Received: 10 January 2022 | Accepted: 27 January 2022

DOI: 10.1002/rcr2.915

CASE REPORT

Respirology Case Reports OPEN ACCESS APSR WILEY

Isolated diaphragm weakness and the diagnostic value of phrenic nerve stimulation

Sarbroop Dhillon[1] | Prarthana Abeyweera[1] | Christopher Kosky[1,2] | Lisa Harrison[1] | Ashvin Isaac[1] | William Noffsinger[1] | Elaine Pang[3] | Merrilee Needham[3,4,5] | Rick Stell[3] | Bhajan Singh[1,2,6]

[1]Department of Pulmonary Physiology & Sleep Medicine, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia

[2]West Australian Sleep Disorders Research Institute, QE II Medical Centre, Nedlands, Western Australia, Australia

[3]Department of Neurology, Fiona Stanley Hospital, Perth, Western Australia, Australia

[4]CMMIT, Murdoch University, Murdoch, Western Australia, Australia

[5]School of Medicine, University of Notre Dame, Fremantle, Western Australia, Australia

[6]School of Human Sciences, University of Western Australia, Crawley, Western Australia, Australia

Correspondence
Sarbroop Dhillon, Sleep Disorders Clinic, Level 5, 'G' Block, Queen Elizabeth II Medical Centre, Hospital Ave, Nedlands, WA 6009, Australia.
Email: sarbroop.dhillon@outlook.com

Associate Editor: Bei He

Abstract

Acute onset, atraumatic, bilateral diaphragm paralysis due to isolated bilateral phrenic neuropathy is uncommon. Respiratory physicians should be alert to this disorder because it is associated with considerable morbidity and diagnosis is often delayed. These case reports highlight important aspects of the presentation, investigations and management of this disorder.

KEYWORDS
diaphragm, magnetic stimulation, orthopnoea, phrenic nerve

CASE REPORT

Case 1

A 60-year-old car salesman with class one obesity and diet-controlled diabetes mellitus presented with progressive dyspnoea over 12 months. He never smoked and drank minimal alcohol. His illness began with severe neck soreness and stiffness that he attributed to sleeping in an unfamiliar bed whilst on holiday. On returning home, he was seen by a physiotherapist for a month. Exertional breathlessness and orthopnoea were noted during physiotherapy sessions but no action was taken. He received a cervical epidural injection a few months later which reduced his neck pain. He had no other respiratory or neurological symptoms. He reported no preceding neck trauma or significant respiratory or gastroenterological infections.

Physical examination revealed obesity (body mass index 33.2 kg/m^2), normoxia (SpO_2 95%), tachypnoea (respiratory rate 22 breaths/min) and accessory muscle use at rest. Even mild recumbency (60° bed angle) caused further tachypnoea, respiratory distress and use of accessory muscles. As bed angle was further reduced, the patient demonstrated paradoxical abdominal movement during inspiration and an inability to lie flat. A full neurological examination was unremarkable.

Respiratory function tests (Table 1) demonstrated moderate reduction in lung volumes and severe reduction in ventilatory capacity that appeared to be extrapulmonary in origin. Although maximal inspiratory and expiratory pressures (MIPS and MEPS) were normal, vital capacity (VC) declined by 53% in the supine posture suggesting diaphragmatic weakness. This was confirmed by a severe reduction in maximum transdiaphragmatic pressure measured by oesophageal manometry. Diaphragm electromyographic (EMG) activity measured by surface electrodes was detectable bilaterally during voluntary inspirations confirming that both phrenic nerves

