
Novel brainstem syndrome associated with prostate carcinoma

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Article abstract—Two patients successfully treated for prostatic cancer developed a progressive neurologic syndrome beginning with loss of voluntary horizontal eye movements followed by severe, persistent muscle spasms of the face, jaw, and pharynx. Both had mild gait unsteadiness, and one exhibited facial and abdominal myoclonus. Extensive diagnostic studies, including MRIs of the brainstem (with and without contrast), were normal. CSF examination showed mild pleocytosis and elevated IgG. Quantitative eye movement recordings documented selective involvement of voluntary horizontal saccades with sparing of horizontal slow eye movements. Neither patient had antineuronal antibodies in the blood. Postmortem examination revealed perivascular chronic inflammatory cells and microglial infiltration of the pons and medulla. One patient also had perivascular infiltrates in both mesial temporal lobes. Neuronal loss was localized to the pontine tegmentum, the medullary sensory nuclei, and the cerebellum. Brainstem motor nuclei were preserved. The clinical and pathologic findings suggest an autoimmune process (probably paraneoplastic) with selective damage to a subpopulation of brainstem neurons critical for horizontal eye movements and recurrent inhibition of bulbar nuclei.

NEUROLOGY 1993;43:2591-2596

There are a number of paraneoplastic syndromes involving the peripheral and central nervous systems.¹ The mechanism by which a tumor can damage the nervous system without directly invading it is not entirely clear, although antineuronal antibodies are present in some cases. The best characterized paraneoplastic CNS syndrome is cerebellar degeneration associated with gynecologic tumors^{2,3}; these patients have antibodies that bind with a specific antigen expressed by Purkinje cells and the tumor cells. If the gynecologic tumor does not express the antigen, the patient does not develop cerebellar degeneration.⁴ Thus, it appears that the cerebellar damage results from an autoantibody that cross-reacts with the tumor and Purkinje cells. By contrast, there is little information regarding the mechanism of the paraneoplastic encephalomyelitis syndromes.¹ Both viral and autoimmune etiologies have been suspected, but neither viral particles nor autoantibodies have been consistently found in these patients.

We now report a paraneoplastic brainstem syndrome associated with adenocarcinoma of the prostate in two patients. Both patients lost voluntary horizontal gaze and then developed spasms of the bulbar musculature. Although we were unable to identify autoantibodies, both patients exhibited elevated CSF gamma globulin, and postmortem ex-

amination showed changes characteristic of paraneoplastic brainstem encephalitis.

Case reports. Patient 1. Summary. A 66-year-old retired dentist with a history of prostate cancer developed progressive loss of voluntary horizontal eye movements, followed by severe, continuous muscle spasms of the face, jaw, pharynx, and larynx.

Chronology. In March 1983, a needle biopsy of his enlarged prostate revealed adenocarcinoma. CT of the pelvis, as part of the staging evaluation, revealed multiple, bulky pelvic lymph nodes. Bone scans were normal. He was treated with bilateral orchiectomy and 1 mg diethylstilbestrol (DES) in May 1983. Serum tumor markers returned to normal, and the pelvic adenopathy disappeared on a follow-up CT in December 1983.

In October 1987, he began experiencing hyperacusis and intermittent episodic vertigo. Neurologic and quantitative eye movement examinations in December 1987 were normal. In January 1988, he experienced blurred and double vision. Neurologic examination revealed some mild gait unsteadiness and slowing of horizontal saccades, although vertical saccades remained normal (figure 1A). Horizontal smooth pursuit, optokinetic, and vestibulo-ocular reflex (VOR) responses were also normal. CT and MRI of the brain were normal. CSF examination revealed pleocytosis (six to eight lymphocytes) and elevated IgG synthesis (21.7 mg/24 hours; normal, less than 3.3 mg/24 hours).

Follow-up examinations over the next several months

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Received March 18, 1993. Accepted for publication in final form June 2, 1993.

