Failing phrenics: an obscure cause of exertional dyspnea
Case report and literature review
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Abstract

Introduction: Idiopathic phrenic nerve palsy is a rare cause of exertional dyspnea. We present a case of a patient presenting with worsening dyspnea of an unknown etiology found to be related to bilateral phrenic nerve palsy.

Discussion: Forty-two-year-old man presented to our emergency department with exertional dyspnea, orthopnea, and a left lower lobe consolidation treated initially as bronchitis by his primary physician as an outpatient, then subsequently as pneumonia at another institution, with no improvement in symptomatology. After admission to our hospital, CT chest demonstrated only supradiaphragmatic atelectatic changes. Echocardiography was normal. Bronchoscopy was contemplated however the patient could not lie flat. A fluoroscopic sniff test demonstrated diaphragmatic dysfunction and pulmonary function tests revealed restrictive pulmonary disease with evidence of neuromuscular etiology. Nerve conduction studies confirmed bilateral phrenic neuropathy. He was referred to a specialized neuromuscular disease center where subsequent workup did not demonstrate any specific etiology. A sleep study confirmed sleep disordered breathing suggestive of diaphragmatic paralysis and he was discharged on bi-level positive pressure ventilation.

Conclusion: This is a unique case of exertional dyspnea and orthopnea from diaphragmatic paresis caused by bilateral phrenic nerve palsy where the initial workup for pulmonary and cardiovascular etiologies was essentially unremarkable. Shortness of breath and orthopnea caused by phrenic neuropathy is a rare condition, yet has a variety of etiologies. Our case suggests a template to the diagnostic approach, management, and follow up of bilateral phrenic nerve palsy.

Abbreviations: AIDP = acute inflammatory demyelinating polyneuropathy, ANA = antineutrophil antibody, anti-ds DNA antibody = antiduallel stranded deoxyribonucleic acid antibody, anti-MuSK antibody = antimuscle specific receptor tyrosine kinase antibody, anti-SS-A antibody = anti-Sjogren’s syndrome A antibody, BIPAP = bi-level positive airway pressure, CMAP = compound motor action potential, CPAP = continuous positive airway pressure, CSF = cerebrospinal fluid, CT = computed tomography, DLAd = DLCO adjusted for hemoglobin, DLVA = DLCO adjusted for volume, DLCO = diffusing capacity of lung, EMG = electromyography, ERV = expiratory reserve volume, ESR = erythrocyte sedimentation rate, FEF25-75 = forced expiratory flow, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IC = inspiratory capacity, IVC = inspiratory vital capacity, JFK = functional residual capacity using nitrogen washout, MVV = maximum voluntary ventilation, pCO2 = partial pressure of carbon dioxide, PFTs = pulmonary function tests, PO2 = partial pressure of oxygen, REM = rapid eye movement, RV = residual volume, TLC = total lung capacity, VA = alveolar gas volume, VC = vital capacity.

Keywords: diaphragmatic paralysis, dyspnea, phrenic nerve palsy, phrenic nerve paralysis, sniff test
1. Introduction

The phrenic nerve contains motor neuron axons innervating the diaphragm, the primary muscle of inspiration. It arises from the fourth cervical root with augmented fibers from third and fifth cervical roots. Paralysis of the diaphragm from phrenic nerve palsy can be unilateral or bilateral. Depending on the extent of weakness, additional activity of the accessory muscles of inspiration may be required. Additionally recruitment of the abdominal muscles may augment exhalation. Diaphragmatic dysfunction explains the presenting symptomatology of dyspnea and orthopnea in these patients. Phrenic nerve paralysis resulting in diaphragmatic dysfunction, whether unilateral or bilateral, can be caused by infectious, traumatic, iatrogenic, malignant, and idiopathic etiologies.

2. Case presentation

A 42-year-old man presented with complaints of exertional dyspnea and nonproductive cough for 2 months, preceded by a viral upper respiratory tract infection. His exercise tolerance had been reduced to one half a block from his baseline of 8 blocks. He required elevating the head end of the couch to sleep as lying supine was associated with dyspnea. His review of systems was significant for loud snoring, witnessed apneas, and excessive daytime sleepiness as well as a recent 5 pound weight loss. He denied any fever, chest pain, joint pain, visual disturbances, swelling of feet, or any other associated complaints. There was a recent travel history to the Dominican Republic. A tuberculin skin test 2 years ago was negative. He had not received an influenza vaccine. He did not smoke cigarettes nor use any illicit drugs however, had a distant history of excessive alcohol consumption. Primary employment was at a car dealership.

