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PARANEOPLASTIC UPBEAT NYSTAGMUS

Abnormal eye movements occur in a range of paraneoplastic syndromes affecting brainstem and cerebellum, including opsoclonus, slow or dysmetric saccades, impaired smooth pursuit, and gaze-evoked and downbeat nystagmus.^{1–3} We report upbeat nystagmus (UBN) and cognitive impairment as paraneoplastic phenomena in a patient with pancreatic cancer.

Case report. A 65-year-old woman developed “dizziness” and an “inability to sense myself in space” during a transcontinental flight. She had difficulty walking off the plane, reporting “there is a sensation of backwards motion, with someone trying to push me off my heels.” She also reported impairment of short-term memory for 2 months and a 20-pound weight loss. Vestibular neuritis was diagnosed and prednisone prescribed, but her symptoms progressed. She was admitted to Massachusetts General Hospital. She had smoked 1–2 packs per day for years, but quit 4 years previously.

On examination the patient was alert and appropriately interactive, but depressed and cognitively impaired. She registered 3 items, but could recall none at 5 minutes. She was unable to name the month or her current location. She followed simple and complex commands and could spell “world” backwards. The cranial nerves were normal, apart from abnormal eye movements. During attempted fixation of a far target, she had prominent UBN, lid nystagmus, and saccadic intrusions (video on the *Neurology*[®] Web site at www.neurology.org). UBN suppressed during near viewing and showed marked dependency on head position, upbeat when erect, absent when supine, reduced when prone, and beating away from the ground (apogeotropic) when lying on either side (see video). Horizontal and vertical saccades were dysmetric, and pursuit saccadic in all directions. Her vestibulo-ocular reflex appeared normal horizontally. Eye movements were measured 6 months after the onset of symptoms (see appendix e-1) when nystagmus with upbeat, divergent, and clockwise components to each quick phase were documented. UBN increased in downgaze and suppressed during convergence. She fell backwards sitting, her gait was unsteady, and she was

unable to walk in tandem. She had impaired joint position and vibration sense in the toes. Muscle strength was normal, with mild lower limb ataxia and symmetric tendon reflexes.

Brain MRI indicated small vessel ischemia, but normal brainstem and cerebellum. CSF protein was 69 mg/dL, sugar 60 mg/dL, with 7 leukocytes/mm³ (97% lymphocytes, 3% monocytes), immunoglobulin G of 22.5 mg/dL (elevated), and albumin of 33.2 mg/dL (normal); negative for malignant cells, oligoclonal bands, and viral titers. Abdominal CT revealed a solid 3.8 × 2.9 × 3.5 cm well-defined, heterogeneous mass in the tail of the pancreas. 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 for anti-Hu antibodies at a titer of 1/15,360. The tumor showed robust reactivity with a monoclonal antibody against Hu confirming the expression of this antigen (figure, A and B). Analysis of patient’s serum and CSF for antibodies against the neuropil of brain, brainstem, and cerebellum (usually 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 brain. Cultures of live, nonpermeabilized rat hippocampal neurons confirmed the presence of an antibody reacting against a neuronal cell surface antigen (figure, C). Analyses for the identity of the antigen using a cell-based assay with cells expressing NMDAR, AMPAR, GABA(B) receptor, GlyR, LGI1, and Caspr2 were all negative, suggesting a novel autoantigen. A spleen-sparing distal pancreatectomy on day 8 of her admission produced a well-circumscribed tan-red tumor diagnosed as a well-differentiated endocrine carcinoma with metastasis to one of 23 regional lymph nodes. She was treated with cyclophosphamide and IV immunoglobulin, but impaired cognition and memory, ataxia, and UBN persisted (appendix e-1).

Discussion. Several mechanisms have been proposed to account for UBN; all concern a disturbance of central pathways conveying vertical eye movement signals from the vestibular nuclei to the oculomotor nuclei.^{3,4} Imbalance of central otolithic projections is

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Supplemental Data

Figure 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 immunoglobulin G used at the same dilution (control section, B). The immunostaining was performed using the avidin-biotin-peroxidase method followed by hematoxylin 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.⁷

a possible mechanism in our patient, since her UBN was strongly dependent on head position and modulated by vergence.⁵ We postulate an immune attack on the nodulus and ventral uvula, which govern otolithic responses.³ Our patient showed high titer anti-Hu antibodies in serum, expression of Hu antigen in the underlying tumor, and antibodies to novel neuronal cell surface antigen. Technical limitations (e.g., tumor embedded in paraffin) preclude analysis of expressing of the cell surface antigen by the tumor. 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.⁶

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Author contributions: Dr. Wray: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Martinez-Hernandez: analysis or interpretation of data, acquisition of data. Dr. Dalmau: analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data. Dr. Maheshwari: drafting/revising the

manuscript, acquisition of data. A. Chen: drafting/revising the manuscript. S. King: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Pitman: drafting/revising the manuscript, acquisition of data. Dr. Leigh: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, obtaining funding.

Acknowledgment: The authors thank Anne Louise Oaklander, MD, PhD, for inviting one of them to see the patient.

Study funding: Supported by the NIH/NEI (EY06717), the US Department of Veterans Affairs, and the Evenor Armington Fund (Dr Leigh).

Disclosure: Dr. Wray reports no disclosures. Dr. Martinez-Hernandez receives research support from the Fondo de Investigaciones Sanitarias, FIS, Spain. Dr. Dalmau serves on the editorial board of Neurology®; receives royalties from the editorial board of Up-To-Date; has filed a patent application for the use of LGI1 as a diagnostic test; has received royalties from Athena Diagnostics, Inc. for a patent re: Ma2 autoantibody test and has patents pending re: NMDA and GABAB receptor autoantibody tests (license fee payments received from EUROIMMUN AG); and receives research support from funding from EUROIMMUN AG, the NIH/NCI, and a McKnight Neuroscience of Brain Disorders award. Dr. Maheshwari has received research support from the NIH. A. Chen receives research support from the US Department of Veterans Affairs. S. King receives research support from the US Department of Veterans Affairs. Dr. Pitman serves on the editorial boards of Diagnostic Cytopathology and Cytopathology and as Co-editor-in-Chief of Cytojournal; is author on a pending patent re: System and method for identifying tissue using low-coherence interferometry; receives publishing royalties for Tumors of the Pancreas (Afip Atlas of Tumor Pathol-

ogy; 4th Series Fascicle 6) (*American Registry of Pathology, Armed Forces Institutes of Pathology, 2007*); receives research support from the NIH/NCI; and has participated in medico-legal cases. Dr. Leigh serves as a member of the NIH/NEI Central Visual Processing study section; receives publishing royalties for *The Neurology of Eye Movements* (Oxford University Press, 2006); and receives research support from the NIH/NEI, the US Department of Veterans Affairs, the Office of Research and Development, Medical Research Service, and the Evenor Armington Fund.

Received February 13, 2011. Accepted in final form May 13, 2011.

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As I noted in another paper, whenever I see a patient with a severe, bizarre, or long-lasting migraine refractory to treatment, I suspect that I am dealing with migraine plus something else—such as a mild psychosis, an unrecognized epilepsy, a cerebral arteriosclerosis, or a constitutional inadequacy. Elsewhere, I have described a series of patients with migraine plus a mild psychosis. Now I present cases in which migraine was complicated by a mild epilepsy or an epileptic carrier state.

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