

# Bilateral isolated phrenic neuropathy causing painless bilateral diaphragmatic paralysis

**Abstract**—The authors report four patients with a syndrome of painless bilateral isolated phrenic neuropathy. Electrophysiologic testing demonstrated active denervation restricted to the diaphragm. Long-term recovery was poor. The authors conclude that bilateral isolated phrenic neuropathy is a cause of painless diaphragmatic paralysis distinguishable from immune brachial plexus neuropathy and other neuromuscular disorders with similar clinical presentation.

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P.T. Lin, MD; P.-B. Andersson, MBChB, DPhil; B.J. Distad, MD; R.J. Barohn, MD; S.C. Cho, MD; Y.T. So, MD, PhD; and J.S. Katz, MD

Bilateral phrenic neuropathy is a rare cause of unexplained dyspnea. Current literature generally describes this presentation in the setting of arm weakness with neck or shoulder pain, often occurring after infectious illness or surgery.<sup>1-3</sup> It follows that these factors have led authors to place this phenomenon within the spectrum of immune brachial plexus neuropathy.<sup>1-4</sup> In contrast, bilateral isolated phrenic neuropathy (BIPN) unaccompanied by pain, arm weakness, or antecedent events has not been emphasized as a distinct entity. In contrast to immune brachial plexus neuropathy, this painless involvement may be difficult to recognize and distinguish from other neuromuscular disorders with similar respiratory symptoms and signs.

**Methods.** We reviewed the records of consecutive patients referred to our neuromuscular centers between 1995 and 2005 for evaluation of bilateral diaphragmatic paralysis. These patients were initially evaluated medically and referred after cardiac, pulmonary, and chest wall disorders were excluded. Presenting symptoms ranged from dyspnea, orthopnea, and exercise intolerance to frank respiratory failure. Pulmonary function testing revealed a restrictive process, with reduction of forced vital capacity with a proportional reduction of forced expiratory volume in one second suggestive of a neuromuscular disorder. Chest radiographs demonstrated bilateral diaphragmatic elevation, whereas fluoroscopy showed paradoxical upward movement of the diaphragm with sniff maneuver.

**Results.** *Illustrative case.* A 43-year-old man noticed shortness of breath that developed over several days.

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From the Department of Neurology (Drs. Lin, Andersson, Cho, So, and Katz), Stanford University, Stanford, CA; the Department of Neurology (Dr. Katz), California Pacific Medical Center, San Francisco, CA; the Department of Neurology (Dr. Distad), University of Washington, Seattle, WA; and the Department of Neurology (Dr. Barohn), University of Kansas Medical Center, Kansas City, KS.

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Address correspondence and reprint requests to Dr. P.T. Lin, Department of Neurology, Stanford University, 300 Pasteur Dr., Room A343, Stanford, CA 94305; e-mail: [perlin@leland.stanford.edu](mailto:perlin@leland.stanford.edu)

There was no history of pain, prodromal illness, trauma, or vaccinations. A chest radiograph demonstrated an elevated left hemidiaphragm. Breathing became more difficult 4 months later and he reported that he could no longer walk 30 feet without becoming short of breath. Forced vital capacity (FVC) was 22% of predicted and the FEV1/FVC ratio was 78%. A repeat chest radiograph showed bilateral hemidiaphragm elevations and fluoroscopy confirmed diaphragmatic paralysis. Spinal fluid protein level was 61 mg/dL with a normal cell count. Antiacetylcholine receptor antibodies, anti-GM-1 antibodies, and serum creatine kinase level were normal.

Electrophysiologic testing revealed unobtainable phrenic nerve conduction responses bilaterally. Nerve conduction testing of the right upper limb and low-frequency repetitive stimulation of the nasalis (facial nerve), trapezius (accessory nerve), and first dorsal interosseous (ulnar nerve) were normal. EMG of the right diaphragm demonstrated more than four fibrillation potentials with no voluntary motor units, whereas EMG of the upper limbs, sternocleidomastoid, and cervical paraspinal muscles were normal.

There was no response to three monthly cycles of IV immunoglobulin (Ig; 2 g/kg). FVC was 38% of predicted 18 months after onset and remains unchanged seven years later.

*Clinical findings in BIPN.* Four of 15 patients referred for bilateral diaphragmatic paralysis (three men and one woman) were eventually diagnosed with BIPN (table). These patients had painless diaphragmatic weakness without abnormalities in other muscle groups. There were no antecedent viral illnesses or surgical procedures. The respiratory involvement reached its peak in a matter of days in three patients. In the other, the history and chest x-rays suggested that one phrenic nerve became involved before the other. FVC measurements ranged from 22% to 47% of predicted values for height, age, and sex. One patient had adult-onset diabetes and died 8 months after the onset of symptoms. There were no other features of peripheral neuropathy. The three other patients had little recovery of respiratory function over periods ranging from 1 to 7 years after onset. Spinal fluid protein levels in two patients were 31 and 61 mg/dL. Phrenic nerve compound muscle action potential amplitudes were reduced by 80% to 95% of the normal limit in three patients and were absent in the other, whereas nerve conduction studies (NCS) of limb muscles were normal. Low-frequency repetitive stimulations of the facial, accessory, or ulnar nerves

**Table** Presenting features of patients with dyspnea caused by bilateral isolated phrenic neuropathy (BIPN)

Patient/ age, y/ sex	Diagnosis	Involvement outside chest	Pertinent abnormal laboratory values	Forced vital capacity at time of presentation (% predicted)	Pertinent electrodiagnostic features
1/42/M	BIPN	None	CSF protein 61 mg/dL	22	Absent phrenic responses, denervation potentials, no voluntary motor units in diaphragm
2/51/M	BIPN	None	None	35	Absent phrenic responses, denervation potentials of diaphragm, no voluntary motor units
3/53/F	BIPN	None	CSF protein normal	38	Absent phrenic responses
4/74/M	BIPN	None	None	47	Low amplitude phrenic potentials, denervation potentials of diaphragm

was unremarkable. EMG demonstrated poor recruitment of motor units and denervation potentials limited to the diaphragm in each case. IV Ig had no effect in three patients. One had no response to high-dose prednisone.