One month before admission to our hospital, he was prescribed antibiotics by his primary medical doctor (PMD) for bronchitis, with no improvement in symptoms prompting admission to another hospital. A chest X-ray (Fig. 1) and computed tomography (CT) of chest (Fig. 2) showed patchy left lower lobe consolidation and atelectatic change prompting treatment for pneumonia with ceftriaxone and azithromycin. An echocardiogram done during that hospital admission showed an ejection fraction of 55% without any diastolic dysfunction. After marginal improvement he was told to complete antibiotic therapy with outpatient follow up. Subsequently his PMD prescribed a trial of furosemide, potassium, and lisinopril without symptomatic improvement.

On presentation to our institution, he appeared anxious and tachypneic. He was afebrile with a blood pressure of 141/89 mm Hg, pulse rate of 80/minute and respiratory rate of 24/minute. His body mass index was 32.8 kg/m². On auscultation the lungs were clear and heart sounds were normal. The rest of the examination was normal.

An electrocardiogram showed normal sinus rhythm with left axis deviation. Chest X-ray (Fig. 3) demonstrated a left lower
lobe density, potentially infectious or atelectatic in etiology, with no effusion. An arterial blood gas showed pH of 7.39, a partial pressure of oxygen (pO2) of 55.3 mm Hg, partial pressure of carbon dioxide (pCO2) of 42.5 mm Hg with an oxygen saturation of 86% on room air. The alveolar-arterial gradient was 42.2 (expected for age: 14.5). He had a lactic acid level of 1.2 mg/dL. Complete blood count, comprehensive metabolic panel, thyroid function test, and cardiac enzymes were within normal limits. C-reactive protein (CRP) of 7.38 mg/dL (normal <5.0) and erythrocyte sedimentation rate (ESR) of 42 mm/hr (normal <30) were mildly elevated. Urine and serum toxicology were negative. In the emergency department (ED) albuterol and ipratropium nebulization was initiated for suspicion of asthma, with minimal improvement and he was admitted to the general medical floor where he was noticed to have labored breathing persistently, especially when lying supine.

An echocardiogram showed an ejection fraction of 79%, a right ventricular systolic pressure of 26 mm Hg and no evidence of right-to-left intracardiac shunt by bubble contrast study. Chest CT with contrast showed no evidence of pulmonary embolism; however, patchy infiltrates were seen in the right middle and both lower lobes above the diaphragms. Lower extremities ultrasound did not demonstrate deep venous thrombosis. A trial of bi-level positive airway pressure (BiPAP) ventilation provided marginal symptomatic improvement. Bronchoscopy was contemplated however deferred due to the patient’s inability to lie flat for any extended period. With a clinical suspicion of diaphragmatic weakness, fluoroscopic evaluation for diaphragmatic movement revealed normal movement of diaphragm in upright position and no movement while supine. Bedside spirometry showed a forced vital capacity of 2.01 L in sitting and 0.97 L in supine position with a >30% change indicating bilateral diaphragmatic weakness. Pulmonary function tests (PFTs) (Table 1) demonstrated a forced expiratory volume in 1 second (FEV1) of 48% with an FEV1/FVC (forced vital capacity) ratio of 82. Total lung capacity (TLC) was 63%, vital capacity (VC) 48%, and diffusion capacity of carbon monoxide (DLCO) 46%. The reduced DLCO corrected to a supranormal value on correction for alveolar volume supportive of the fact that the observed physiological restrictive defect is extrinsic in origin (neuromuscular). Maximum inspiratory pressure was −30 cm H2O (normal <−70 cm H2O) and maximal expiratory pressure was 110 cm of H2O (normal >80 cm H2O).

To assess for myopathy, antineutrophil antibody (ANA), antidual stranded deoxyribonucleic acid antibody (anti-dsDNA antibody), anti-Sjogren syndrome A antibody (anti-SS-A), anti-SS-B, and anti-Jo antibody assays were performed and were negative. Serum aldolase and creatinine phosphokinase (CPK) levels were normal. Human immunodeficiency (HIV) virus assay was negative.

To evaluate for any neurological etiology, magnetic resonance imaging (MRI) of head and cervical spine were contemplated, but the patient was unable to maintain supine position. A CT scan of the head and cervical spine without contrast were then done which were unremarkable. Acetylcholine receptor antibody assay was negative. Lumbar puncture ruled out any infectious pathology. Cerebrospinal fluid (CSF) analysis was normal with normal opening pressure. Electromyographic (EMG) evaluation showed no reproducible response following stimulation of the left phrenic nerve, although patient did experience singultus. Right phrenic nerve stimulation revealed delayed latency and moderately decreased amplitude. Diaphragmatic monopolar needle study revealed decreased recruitment, no signs of acute denervation, however, the presence of polyphasic potentials suggesting mild, subacute (compensated) denervation. The final impression from these evaluations was that of bilateral phrenic neuropathy, worse on the left. He was then referred to a tertiary neuromuscular center. He was provided with semi-electrical hospital bed for symptom relief at home.