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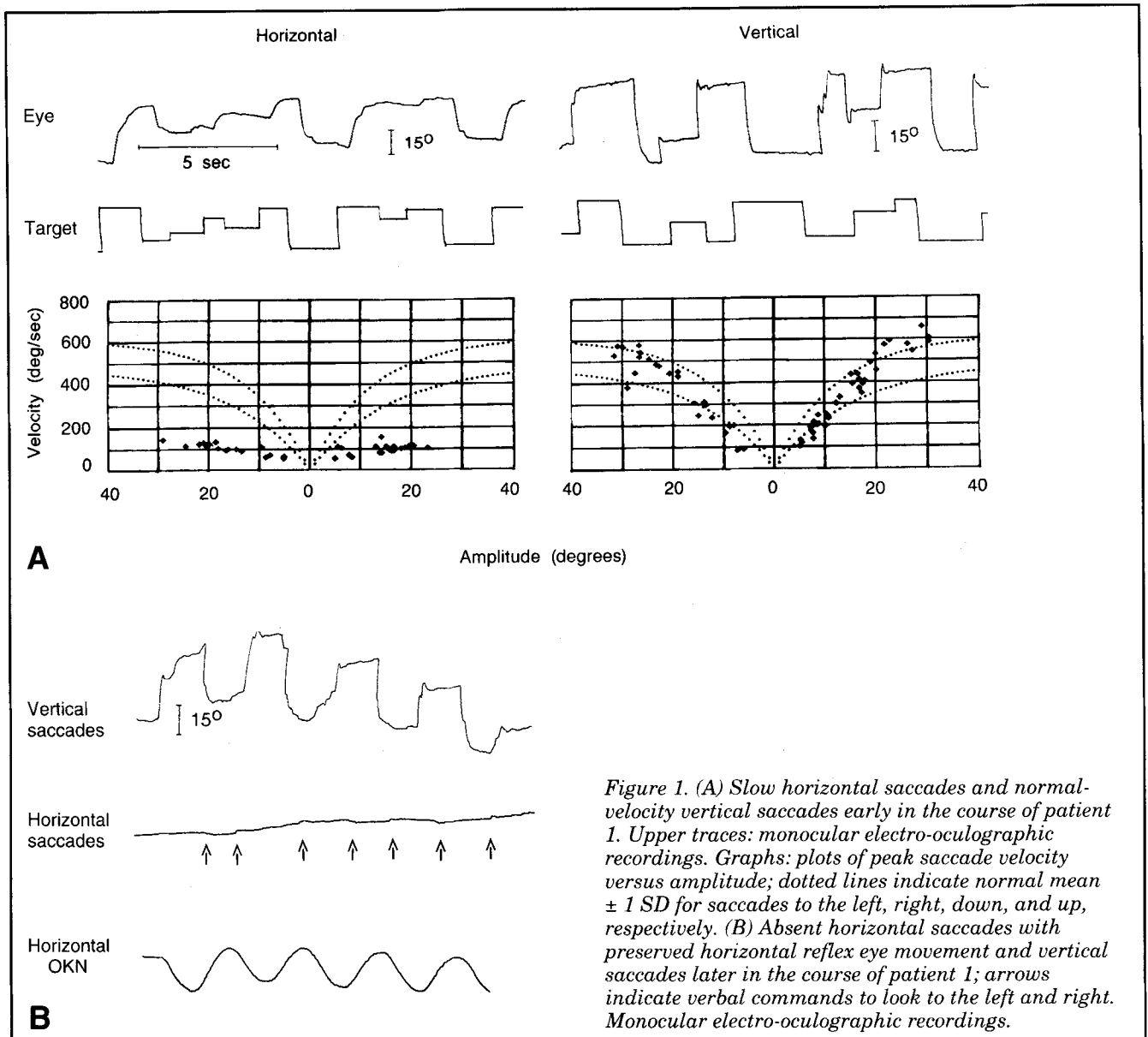