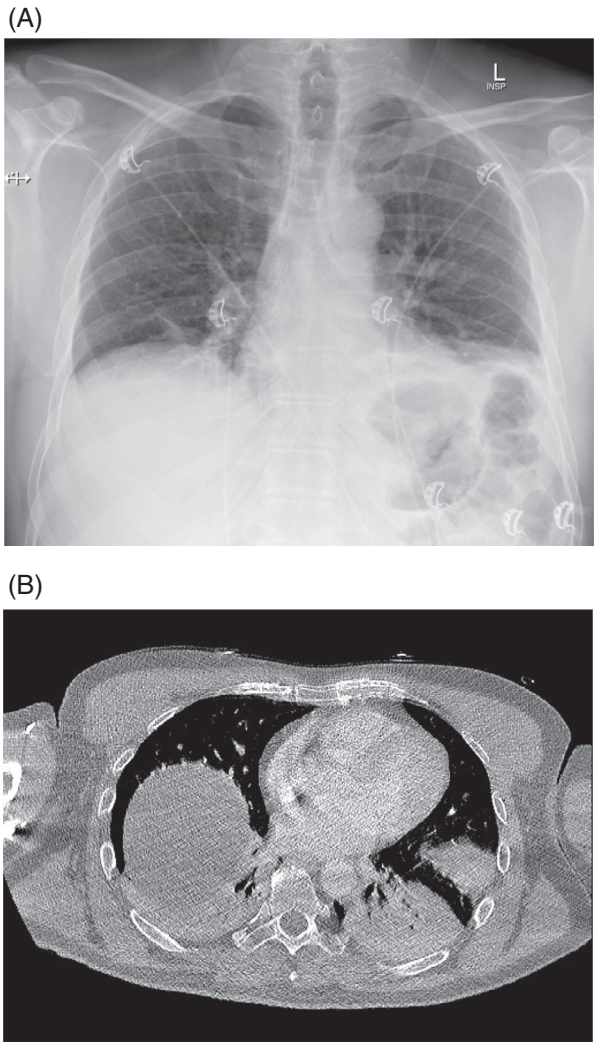

FIGURE 1 (A) X-ray demonstrating incomplete inspiration and lower zone opacities more prominent on the left. (B) Lower zone atelectasis, more prominent on the left

were intact. Magnetic stimulation of the phrenic nerves as they traversed the anterior neck (Magstim® 2002, The Magstim Company Ltd, Whitland, UK) demonstrated delayed nerve conduction latency bilaterally suggestive of demyelination (Figure 2). Peripheral nerve conduction studies and extensive EMG of other muscles including periscapular and paraspinal muscles were normal.

X-ray and high-resolution chest computerized tomography (HRCT) showed bilateral lower lobe atelectasis, but no mediastinal abnormalities that could damage the phrenic nerves (Figure 1). Magnetic resonance imaging of the cervical spine demonstrated no compromise of the spinal cord or its nerve roots. Polysomnography demonstrated very severe obstructive sleep apnoea (apnoea–hypopnoea index 152.6/h) with significant hypoxaemia. He was commenced on bi-level positive airways pressure therapy.

Inflammatory markers, creatinine kinase, vasculitis screen and serum immunoglobulins were normal. Cerebrospinal fluid protein was mildly elevated (0.58 g/L) with a normal cell count. Following specialist neurology assessment, a presumptive diagnosis was made of a variant of chronic inflammatory demyelinating polyneuropathy, exclusively involving both phrenic nerves. He was commenced on intravenous immunoglobulin (IVIG) therapy (2 g/kg). The patient underwent three further fortnightly maintenance doses.

Symptoms improved significantly within 3 months. After 2 years, orthopnoea had completely resolved and exertional breathlessness had mostly resolved. Repeat respiratory function tests showed normalization of lung volumes and ventilatory capacity, and no decline in VC in the supine posture, suggesting full recovery of respiratory muscle strength (Table 1). Magnetic phrenic nerve conduction studies showed normalization of phrenic nerve latency bilaterally suggesting remyelination (Table 1, Figure 2). In the event, this was a variant of acute brachial neuritis; given the severe pain at onset and apparent monophasic course, IVIG was slowly weaned off and ceased. However, he relapsed within 3 months. IVIG was recommenced and he remains in remission on maintenance IVIG.