### Table 1

| Pulmonary function tests showing evidence of restrictive lung disease. | Reference | Prebronchodilator | % of Predicted (% reference) |
|---|---|---|---|
| FEV1, L | 3.55 (2.7–4.4) | 1.71 | 48 |
| FEV1/FVC, % | 82 (71–92) | 82 | 48 |
| FEF25–75%, L/s | 3.68 (1.9–5.5) | 1.85 | 50 |
| FEF, L/s | 9.17 (6.5–11.8) | 6.11 | 67 |
| FVC, L | 1.80 | 61 |
| Lung volumes, L | | | |
| TLC | 6.01 (5.0–7.0) | 3.90 | 65 |
| VC | 4.36 (3.4–5.3) | 2.10 | 48 |
| IC | 2.92 | 1.31 | 45 |
| FRC N2 | 3.07 | 2.59 | 84 |
| RV | 1.42 (1.1–1.8) | 0.50 | 35 |
| RV/TLC | 1.65 | 1.80 | 109 |
| Diffusing capacity | | | |
| DLCO, mL/mm Hg/min | 28.6 (20.7–36.6) | 13.2 | 46 |
| DL Adj, mL/mm Hg/min | 28.6 (20.6–36.6) | 13.2 | 46 |
| DLCO/VA, mL/mm Hg/min/L | 4.77 | 7.11 | 149 |
| DL/VA Adj, mL/mm Hg/min/L | 4.77 | 7.11 | 149 |
| VA | 4.01 | 1.85 | 51 |
| IC | 4.36 (3.4–5.3) | 1.16 | 27 |

DL Adj = DLCO adjusted for hemoglobin, DL/VA = DLCO adjusted for volume, DLCO = diffusing capacity of lung, ERV = expiratory reserve volume, FEF = forced expiratory flow, FEV1 = forced expiratory volume in 1 second, FRC = forced inspiratory vital capacity, FRC N2 = functional residual capacity using nitrogen washout, FVC = forced vital capacity, IC = inspiratory capacity, IC = inspiratory vital capacity, MVV = maximum voluntary ventilation, PEF = peak expiratory flow, RV = residual volume, TLC = total lung capacity, VA = alveolar gas volume, VC = vital capacity.
At the neuromuscular disease center his repeat labs showed normal ACE and aldolase levels. A repeat EMG confirmed our findings of bilateral phrenic nerve palsy. CT abdomen was reported normal and CT chest was unchanged. Sitting PFTs demonstrated an FEV1/FVC of 84, FEV1 of 1.54 L (37%) and FVC of 1.84 L (35%) while semi-recumbent at 45° an FVC of 1.13 L (22%), and an FEV1 of 0.89 L (21%). Respiratory muscle pressures were Pmax 56 cm H2O (47% predicted) and PEmax 196 cm H2O (87% predicted). A sleep study revealed severe sleep disordered breathing with evidence of increased upper airway resistance in nonrapid eye movement sleep (NREM) sleep and rapid eye movement (REM) related hypoaxemia and hypoventilation compatible with neuromuscular disease. During sleep he had increased work of breathing with thoracoabdominal paradoxical breathing and use of accessory muscles, arousals, and mildly elevated end tidal carbon dioxide tension seen particularly in the supine position, with more severe worsening when such patients are asleep. Patients can have morning headaches, confusion and may also develop signs of cor pulmonale in this setting.

On chest X-ray, unilateral diaphragmatic paralysis may be suggested by an elevated hemidiaphragm. In bilateral diaphragmatic paralysis this discrepancy can be absent. Fluoroscopic imaging helps confirm diaphragmatic dysfunction by demonstrating resting elevation of the diaphragm above the normal range, diminished, absent or paradoxical movement on inspiration, mediastinal shift on inspiration, and paradoxical movement of diaphragm under an added load like sniffing. Never the less, paradoxical movements of a normal diaphragm can occur in hydropneumothorax, lung fibrosis, atelectasis, subphrenic abscess, or liver enlargement. In unilateral disease fluoroscopic findings can be unreliable as unequal movement of the two halves of the diaphragm can be a normal finding unless one excursion is at least twice that of the other. In addition, the hemidiaphragm rises 2 cm during a sniff. Sniff fluoroscopy is seen to be positive in 90% of patients with unilateral diaphragmatic paralysis. Other imaging techniques such as diaphragmatic ultrasound and MRI can also be useful diagnostic adjuncts with ultrasound evaluation becoming the standard of care.