Figure 1. (A) Slow horizontal saccades and normal-velocity vertical saccades early in the course of patient 1. Upper traces: monocular electro-oculographic recordings. Graphs: plots of peak saccade velocity versus amplitude; dotted lines indicate normal mean ± 1 SD for saccades to the left, right, down, and up, respectively. (B) Absent horizontal saccades with preserved horizontal reflex eye movement and vertical saccades later in the course of patient 1; arrows indicate verbal commands to look to the left and right. Monocular electro-oculographic recordings.

documented progressive loss of voluntary horizontal eye movements—first to the left and then to the right. By July 1988, there was almost total absence of voluntary horizontal gaze, but reflex horizontal eye movements (optokinetic and VOR) and vertical voluntary gaze remained normal (figure 1B). Extensive laboratory studies were unremarkable except for continued pleocytosis and elevated IgG synthesis in the spinal fluid. CSF cultures and smears, sedimentation rate, angiotensin converting enzyme, ANA, antimicrosomal antibody, antithyroid antibody, viral serologies, bone scan, HIV, acid phosphatase (prostatic), and coagulation studies were normal. Two follow-up MRIs of the brain were unremarkable. Despite the lack of a specific diagnosis, the patient was given two courses of high-dose steroids (80 mg prednisone \times 10 days and 1 gram methylprednisolone \times 7 days) without any change in symptoms or signs. In September 1988, he developed periodic alternating gaze with an average cycle length of about 3 minutes. There were no voluntary horizontal eye movements; a decreased horizontal VOR gain and some slowing of vertical saccades were noted for the first time. A trial of baclofen had no effect on the pe-

riodic alternating gaze. Immunohistochemical studies were negative for antineuronal antibodies.

In January 1989, the patient developed continuous muscle spasms, beginning on the right side of the face and progressing to involve both sides of the face, the masseter muscles, and then the pharyngeal and laryngeal muscles. He complained of severe hyperacusis and noted that loud noises markedly aggravated the muscle spasms. His vocal cords were tightly approximated, and a tracheotomy was performed because of respiratory insufficiency. On neurologic examination, he had muscle spasms involving all the bulbar muscles and periodic alternating gaze but no voluntary horizontal gaze. He also had a mild gait ataxia. EMG of the facial muscles revealed continuous spontaneous discharge of normal motor units. Brainstem auditory evoked responses revealed prolonged I-III and I-V intervals bilaterally. A repeat MRI of the brain with gadolinium was normal. The diagnosis of CNS Whipple's disease was entertained and, despite negative biopsies of the intestine, the patient was given a course of intravenous penicillin and chloramphenicol. Numerous medications (including diazepam,

valproic acid, baclofen, and lorazepam) had minimal effect on the continuous muscle spasms. Botulinum toxin was injected into the facial, masseter, and laryngeal muscles with some relief of the muscle spasm, but the patient continued to require a tracheotomy because of intermittent respiratory insufficiency.

After 1 month of hospitalization, the patient was discharged with a respirator. In May 1989, he became distraught and committed suicide.

Patient 2. Summary. While being treated for prostate cancer, a 71-year-old retired executive developed progressive loss of voluntary horizontal eye movements, followed by spasms and myoclonic jerks of the face, masseter, pharyngeal, and abdominal muscles.

Chronology. In August 1988, the patient was found to have a retroperitoneal pelvic mass contiguous with the prostate. A biopsy yielded the diagnosis of adenocarcinoma. He was treated with leuprolide acetate (a gonadotropin-releasing hormone analog) with subsequent complete resolution of the pelvic mass. In January 1989, he developed blurred and double vision. Neurologic examination revealed impaired voluntary horizontal gaze and mild gait unsteadiness. An MRI of the brain showed only evidence of an old frontal infarct. CSF examination revealed mild pleocytosis (eight lymphocytes), five oligoclonal bands, and an elevated IgG index of 1.2. The leuprolide acetate was discontinued, and he underwent a bilateral orchiectomy.

