myoclonus syndrome has been described in one patient, each disorder probably being due to a distinct antibody.¹⁴

Disordered eye movements in the paraneoplastic disorders are potentially important because much is known about the neural substrate underlying each functional class of eye movement.³ Thus, this reductionist system, for which anatomical circuits, neurotransmitters, and channels are relatively well known, may provide further clues to the mechanisms underlying clinical findings in paraneoplastic disorders. Here, we provide a specific example of one such case in which a patient with pancreatic cancer showed gravity-dependent upbeat nystagmus (UBN), implying a central imbalance of otolithic circuits and both anti-Hu antibodies and antibodies to a novel neuronal cell surface antigen. This case has been previously published as a brief communication.¹⁵

Illustrative case

During the course of an intercontinental flight in August 2009, a 65-year-old woman developed “dizziness” and an “inability to sense myself in space.” Her feelings of imbalance intensified to the point that she had difficulty standing and was unable to walk off the plane on arrival. Fully upright, she felt as though “there is a sensation of backwards motion, with someone trying to push me off my heels.” She also had a two-month history of impairment of short-term memory, intermittent blurring of vision (“eyes bobbing up and down”), and a twenty-pound weight loss. Vestibular neuritis was diagnosed, and prednisone was prescribed. Her symptoms progressed and she was admitted to the Massachusetts General Hospital. She smoked one to two packs per day for years, but quit four years previously. She drank two glasses, or more, of wine per night. On examination she was alert and appropriately interactive, but depressed and cognitively impaired. She showed normal registration of three items, but could recall none at five minutes. She was unable to name the month or her current location. She followed simple and complex commands and could spell “world” backwards without error. The cranial nerves were normal, apart from abnormal eye movements. During attempted fixation of a far target, she had prominent upbeat nystagmus, accompanied by lid nystagmus and saccadic intrusions. The upbeat nystagmus suppressed during near viewing. Horizontal and vertical saccades were dysmetric, and pursuit was saccadic in all directions. Prominent upbeat nystagmus made evaluation of vertical optokinetic and vestibular responses difficult; horizontally, her optokinetic responses were

impaired, but her vestibulo-ocular reflex (VOR) appeared preserved. While sitting, she had a pronounced tendency to fall backwards. Her nystagmus showed marked dependency on head position. When evaluated, six months later, her nystagmus was upbeat when erect, absent when supine, reduced when prone, and beating away from the ground (apogeotropic) when lying on either side. Her gait was broad-based and unsteady, and she was unable to walk in tandem. Sensory examination showed mild impairment of joint position and vibration sense in the toes. Muscle strength was normal with symmetrical tendon reflexes and mild ataxia of the lower limbs. Investigations were directed towards detecting an occult malignancy. Brain MRI showed signal changes consistent with small vessel ischemic change, but normal brainstem and cerebellum; cerebrospinal fluid (CSF) showed protein of 69 mg/dl, sugar of 60 mg/dl, 7 WBC/mm³ (97% lymphocytes, 3% monocytes), IgG of 22.5 mg/dl (elevated), and albumin of 33.2 mg/dl (normal). CSF tested negative for malignant cells, oligoclonal bands, and viral titers. An abdominal CT revealed a solid 3.8 × 2.9 × 3.5 cm well-defined, heterogeneous mass in the tail of the pancreas (Fig. 1). A CT-guided core biopsy revealed a pancreatic endocrine neoplasm.

