

# Bilateral Horizontal Gaze Palsy in Presumed Paraneoplastic Brainstem Encephalitis Associated With a Benign Ovarian Teratoma

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**Abstract:** A 28-year-old woman with a previous history of recurrent benign ovarian teratoma developed a bilateral horizontal gaze palsy, a right facial paresis, and bilateral trigeminal hypesthesia. Magnetic resonance imaging disclosed high signal in the rostral pons. Results of all other laboratory studies, including those for antineuronal antibodies (anti-Hu, anti-Yo, anti-Ri, anti-Tr, anti-Ma1, anti-Ma2, and anti-CV2/CRMP5), were negative. Pelvic ultrasound revealed a residual mass in the left ovary, which was confirmed as teratoma on surgical pathological examination. Complete neurologic recovery occurred within two weeks of surgical removal of the teratoma and treatment with intravenous corticosteroids and immunoglobulin. This case demonstrates that a search for an occult neoplasm is extremely important in the diagnosis of presumed paraneoplastic encephalitis even if antineuronal antibodies are not found.

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Paraneoplastic syndromes are remote effects of cancer that are not directly related to tumor growth, metastases, metabolic or nutritional derangements, or side effects of therapy. The clinical manifestations of a paraneoplastic

process are often the first presentation of an underlying tumor (1). Paraneoplastic encephalomyelitis–sensory neuropathy (PEM-SN) is a well-characterized syndrome that is typically irreversible and most commonly associated with small-cell lung cancer and anti-Hu antibodies (2). The clinical manifestations are variable, including multifocal involvement of the central or peripheral nervous system or both, and brainstem or limbic encephalitis. There are a few case reports of supranuclear, nuclear, or internuclear ocular motor abnormalities affecting horizontal or vertical eye movements or both in patients with PEM-SN (3–8). We report a case of complete bilateral horizontal gaze palsy in a patient with a presumed paraneoplastic brainstem encephalitis associated with a benign ovarian teratoma. Surgical removal of the tumor, combined with intravenous corticosteroid and immunoglobulin treatment, rapidly reversed all neuro-ophthalmic manifestations.

## CASE REPORT

In 1998, a 28-year-old woman of Chinese descent developed impaired memory, personality change, auditory hallucinations, inappropriate behavior, and hypersomnolence followed by acute central respiratory failure that required mechanical ventilation. Findings on magnetic resonance imaging (MRI) scans and extensive laboratory work-ups were normal, except for a mild cerebrospinal fluid (CSF) pleocytosis and minimal electroencephalographic bilateral background irregularities. A palpable pelvic mass was confirmed on ultrasound and computed tomography as a  $14 \times 10 \times 10$ -cm complex cystic lesion in the right ovary. Neurologic symptoms resolved eight weeks after a complete right salpingo-oophorectomy and removal of a mature cystic ovarian teratoma, in conjunction with 400 mg/kg intravenous immunoglobulin (IVIG) per day for five days and 1 g intravenous methylprednisolone daily for five days, followed by a gradual taper of oral prednisone starting at a daily dose of 60 mg.

Nearly three years later, she developed slurred speech. An MRI scan showed a small, hyperintense T2-