In July 1989, following a tooth extraction, the patient developed twitching and spasms of his left masseter muscle. Over the subsequent several days, the muscle spasms spread to involve the masseter, facial, and pharyngeal muscles bilaterally. He noted progressive difficulty swallowing. Neurologic examination revealed markedly limited voluntary horizontal eye movements along with continuous muscle spasms of the face, masseter, and pharyngeal muscles. There was also intermittent abdominal myoclonus, bradyphrenia with preserved cognition, and mild gait unsteadiness. Repeat MRIs of the brain in July and again in September 1989 were normal except for the old frontal infarct. A follow-up CSF examination in September 1989 showed no cells, but there were seven oligoclonal bands and an IgG index of 1.2. Serum ANA was positive at 1 to 640, but the anti-double-stranded DNA was negative. Cerebral angiography was normal without evidence of vasculitis. An intestinal biopsy for Whipple's disease was negative. Immunohistochemical studies for antineuronal antibodies were negative.

The patient's diplopia and bulbar muscle spasms continued, and examination in November 1989 revealed complete absence of saccades to the left, with markedly slow saccades to the right limited to about 15 degrees. Vertical saccades were grossly intact. He was given antibiotics for Whipple's disease, without response. Administration of clonazepam and valproic acid resulted in moderate improvement in the muscle spasms and myoclonus. Fluoxetine was begun for depression. B₁₂ level was marginally low with a normal Schilling test, and the patient received B₁₂ repletion without improvement. A brief course of oral steroids as well as a trial of carbidopa/levodopa were also without benefit.

Quantitative eye movement testing, performed in April 1990, identified complete absence of horizontal saccades, with normal horizontal VOR gain. Vertical saccades were present, but peak velocity measurements were low (25-degree vertical saccades showed a mean

peak velocity of 225 deg/sec downward and 197 deg/sec upward; normal >325 deg/sec).

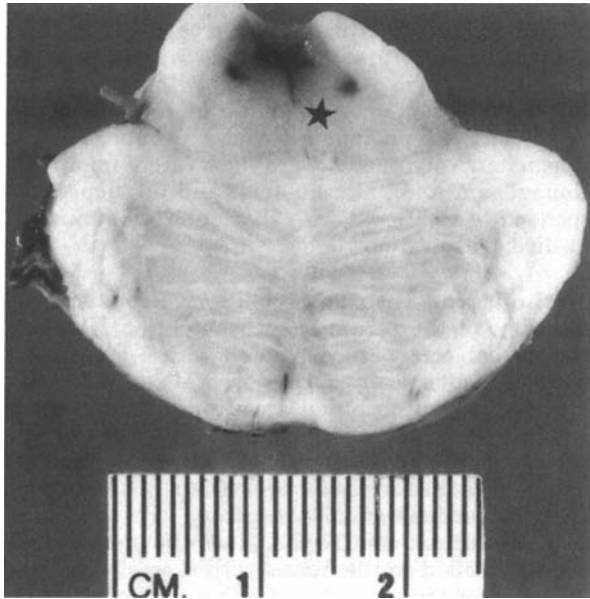
The patient's gait instability progressed, and in July 1990, a trial of plasmapheresis with five complete plasma exchanges was performed with no improvement. Cine-esophagram showed significant swallowing impairment, but the patient refused a G-tube. His muscle spasms and myoclonus were moderately improved with clonazepam and valproic acid, and his depression responded to treatment with fluoxetine. In January 1991, he died of aspiration.

Methods and results. Serum antibody studies. Serial dilutions of the serum from both patients and several control subjects were incubated with 6-mm frozen sections of histologically normal frontal cortex, cerebellum, and brainstem obtained at autopsy from individuals without neurologic disease. The sections were screened for antineuronal autoantibodies using indirect immunoperoxidase methods as previously described.² As a control, sections were also incubated with the buffer used to dilute the patients' serum. No antineuronal antibodies were identified on the frontal cortex, cerebellar, or brainstem sections incubated with either patient's serum.