Paraneoplastic antibody testing, including anti-Ri, Anti-Yo, anti-Hu, anti-Ma1 and Ma2, anti-ZiC4, and anti-CV2, was positive only for anti-Hu antibodies at a titer of 1/15,360. The tumor showed strong reactivity with a monoclonal antibody against Hu, confirming the expression of this antigen. (Fig. 1A, B). Analysis of patient's serum and CSF for antibodies against the neuropil of brain, brainstem, and cerebellum (typically indicating a cell membrane or cell surface autoantigen) showed both samples had reactivity with the nuclei of neurons (Hu antigen) as well as with an unknown antigen expressed in the neuropil of the brain. In further studies, cultures of live, non-permeabilized rat hippocampal neurons confirmed the presence of an antibody reacting against a neuronal cell surface antigen (Fig. 1C). Although analyses for the identity of the antigen were conducted, using a cell-based assay with cells expressing NMDAR, AMPAR, GABA(B) receptor, GlyR, LGI1, and Caspr2, all were negative, suggesting a novel autoantigen. A spleen-sparing distal pancreatectomy on the eighth day of the patient's admission produced a well-circumscribed tan-red tumor diagnosed as a well-differentiated endocrine carcinoma with metastasis to one of 23 regional lymph nodes.

The patient was treated with cyclophosphamide, one dose intravenously 1100 mg (600 mg/m²) followed by oral 75 mg daily (1 mg/kg/day), and a course of intravenous immunoglobulin (0.5 g/kg/day for five days). During the initial two months in hospital, she showed progressive decline in cognitive function and memory, increasing gait ataxia and inability to converse intelligibly. However, six weeks post-surgery, she started to improve cognitively, becoming more attentive, conversational, and oriented. Her upbeat nystagmus persisted; at this point, her eye movements were recorded. Subsequently, she received a four-month therapeutic trial of Memantine 10 mg. b.i.d. for her upbeat nystagmus, starting in December 2009, and she tolerated it well with no side effects. Unfortunately, as she had no improvement in her visual acuity in primary gaze and no suppression of the nystagmus, the drug was stopped in March 2010.

In 2011, the patient rapidly deteriorated with marked ataxia, dysarthria, and declining cognitive function, and she is now confined to a wheelchair. She was readmitted on two occasions, most recently in March 2011, when she started on a trial of Rituximab. She initially received IV Ig 0.4 g/kg for five days, (subsequently monthly) and then Rituximab 375 mg/m² weekly for four weeks. Her oncologist reports that she is currently stable on this regime.

Measurement of eye movements

The patient and her family gave written, informed consent in accordance with the Cleveland Veterans Affairs Institution Review Board and the Declaration of Helsinki. We measured 3-D binocular eye and head rotations using the magnetic search technique, as previously described.¹⁶ Nystagmus was recorded as she attempted to fixate, with each eye in turn, at a small laser spot projected onto a tangent screen at a viewing distance of 1.2 meters. The position of the laser spot was held, for several 20-second epochs, at a straight-ahead position and at horizontal and vertical eccentricities of ± 20 degrees. Horizontal and vertical saccades were measured as the patient followed target jumps, either horizontally or vertically, ranging from 5–40 degrees. Smooth pursuit was tested as the patient attempted to track sinusoidal motion of the target in a diagonal direction through ± 20 degrees at 0.17 Hz. The VOR was tested in response to impulsive head rotations in the horizontal or vertical directions administered by an investigator. The effect of vergence angle on her nystagmus was measured as she fixed upon a visual target located at either near (20 cm) or far (1.2 m).

A representative record of her nystagmus during attempted fixation is shown in Figure 3A–C. The predominant component was upbeat (Fig. 3B), with a small divergent (Fig. 3A, arrows) and clockwise (Fig. 3C) component to each quick phase. There was a small increase of upbeat nystagmus in down-gaze, but not in right- or left-gaze. Her upbeat nystagmus was suppressed during convergence (Fig. 3D, View Near), with peak slow-phase velocity decreasing from > 20 degrees/second during far viewing to < 10 degrees/second during near viewing. Saccades were of normal velocity, and showed vertical dysmetria (partly due to upbeat nystagmus) but no internuclear ophthalmoplegia. Smooth pursuit was severely disrupted vertically, due to upbeat nystagmus (but with the ability to allow the eye to drift upward with the target); horizontal smooth-pursuit gain (eye velocity/target velocity) was < 0.1 . The gain of the VOR was estimated to be 0.8 horizontally and 0.75 vertically.