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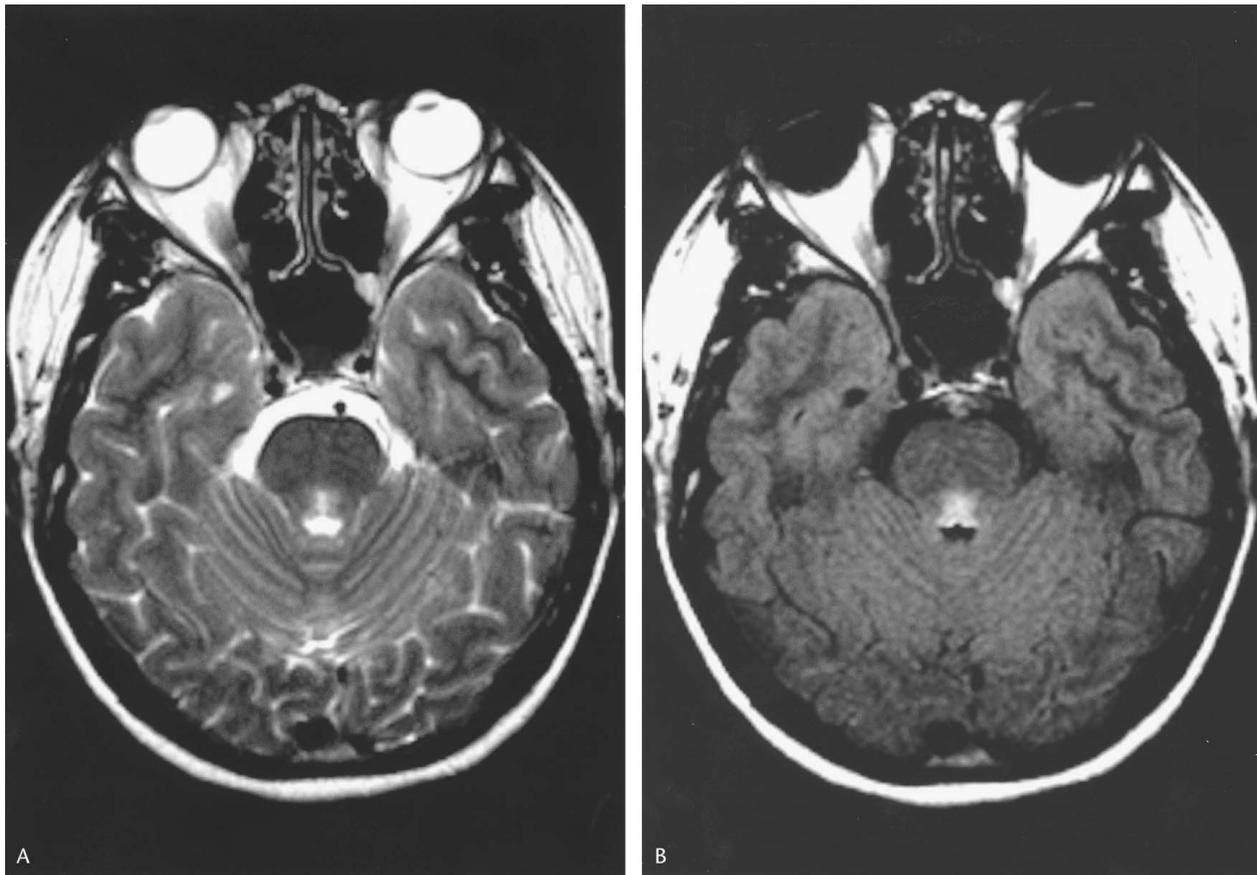
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weighted signal in the dorsal posterior aspect of the medulla just anterior to the fourth ventricle. Again, findings on extensive laboratory testing, including CSF oligoclonal bands and evoked potentials, were normal. Ultrasonography revealed the presence of two small, 2-cm cystic masses in the left ovary that were not present at the time of her first illness. Six weeks after partial left salpingo-oophorectomy with resection of a benign ovarian teratoma and IVIG and corticosteroid therapy, her neurologic manifestations resolved (9).

Seven months later, she developed a one-week history of progressive diplopia, numbness of both sides of the face (including the anterior half of the tongue), and ataxia. Visual acuity was 20/20 in each eye. Pupils, visual field, color vision, and findings on slit-lamp and fundoscopic examinations were normal. She had a complete bilateral horizontal gaze palsy affecting saccades, smooth pursuit, and the vestibulo-ocular reflex (VOR). Vertical eye movements and convergence were normal. She had reduced sensation to pinprick over the face and anterior scalp bilaterally. A mild right facial weakness was present. Corneal sensation

was mildly reduced OD. She had moderate difficulty with tandem gait. Mental status examination was normal. Results of cardiovascular, respiratory, and abdominal examinations were normal.