Case 2

A 51-year-old previously well carpenter was referred with 3 weeks of neck pain and 1 week of orthopnoea. The illness began with a 24-h self-limiting episode of gastroenteritis. Two days after resolution of diarrhoea, he awoke from sleep with severe lower neck pain. A few days later he was seen by a physiotherapist and received dry needling. On his third scheduled therapy, he was unable to lie down due to orthopnoea. He presented to hospital that night, was thought to have a community-acquired pneumonia and was treated with intravenous antibiotics. His dyspnoea failed to improve and he was later transferred to our hospital for further assessment.

On examination, paradoxical abdominal movement on inspiration was observed when supine. Oxygen saturation was 96% on room air. Neurological examination was unremarkable. A chest x-ray and HRCT showed poor inspiration with bibasal atelectasis. Similar to Case 1, respiratory function tests demonstrated moderate lung volume restriction, severe reduction in ventilatory capacity, preserved maximum respiratory pressures but a significant decline (52%) in VC in the supine posture. This suggested severe diaphragmatic weakness.

As with Case 1, diaphragm EMG was present bilaterally during voluntary inspirations but magnetic phrenic nerve stimulation at the anterior neck showed delayed phrenic nerve conduction bilaterally suggestive of a demyelinating neuropathy. Peripheral nerve conduction studies and extensive EMG were normal. CT neck was normal, and blood tests did not reveal an autoimmune or neuropathic cause. Following specialist neurology review, a presumptive diagnosis of an acute inflammatory demyelinating phrenic neuropathy was made. He was commenced on 1 g/kg of IVIG

TABLE 1 Respiratory function tests, transdiaphragmatic pressure and phrenic nerve conduction latency before and after immunoglobulin therapy

	Case 1		Case 2	
Time	**Baseline**	**Two years after presentation**	**Baseline**	**Six months after presentation**
FEV_1, L (% predicted)	1.72 (47%)[a]	2.93 (83) %	1.58 (38%)[a]	1.99 (48%)
FVC, L (% predicted)	2.22 (46%)[a]	3.72 (79%)	2.15 (29%)[a]	2.81 (52%)[a]
FEV_1/FVC, %	0.77	0.79	0.95	0.71
Decline in vital capacity in the supine posture, %	53[a]	9	52	—
TLC, L (% predicted)	3.8 (52%)[a]	6.33 (88%)	5.14 (65%)[a]	—
Maximal inspiratory pressure, cm H_2O (% predicted)	−132 (125%)	−126 (88%)	−108 (101%)	−71 (67%)[a]
Maximal expiratory pressure, cm H_2O (% predicted)	160 (75%)	183 (121%)	248 (111%)	199 (89%)
Maximum transdiaphragmatic pressure during inspiration to total lung capacity, cm H_2O (% predicted)	<50% predicted[a]	—	—	—
Right phrenic nerve latency, ms	14–19[a]	5.3	14.5[a]	—
Left phrenic nerve latency, ms	9–12[a]	5.0	12.6[a]	—

Abbreviations: FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity.
[a]Outside the normal ranges.