Discussion

UBN has not been previously described as a paraneoplastic phenomenon associated with an identified tumor. Several specific mechanisms have been proposed to account for UBN, all of which concern disturbance of central pathways conveying upward eye movement signals from the vestibular nuclei to the oculomotor nuclei.³ First, interruption of brainstem pathways from the labyrinthine semicircular canals mediating upward eye movements, including the ventral tegmental tract, medial longitudinal fasciculus, and brachium conjunctivum,^{3,17} may cause UBN. Second, as imbalance of central otolithic projections may also cause UBN,³ this seems a likely mechanism in our patient, since her UBN was strongly dependent on head position and modulated by vergence (otolith-ocular responses are strongly modulated by viewing distance).¹⁶ Our patient also showed marked retropulsion, consistent with a central otolithic disturbance. Third, there is evidence that disturbed cerebellar influences upon otolithic projections from the vestibular labyrinth can cause UBN. Thus, patients with cerebellar disease often show modulation of downbeat nystagmus,¹⁸ or even reversal to UBN, with change in head position.¹⁹ What cellular mechanisms contribute to such modulation? In one patient whose nystagmus was upbeat when supine but downbeat when prone, the potassium channel blocker 3,4-diaminopyridine suppressed the downbeat nystagmus but increased the UBN.¹⁹ Also pertinent is the report that, in normal subjects, nicotine induces UBN that is modulated by head position.²⁰ Thus, in our patient, for whom we have strong evidence for a paraneoplastic pathogenesis of her UBN, immune attack on either neuronal channels in the nodulus and ventral uvula, which govern otolithic responses,³ or on acetylcholine receptors in brainstem pathways subserving the otolithic-ocular responses might be the mechanism. Based on the several hypotheses for UBN outlined above, we are currently considering trials of drugs with effects either on

central cholinergic mechanisms or on potassium channels, such as 4-aminopyridine, which are reported to be effective in some patients with vertical forms of nystagmus.²¹

Our patient showed anti-Hu antibodies, which target intracellular antigens. However, current concepts of paraneoplastic syndromes suggest that antibodies against surface neuronal antigens, including receptors and channels, seem more likely to account for the clinical findings.⁴ In interpreting the mechanisms by which such antibodies against neuronal surface antigens cause specific clinical manifestations, the study of specific disorders of eye movement may have much to contribute, since a good deal is known about their neurobiology and pharmacology.³

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Figure 1.
CT of abdomen and pelvis with intravenous contrast: solid appearing $3.8 \times 2.9 \times 3.5$ cm well-defined heterogenous mass arising from the tail of the pancreas.

Figure 2.

Expression of Hu antigen by the patient's tumor and demonstration of an antibody against a neuronal cell surface antigen. The tumor shows intense reactivity with a mouse monoclonal antibody against human Hu (Molecular Probes; Eugene, OR; Cat# A-21271) used at dilution 1:50 (A). As a contrast, the tumor does not show reactivity with normal mouse IgG used at the same dilution (control section, B). The immunostaining was performed using the avidin-biotin-peroxidase method followed by hetamoxyl counterstaining ($\times 200$). Using cultures of dissociated rat hippocampal neurons, patient's serum (diluted 1:100) shows reactivity with the neuronal cell surface (C). The immunolabeling was done using live, not permeabilized, neurons, as reported.²²

Figure 3.

Representative records of the patient's eye movements. A–C show a five-second epoch of her nystagmus, which had divergence quick phases (A), a large vertical component (B), and a smaller clockwise quick phases (C). D illustrates how her UBN decreased during convergence (approximately 20 degrees as she viewed a near target). Positive values indicate rightward, upward, clockwise, and convergence movements, from the patient's perspective. Note that amplitude scales differ in A–C.