In the 11 other cases with a similar clinical presentation, diaphragmatic involvement was the presenting feature of another neuromuscular disorder (see table E-1 on the *Neurology* Web site at [www.neurology.org](http://www.neurology.org)). In two cases, the dyspnea was accompanied by pain or arm weakness. The remaining nine had painless involvement, but there were additional neurologic findings outside of the chest that clarified the diagnosis.

**Discussion.** This report highlights a painless paralysis of the diaphragm caused by bilateral phrenic neuropathies with relatively acute onset and without antecedent factors such as infection or prior surgery. This presentation should be contrasted with the majority of reports on bilateral phrenic neuropathies, which are commonly described within the setting of immune brachial plexus neuropathy or Parsonage-Turner syndrome.<sup>1-3</sup> One large series suggests that phrenic neuropathy occurs unilaterally in about 6% and bilaterally in 1% of immune brachial plexus neuropathies,<sup>4</sup> but these cases generally have pain, upper limb weakness, and a tendency to recover with time. There are a number of reports that specifically describe isolated bilateral phrenic paralysis in immune brachial plexus neuropathy, but the association with pain has also been characteristic.<sup>1-3,5</sup> In fact, we were only able to find two prior descriptions of painless bilateral phrenic neuropathy. In one, respiratory difficulty began 6 weeks after a liposuction procedure and recovered a few months later.<sup>1</sup> In the other, dyspnea developed 2 weeks after a febrile illness, although there was no recovery after more than a year.<sup>3</sup> Both were reported within a broader case series where the remainder of cases had typical painful brachial plexus involvement.

There are reasons to be cautious about labeling BIPN as a *forme fruste* of immune brachial plexus neuropathy. For one, the nerves involved are not part of the brachial plexus. In addition, one can find reports of immune brachial plexus neuropathy with bilateral involvement, with focal weakness limited to

individual muscles of one extremity and with absence of pain at the time of onset.<sup>4</sup> However, the presence of painless, symmetric, bilateral involvement of the same muscle group is not known in this condition and may point toward a distinct immunologic process directed specifically at components of the phrenic nerve. Finally, from a practical standpoint, BIPN must be separated from other neuromuscular conditions that can also present with painless diaphragmatic paralysis. Our experience suggests that isolated clinical and electrodiagnostic involvement is unlikely in other disorders.

BIPN appears to be distinct from other neuropathies that may cause diaphragmatic failure. Prior reports describing phrenic involvement in the setting of multifocal motor neuropathy<sup>6</sup> led us to treat three of our patients with IV Ig. We found it difficult to exclude this potentially treatable disorder based solely on our clinical and electrophysiological findings since it may present focally<sup>7</sup> and because it is not possible to demonstrate conduction block by stimulating the phrenic nerve at only a single point. The failure to respond supports the notion that these conditions are distinct. One of our four patients was diabetic but bilateral phrenic involvement has been reported only within the context of mononeuropathy multiplex in diabetes.<sup>8</sup> Charcot Marie Tooth type 2C is an established cause of diaphragmatic paralysis but occurs with limb weakness, areflexia, and vocal cord paralysis.<sup>9</sup> A single report describes an acute, isolated bilateral phrenic neuropathy caused by sarcoidosis,<sup>10</sup> but this patient had enlarged mediastinal lymph nodes and abnormal numbers of white blood cells in CSF.

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Figure. Noncontrast CT of the head demonstrating extensive intracranial bilateral symmetric calcification more impressive in the cerebellum, basal ganglia, and periventricular regions.

## Extensive brain calcification and dementia in postsurgical hypoparathyroidism

Andrea Adorni, MD; Giulia Lussignoli, MD;  
Cristina Geroldi, MD; and Orazio Zanetti, MD, Brescia, Italy

A 72-year-old woman, 41 years after a total thyroidectomy, presented with progressive dementia, behavioral disorders (psychosis, agitation, and insomnia), hypocalcemia (7.69 mg/dL), hyperphosphatemia (5.14 mg/dL), and low parathyroid hormone

level ( $<1.0$  pg/mL). Her past medical history was remarkable for mood changes and syncope. Examination revealed movement disorders and primitive reflexes. Neck surgery is the most common cause of hypoparathyroidism. Symmetric, bilateral brain calcifications (figure) are found in approximately 50% of these patients, can be silent for many years, and are related to the duration of metabolic abnormalities.<sup>1</sup> Brain calcifications can be due to many causes or be an incidental finding in CT studies. Calcification extent correlates with the severity and persistence of symptoms.<sup>1,2</sup>

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Address correspondence and reprint requests to Dr. A. Adorni, Alzheimer's Unit–Memory Clinic, IRCCS, Centro S. Giovanni di Dio-Fatebenefratelli, Brescia, Italy; e-mail: aadorni@fatebenefratelli.it

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