Findings on investigation of the following were all normal: complete blood cell count; electrolytes, creatinine, blood urea nitrogen, glucose, calcium, magnesium, and phosphate; INR, partial thromboplastin time, AST, ALP, bilirubin, lactate dehydrogenase, creatine kinase, and C-reactive protein; CSF studies (cell count, oligoclonal bands, glucose, protein, albumin, Venereal Disease Research Laboratories test, immunoglobulin G [IgG], polymerase chain reaction for cytomegalovirus, herpes simplex virus, and Epstein-Barr virus, immunofluorescent assay for cytomegalovirus, cryptococcal antigen, bacterial, viral and fungal cultures); anti-dsDNA, anti-Sm, anti-RNP, anti-Ro, anti-La, ANCA, rheumatoid factor, anti-centromere, anti-mitochondrial, and smooth muscle antibodies; cryoglobulin, C3, C4, human immunodeficiency virus (HIV), hepatitis B and C serological testing; alpha fetoprotein and Ca125 tumor markers; antineuronal antibodies (anti-Hu,



**FIG. 1. A.** Axial T2-weighted magnetic resonance imaging scan at the level of the mid pons shows high signal in the periaqueductal region. **B.** Axial FLAIR at the same level accentuates the high signal area noted on the T2-weighted study.

anti-Yo, anti-Ri, anti-Tr, anti-Ma1, anti-Ma2, and anti-CV2/CRMP5); visual, somatosensory, and brainstem auditory evoked potentials; chest x-ray; urinalysis; and beta-HCG. Serum immunoglobulin quantification revealed an elevated IgG level (31.9g/L) and normal immunoglobulin A and immunoglobulin M levels, with no M-spike.

Pelvic ultrasound revealed a  $1.7 \times 1.5 \times 1.1$ -cm mass in the left ovary, consistent with a residual or recurrent teratoma. Brain MRI scan demonstrated a region of hyperintense signal on T2-weighted scan and FLAIR in the midline dorsal pons involving the facial colliculus extending to the floor of the fourth ventricle (Fig. 1). No abnormality was found in the cerebral hemispheres.

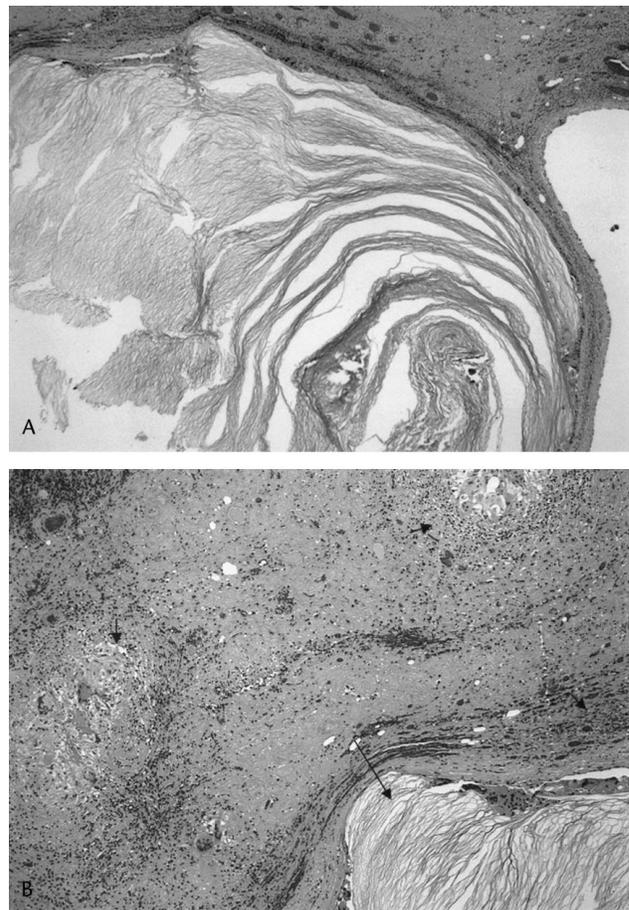
The patient was started on a daily regimen of 1 g intravenous methylprednisolone and 24 g IVIG. Despite treatment, she continued to deteriorate with new onset of dysphagia after five days. She underwent a partial left salpingo-oophorectomy. Surgical pathological findings revealed a benign residual cystic teratoma characterized by a small, keratin-filled cyst of 1.4 cm in maximum dimension with an associated granulomatous reaction (Fig. 2). Following surgery, she was treated with another three-day course of 24 g IVIG daily. Within two weeks after surgery, her bilateral horizontal gaze palsy, dysphagia, and bilateral facial numbness had resolved. She was discharged on a tapering dose of oral prednisone and remained free of symptom at a 10-month follow-up.