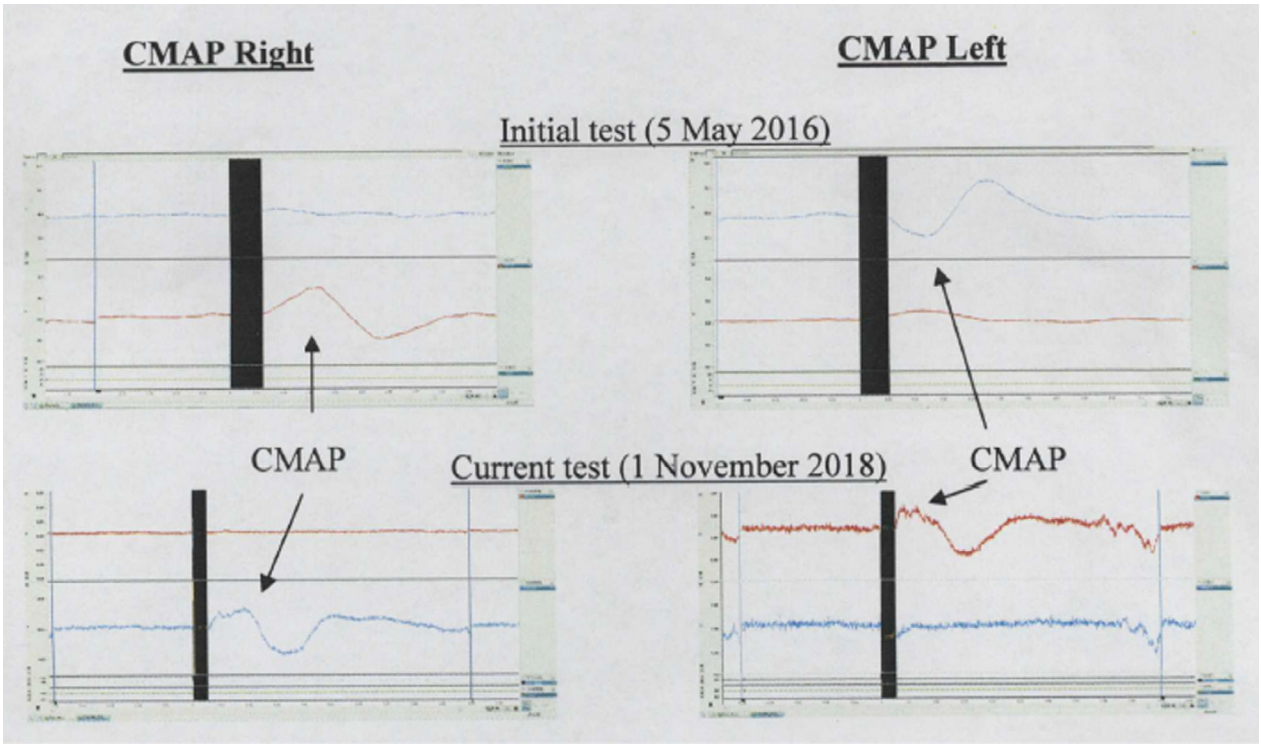

FIGURE 2 Phrenic nerve stimulation studies pre- and post-immunoglobulin therapy. The four images show the compound motor unit action potential (CMAP) following magnetic phrenic nerve stimulation of the right and left phrenic nerves as they traverse the anterior aspect of the neck. Each image has the same time scale on the x-axis and amplitude on the y-axis, and show the nerve conduction latency (represented by the width of the black bars) and a CMAP. There was a decrease and normalization in nerve conduction latency in 2018 compared to 2016 after 2 years of treatment with intravenous immunoglobulin

and subsequently maintained on monthly dosing. He was commenced on nocturnal non-invasive ventilation for severe orthopnoea.

At follow-up up to 9 months later, the patient's symptoms were relatively unchanged. Neck pain persisted requiring ongoing pregabalin. VC improved by 31%.

DISCUSSION

These cases demonstrate that diaphragm weakness is often overlooked as a cause of exertional breathlessness. However, the diagnosis can readily be identified from the clinical history, physical examination and simple bedside