PFTs are instrumental in the evaluation of diaphragmatic weakness and manifest primarily as restrictive lung disease. VC and FVC are influenced by tidal inspiratory pressure to generate inspiratory change in volume and can worsen with positional change from the upright to supine position in respiratory and other pathologies. In patients with bilateral diaphragmatic paralysis, VC characteristically falls by half or more in supine position, which in normal subjects is reported to be as much as 20% decrease. Those values falling between 20% to 50% suggest weakness of diaphragm. Reductions in maximum inspiratory pressure and transdiaphragmatic pressures are characteristic. Serial PFTs are valuable to assess the degree of weakness and follow disease progression.

Phrenic nerve conduction time is a sensitive indicator of phrenic nerve function and contributes toward identifying phrenic nerve disease as the cause of diaphragmatic dysfunction. Prolongation of phrenic nerve conduction time has been demonstrated in phrenic neuritis, mediastinal tumors, surgical trauma, and also in peripheral neuropathies. Compound motor action potential (CMAP) of diaphragm is often decreased in amplitude in diaphragmatic paresis. In complete paralysis, no CMAP can be recorded from phrenic nerve stimulation.

Spontaneous recovery in phrenic nerve neuropathy is rare and difficult to treat. Recovery of paresis may occur over a period of many months and in some cases, it is irreversible. In patients who improve 26% may relapse. When dyspnea is disproportionate to the degree of physical activity or to the severity of pulmonary disease, treatment options of the diaphragmatic paralysis should be considered. Topiramate has nontraumatic diaphragmatic paralysis. Unilateral paralysis may be asymptomatic and incidentally found on routine chest X-ray or can present as an abrupt onset of dyspnea. In unilateral paralysis, asymmetry of abdominal wall motion or a decrease in the expansion of the ipsilateral costal margin may be detected in deep inspiration but these findings are unreliable and insensitive. The most suggestive finding of bilateral diaphragmatic dysfunction is abdominal paradox, which is the inward movement of the abdomen while the chest expands during inspiration. Rare cases of bronchospasm associated with phrenic nerve palsy have been reported in literature. There can be elevation in the arterial carbon dioxide tension seen particularly in the supine position.
been successfully used in patients with phrenic nerve paralysis secondary to diabetes mellitus.\textsuperscript{[11]} Other treatment options for severe cases include positive pressure ventilation, negative pressure cuirass, rocking beds and positive pressure pneumobolts. In life threatening cases, tracheotomy with positive pressure ventilation is necessary.\textsuperscript{[2,20]} There are case reports in which infants with respiratory failure secondary to unilateral phrenic nerve palsy responded to continuous positive airway pressure (CPAP) therapy.\textsuperscript{[22]} For select cases, phrenic nerve pacing may benefit in patients who have lesions located proximally in the upper cervical cord or brainstem as it requires intact lower phrenic nerve function.\textsuperscript{[2]} Surgical plication can be done in patients with unilateral diaphragmatic paralysis with good results. This prevents the paralyzed hemidiaphragm being pulled up by the movement of the healthy hemidiaphragm. It improves ventilation and enhances respiratory muscle function, exercise performance, and blood gas exchange.\textsuperscript{[23]}

A small retrospective study by Gayan-Ramirez et al found that improvement is not predictable from baseline measurements obtained from PFTs or phrenic nerve conduction evaluation. Partial functional reversal was seen in 43% of patients after 1 year in those with unilateral or bilateral diaphragm paralysis. Disease etiology and type, whether unilateral or bilateral palsy, also did not influence functional respiratory recovery. It is uncertain whether inspiratory function training is associated with pulmonary function improvement but can be employed in such patients and may help improve pulmonary status.\textsuperscript{[11]}

4. Conclusion

Our case emphasizes several characteristic features of the diagnosis, workup, and management of diaphragmatic paralysis. In any patient who presents with orthopnea and/or abdominal paradox, although a rare entity, diaphragmatic dysfunction should be included in the differential especially without cardiopulmonary disease. Sleep disordered breathing as seen in our patient is not uncommon and provides an additional diagnostic clue. Diaphragmatic ultrasound is an easily performed screen for diaphragmatic dysfunction and may obviate further, more expensive and invasive diagnostic workup. Abnormal phrenic nerve EMG can narrow the differential to neuropathic causes of diaphragmatic dysfunction and help locate and quantify the degree of palsy.