## DISCUSSION

Our patient, who had history of recurrent benign ovarian teratoma, manifested recurrent central nervous system (CNS) symptoms and signs, starting with a limbic encephalopathy and later brainstem involvement. All neurologic manifestations disappeared promptly after surgical removal of the teratoma, in combination with corticosteroid and IVIG therapy.

In the most recent episode, she presented with a brainstem encephalitis manifested by hypesthesia in the trigeminal distribution, bilateral horizontal gaze palsy, and a right lower motor neuron facial paresis. The absence of horizontal saccades, smooth pursuit, and VOR, with sparing of convergence, was consistent with a lesion in the sixth nerve nuclei bilaterally, with or without involvement of the paramedian pontine reticular formation.

It is conceivable that the tumor was a coincidental finding and that the neurologic manifestations were due to another disease process. However, results of our extensive investigations for an infectious, vasculitic, or other neoplastic condition were negative. A relapsing demyelinating disease is unlikely, considering the prolonged psychiatric disturbance followed by acute central respiratory arrest, normal laboratory findings (including the absence of oligoclonal bands in the CSF), the absence of white matter



**FIG. 2.** Histopathological appearance of the left ovary (hematoxylin and eosin stain). **A.** Low magnification (original magnification  $\times 25$ ) shows a keratin-filled cyst of 1.4 cm in maximum dimension. **B.** Higher magnification (original magnification  $\times 50$ ) shows a keratin-filled cyst (long arrow) and associated granulomatous reaction (short arrows).

abnormalities in either hemisphere on multiple MRI scans, and the dramatic recovery following surgical resection of the tumor in each episode. These phenomena support a diagnosis of paraneoplastic encephalitis.

PEM-SN, first described by Henson (10) in 1965, is a rare disorder with variable clinical manifestations depending on the location of degeneration in the central or peripheral nervous system, or both. Dalmau et al (11) found that 78% of patients with PEM-SN and anti-Hu antibodies in their serum had small-cell lung cancer, whereas 13% had no detectable tumor. Other malignancies associated with PEM-SN include ovarian and breast carcinomas, Hodgkin's disease, non-Hodgkin's lymphoma, other lung tumors, and cancers of the gastrointestinal tract, kidney, bladder, and prostate gland (1). Seventy-three percent of patients with PEM-SN present with multifocal involvement of the nervous system (11). Predominant findings include

sensory neuronopathy (62%), motor neuron dysfunction (20%), limbic encephalopathy (20%), cerebellar involvement (15%), brainstem encephalopathy (14%), and autonomic nervous system dysfunction (10%) (11).

A number of antibodies have been associated with PEM-SN (2,12). Because the sensitivity of available tests for these antibodies is only 50% to 60% (12), the diagnosis of PEM-SN should be entertained even without positive serological findings.

Pathologically, PEM-SN is characterized by gliosis and glial nodule formation, neuronal loss and degeneration, and perivascular lymphocytic infiltration without concomitant vasculitis in small arterioles (13). Treatment consists of removal of the underlying tumor. Immunomodulatory therapy using corticosteroids, plasmapheresis, or IVIG is rarely effective (11,14), but improvement has been reported in single patients (15,16). Even with tumor removal, the majority of patients have progressive neurologic decline, often ending in death within weeks to months as a result of autonomic dysfunction or respiratory failure of central or neuromuscular origin (11). There are a few cases with an indolent (17) or fluctuating (18,19) natural course, as well as those with spontaneous improvement of neurologic symptoms (20) or tumor regression (21).