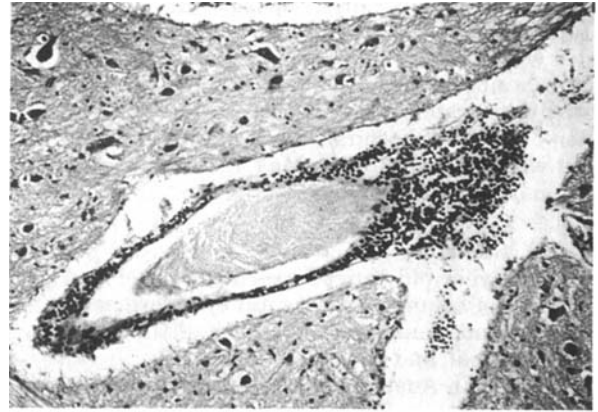
Postmortem examinations. General postmortem examination revealed no evidence of occult malignancy or gross evidence of prostate cancer. Pelvic lymph nodes were negative in patient 1, but one node was positive for adenocarcinoma in patient 2. Gross examination of the brain in patient 1 revealed a gunshot wound of the brain with entry at the left occipital pole and exit at the central sulcus region. The brains were otherwise unremarkable. Sections of the brainstems at the level of the midbrain, pons, and medulla were grossly normal (figure 2A).

On microscopic examination, pathology in both cases was mainly localized to the medulla and pons. There were perivascular cuffs of chronic inflammatory cells, microglial proliferation, microglial nodules, and diffuse astrogliosis (figure 2). These changes were most pronounced in the paramedian pontine reticular formation, the vestibular nuclei, the dorsal cochlear nuclei, and the lateral cuneate nuclei. The sensory nuclei of the trigeminal nerves were mildly affected, whereas the motor nuclei of V were normal. Other bulbar motor nuclei, including the abducens, facial, hypoglossal, and dorsal vagal nuclei, were also normal. The cerebellar cortex showed mild, patchy loss of Purkinje cells (including the flocculonodular lobe), with mild, reactive hyperplasia of the Bergmann glia. In patient 2, both hippocampi had a few vessels surrounded by chronic inflammatory cells. Spinal cord and peripheral nerves were unremarkable.

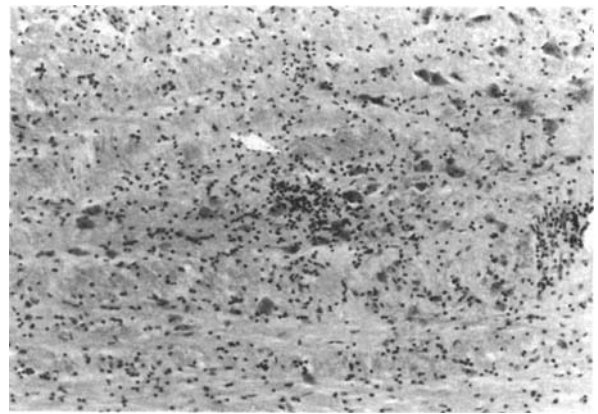
Discussion. What is the evidence for a paraneoplastic autoimmune pathogenesis in these two patients? Both had prior adenocarcinoma of the prostate treated with different medications. At postmortem examination, residual cancer was present in patient 2 but not in patient 1. Both patients had prominent perivascular round-cell infiltrates and microglial nodules in the brainstem—typical of paraneoplastic encephalitis. Viral serologies were negative and no viral inclusions were identified. Furthermore, the chronic progressive course is atypical for viral brainstem encephalitis. The remarkable localization of clinical signs supports an autoimmune pathogenesis with selective damage to



A



B



C

Figure 2. (A) Cross-section of the pons in patient 1 showing normal gross appearance. Microscopic sections of the paramedian pons in patient 1 (B) showing perivascular round-cell infiltration and (C) a microglial nodule (below arrow). The star in panel A indicates the approximate area of microscopic sections. Magnification in B and C $\times 100$ before 52% reduction.

a subpopulation of neurons. We hypothesize that the prostate cancer expressed an antigen that was also expressed by a class of brainstem neurons. That we were unable to identify antineuronal antibodies in the patients' sera may indicate that the targeted antigens were not accessible with standard immunohistochemical techniques or that the immunologic damage was cell-mediated.