The etiologic spectrum of phrenic nerve palsy is wide. An extensive workup in our patient was inconclusive and therefore his case was believed to be secondary to a postviral inflammatory process. Recovery can be prolonged. Serial positional PFTs are objective, invaluable tools to assess disease course.

References

\textsuperscript{[1]} Gayan-Ramirez G, Gosselin N, Troosters T, et al. Functional recovery of diaphragm paralysis: a long-term follow-up study. Respir Med 2008;102:690–8.
\textsuperscript{[2]} Gibson GJ. Diaphragmatic paralytic pathophysiology, clinical features, and investigation. Thorax 1989;44:960–70.
\textsuperscript{[3]} Akhtar J, Siddiqui MA, Khan NA, et al. Right phrenic nerve palsy: a rare presentation of thoracic aortic aneurysm. Malays J Med Sci 2013;20:98–101.
\textsuperscript{[4]} Chaudhuri S, Gopalkrishna M, Paul C, et al. Can bilateral bronchospasm be a sign of unilateral phrenic nerve palsy after supraclavicular brachial plexus block? J Anaesthesiol Clin Pharmacol 2012;28:249–51.
\textsuperscript{[5]} Tang EW, Jardine DL, Rodins K, et al. Respiratory failure secondary to diabetic neuropathy affecting the phrenic nerve. Diabet Med 2003;20:599–601.
\textsuperscript{[6]} Laghi F, Tobin MJ. Disorders of the respiratory muscles. Am J Respir Crit Care Med 2003;168:10–48.
\textsuperscript{[7]} McCool FD, Taelepis GE. Dysfunction of the diaphragm. N Engl J Med 2012;366:932–42.
\textsuperscript{[8]} Chan CK, Loke J, Virgulto JA, et al. Bilateral diaphragmatic paralysis: clinical spectrum, prognosis, and diagnostic approach. Arch Phys Med Rehabil 1988;69:976–8.
\textsuperscript{[9]} Laguerre A, Eller E, Saintarailles J, et al. Unilateral diaphragmatic paralysis: an electrophysiological study. J Neurol Neurosurg Psychiatry 1992;55:316–8.
\textsuperscript{[10]} Davis J, Goldman M, Loh L, et al. Diaphragm function and alveolar hypoventilation. Q J Med 1976;45:87–100.
\textsuperscript{[11]} Qureshi A. Diaphragm paralysis. Semin Respir Crit Care Med 2009;30:315–20.
\textsuperscript{[12]} Alexander C. Diaphragm movements and the diagnosis of diaphragmatic paralysis. Clin Radiol 1966;17:79–83.
\textsuperscript{[13]} Mantuani D, Nagdev A. Sonographic evaluation of a paralyzed hemidiaphragm from ultrasound-guided interscalene brachial plexus nerve block. Am J Emerg Med 2012;30:2099.e5–7.
\textsuperscript{[14]} Sarwal A, Walker FO, Cartwright MS. Neuromuscular ultrasound for evaluation of the diaphragm. Muscle Nerve 2013;47:319–29.
\textsuperscript{[15]} Gourie-Devi M, Ganapathy GR. Phrenic nerve conduction time in Guillain-Barre syndrome. J Neurol Neurosurg Psychiatry 1985;48:243–9.
\textsuperscript{[16]} Estenne M, Yernault JC, De Smet JM, et al. Phrenic and diaphragm function after coronary artery bypass grafting. Thorax 1985;40:293–9.
\textsuperscript{[17]} Davis JN. Phrenic nerve conduction in man. J Neurol Neurosurg Psychiatry 1967;30:420–6.
\textsuperscript{[18]} Chen R, Collins S, Remtulla H, et al. Phrenic nerve conduction study in normal subjects. Muscle Nerve 1995;18:330–5.
\textsuperscript{[19]} Wilcox PG, Pardy RL. Diaphragmatic weakness and paralysis. Lung 1989;167:323–41.
\textsuperscript{[20]} Minicucci MF, Issue RM, Zornoff LA, et al. Spontaneous recovery from long-term phrenic nerve palsy. South Med J 2009;102:115–6.
\textsuperscript{[21]} Rice AL, Ullal J, Vinik AI. Reversal of phrenic nerve palsy with topiramate. J Diabetes Complications 2007;21:63–7.
\textsuperscript{[22]} Bucci G, Marrzetti G, Picece-Bucci S, et al. Phrenic nerve palsy treated by topiramate causing bilateral phrenic nerve palsy. Arch Dis Child 1994;49:230–2.
\textsuperscript{[23]} Ciccolrella DE, Daly BD, Celli BR. Improved diaphragmatic function after surgical plication for unilateral diaphragmatic paralysis. Am Rev Respir Dis 1992;146:797–9.