Our patient is the first documented case of complete bilateral horizontal gaze palsy secondary to a reversible presumed paraneoplastic brainstem encephalitis associated with a benign ovarian teratoma. There have been two other reported cases of limbic encephalitis associated with immature ovarian teratomas. In both cases, antineuronal antibodies were not detected and symptoms improved or stabilized after tumor removal (22,23). In fact, our patient's initial presentation was in many ways similar to these two reported cases, lending further support to a paraneoplastic origin.

Ocular motor abnormalities have been associated with several different CNS paraneoplastic syndromes. In subacute paraneoplastic cerebellar degeneration, there have been descriptions of downbeat, upbeat, rotary, gaze-evoked, and rebound nystagmus, as well as opsoclonus, ocular flutter, saccadic dysmetria, saccadic pursuit, and skew deviation (1). In paraneoplastic opsoclonus syndrome, involuntary, arrhythmic, multidirectional saccades in all three dimensions have been documented (24).

Supranuclear, nuclear, and internuclear abnormalities of ocular motility have been described in PEM-SN, but not with a benign ovarian teratoma (3–8). Baloh et al (4) reported two patients with prostate cancer who had selective loss of horizontal saccades with sparing of horizontal slow eye movements. Postmortem examination revealed perivascular chronic inflammatory cells and microglial infiltration of the pons and medulla; neuronal loss in the

pontine tegmentum, medulla, and cerebellum; but preservation of brainstem motor nuclei. Both patients had prominent inflammatory cell infiltrates and microglial nodules in the paramedian pontine reticular formation, accounting for the selective loss of horizontal saccades. Neither patient had antineuronal antibodies detected in the blood.

Crino et al (13) reported three patients with ophthalmoparesis who had paraneoplastic brainstem encephalitis. One of them, who had a small-cell lung cancer and anti-Hu antibodies, had a bilateral horizontal gaze palsy affecting saccades, pursuit, and the VOR. Another patient had a complete external ophthalmoplegia and positive anti-Hu antibodies, but no evidence of systemic malignancy. On postmortem examination, the oculomotor, abducens, and trochlear nuclei were devoid of normal neurons. A third patient exhibited supranuclear ophthalmoparesis with profoundly reduced voluntary vertical and horizontal eye movements. Anti-Hu antibodies were negative. Following a course of methylprednisolone, the patient's neurologic status continued to decline, and she subsequently died of pneumonia. On postmortem examination, a papillary follicular thyroid carcinoma and an uterine leiomyoma were detected.

Pillay et al (5) described internuclear ophthalmoplegia and "optic neuritis" in a patient with bronchial carcinoma. Pathological examination revealed secondary demyelination of the medial longitudinal fasciculus and focal neuronal loss in the nuclei of the third, fourth, and sixth nerves. Reddy and Vakili (6) described a patient with mid-brain encephalitis and lung cancer who had a bilateral third nerve palsy. Pathological correlation revealed focal neuronal loss and gliosis involving the oculomotor nuclear complex.

Schiff et al (7) reported a patient with small-cell carcinoma of the lung and anti-Hu-associated encephalopathy, with vertical gaze paresis, absent downgaze, poor fixation, and hypometric horizontal saccades. Bennett et al (8) reported two patients with testicular cancer who exhibited supranuclear gaze disorders as a manifestation of PEM-SN. The first patient had a vertical gaze palsy with oculogyric crisis, lid retraction, and ocular tilt reaction. The second patient had a left hypertropic skew deviation, accompanied by a fluctuating, mixed pendular and jerk nystagmus. Both were positive for anti-Ta antibodies.

In our case, we presume that an immune response directed against the teratoma cross-reacted with normal brain antigens and caused the varied neurologic symptoms each time the tumor recurred. Specific antineuronal antibodies were not identified in our case or in the two reported cases of PEM-SN associated with immature ovarian teratoma (22,23). Whether such antibodies exist or, as an alternative, whether teratoma-associated paraneoplastic disorders arise from a cell-mediated mechanism is not known.

The present case demonstrates that a search for an occult neoplasm is extremely important in the presence of an unexplained encephalitis even if conventional paraneoplastic antibodies are absent. Resection of the tumor, even a benign one, may lead to symptom resolution. Although immunomodulatory therapy is not uniformly effective, empiric treatment with these agents may also be beneficial.

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