The two main clinical signs in our patients were loss of voluntary horizontal eye movements and continuous spasms of the bulbar musculature. The premotor neuronal network critical for voluntary horizontal gaze is located in the paramedian pontine reticular formation (PPRF). Both patients had prominent inflammatory cell infiltrates and microglial nodules in the PPRF. Localized lesions in this area in animals result in a loss of horizontal eye movements with preservation of reflex horizontal eye movements.⁵ Excitatory and inhibitory "burst neurons" in the PPRF activate ocular motor neurons of agonist and antagonist eye muscles to produce high-velocity horizontal saccades. By contrast, neurons providing recurrent inhibition to the bulbar motor nuclei are scattered throughout the brainstem reticular formation. A localized, structural lesion could not selectively damage these inhibitory neurons without also damaging nearby

fiber tracts and motor nuclei. An immune reaction directed against a specific neuron or synapse, however, could selectively damage this subclass of inhibitory neurons.

Remote effects of cancer on the nervous system were first described at the end of the last century, but case reports were largely anecdotal, and since similar syndromes occur without cancer, many authors questioned a cause-and-effect relationship.¹ In 1965, Henson et al⁶ introduced the term "encephalomyelitis with carcinoma." Patients with cancer presented with clinical signs localizing to multiple levels of the nervous system including the cortex, brainstem, cerebellum, spinal cord, posterior root ganglia, and nerve roots. The characteristic pathologic findings were perivascular cuffing by lymphocytes, activation of microglia with the formation of microglial nodules, and selective loss of neurons. The process was predominantly, although not exclusively, confined to gray matter. Most cases of paraneoplastic encephalomyelitis have been associated with small-cell carcinoma of the lung¹; some have been associated with small-cell carcinoma of the prostate,⁷ but none with adenocarcinoma of the prostate. Henson et al⁸ used the term "bulbar encephalitis" to describe the condition of two patients who presented with primarily brain-

stem symptoms and signs but who, at postmortem, also exhibited some involvement of the cerebellum and spinal cord. As in our patients, the patients of Henson et al showed prominent involvement in the medulla at the floor of the fourth ventricle, but unlike our patients, the inferior olives and the bulbar motor nuclei were also involved. McGill⁹ reported an unusual case with auditory and vestibular symptoms and typical pathologic changes involving only one side of the medulla. Finally, Pillay et al¹⁰ described a patient with brainstem encephalomyelitis associated with bronchial carcinoma who presented with multiple cranial neuropathies, optic neuritis, and bilateral internuclear ophthalmoplegia. There are no prior reports of involvement of the PPRF and brainstem sensory nuclei as seen in our patients.

Autoantibodies directed against Purkinje cells and tumor cells in women with gynecologic tumors are convincing evidence of a cause-and-effect linkage,^{2,4} but only about one-half of all patients with paraneoplastic cerebellar degeneration have antineuronal antibodies.¹¹ Antineuronal antibodies are less common in patients with paraneoplastic encephalomyelitis,¹² and there have been no reports of antineuronal antibodies in patients with localized brainstem or bulbar syndromes.

Remote involvement of the nervous system has rarely been reported with prostatic cancer. In a review of carcinomatous neuromyopathy, Croft and Wilkinson¹³ reported that two of 31 patients with prostatic cancer had some type of neuropathy (no details were given). Têtu et al¹⁴ reported the myasthenic syndrome (Eaton-Lambert syndrome) in a patient with small-cell carcinoma of the prostate initially thought to have adenocarcinoma. Greenlee et al⁷ described two patients with small-cell cancer of the prostate who had antinuclear antibodies (anti-Hu) and cerebellar degeneration.

The syndrome of opsoclonus-myoclonus, the best-described brainstem paraneoplastic syndrome,¹⁵ usually occurs in children with neuroblastoma but also occurs in adults with tumors of the breast, uterus, lung, and thyroid. These patients exhibit chaotic, rapid, conjugate eye movements (opsoclonus) along with myoclonus of the trunk and limbs. Pathologic studies have identified perivascular mononuclear cell infiltrates of the brainstem and cerebellum in some patients¹⁶; others show no abnormalities.¹⁷ Zee and Robinson¹⁸ speculated that selective involvement of the omnipause neurons in the pontine reticular formation could account for the ocular oscillations. An intriguing hypothesis is that common antigens expressed by the omnipause neurons and tumor cells trigger an immune attack against the omnipause neurons. Although some patients do have antineuronal nuclear antibodies (anti-Ri), there is no evidence for a humoral or cellular immune attack against a subpopulation of neurons in patients with opsoclonus-myoclonus.^{15,19}

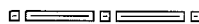
Stiff-man syndrome is a rare neurologic disorder

manifested by axial and appendicular muscular rigidity. The bulbar musculature is infrequently involved. Some cases show pathologic changes typical of encephalomyelitis,^{20,21} and a few have been associated with cancer.²²⁻²⁴ Some patients have autoantibodies directed against glutamic acid decarboxylase.^{25,26} Presumably, selective damage of the GABAergic inhibitory neurons in the spinal cord causes the muscular rigidity. Our patients may have had a bulbar equivalent of stiff-man syndrome. Glycine is an inhibitory neurotransmitter of neurons in the medullary reticular formation, providing inhibitory feedback to the cranial nerve motor nuclei.^{27,28} Glycine is also an inhibitory neurotransmitter within the vestibular nuclei and the PPRF.²⁷ An autoimmune process directed against glycine-producing neurons or receptors could lead to the combination of clinical symptoms and signs in our patients.

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Rapid-onset dystonia-parkinsonism

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Article abstract—We studied a large family with a previously undescribed, autosomal dominant dystonia-parkinsonism syndrome. We chose to call the disorder "rapid-onset dystonia-parkinsonism" (RDP) based on the unusually rapid evolution of signs and symptoms. Affected individuals developed dystonia and parkinsonism between 14 and 45 years of age. The onset was acute in six individuals with the abrupt onset of symptoms over the course of several hours, and subacute in four others who had evolution over several days or weeks. Thereafter, progression of symptoms was usually very slow. Two had intermittent focal dystonia without parkinsonism, and one obligate gene carrier was asymptomatic at 68 years. CSF levels of homovanillic acid were decreased in the two individuals tested, but dopaminergic therapy provided only slight benefit. The *DYT1* gene responsible for early-onset, generalized idiopathic torsion dystonia in Jewish and some non-Jewish families has been mapped to chromosome 9q34. Linkage analysis with three markers near the *DYT1* gene showed several obligate recombinations, excluding *DYT1* as a candidate gene for RDP. We believe RDP is unique and should be classified separately from other forms of hereditary dystonia-parkinsonism.

NEUROLOGY 1993;43:2596-2602

Dystonia and parkinsonism have been described both separately¹⁻³ and together⁴⁻¹⁵ in many hereditary neurologic disorders. Although the cause remains unknown for all of them, the gene responsible for idiopathic torsion dystonia (ITD)^{1,2} in some

families was mapped to chromosome band 9q34,¹⁶⁻¹⁹ and the gene causing X-linked dystonia-parkinsonism^{14,15} was mapped to chromosome band Xq13.²⁰⁻²²

We recently evaluated a large Indiana family with a new autosomal dominant syndrome affect-

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I.J.B. was supported in part by Clinical Research Center grant no. RR02558 at the University of Texas Medical School, Houston. X.O.B. was supported by NINDS grant no. NS28384 and a grant from the Dystonia Medical Research Foundation.

Received December 14, 1992. Accepted for publication in final form May 28, 1993.

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