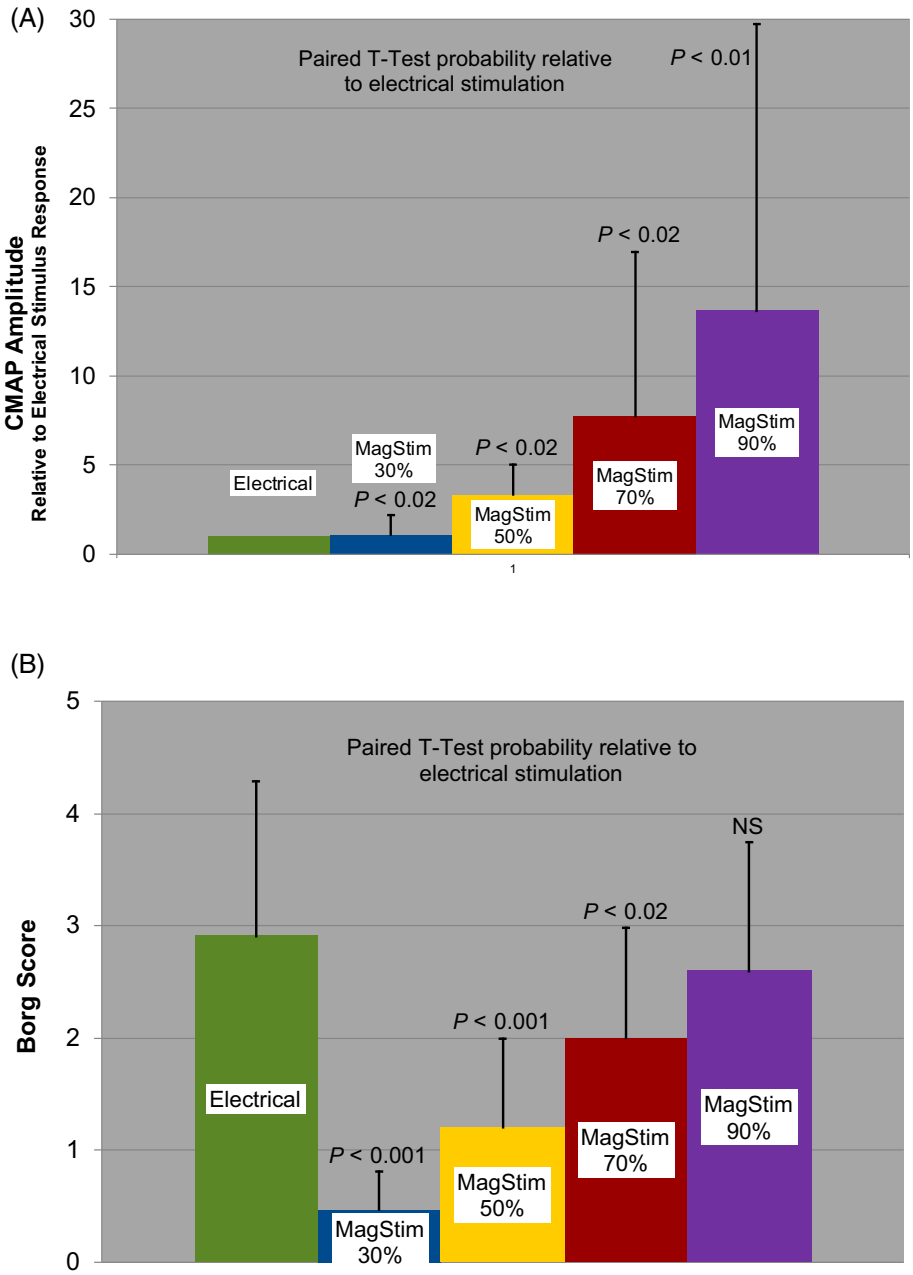

FIGURE 3 Comparison of electrical and magnetic phrenic nerve stimulation at the anterior neck in 16 healthy subjects ([mean ± SD] age 40.9 ± 12.9 years, BMI 25.1 ± 3.4 kg/m^2, 50% male). Electrical stimulation parameters were at 150 V, duration 0.1 ms, rate 1 Hz and magnetic stimulation was delivered at several intensities (30%, 50%, 70%, and 90%) using a MagStim 200^2 stimulator. (A) Compound muscle action potential amplitude. (B) Level of discomfort measured by Borg CR-10 questionnaire

tests. A complaint of orthopnoea or breathlessness during submersion in water should alert the clinician to the possibility of diaphragm weakness. Clinical suspicion can be confirmed by detecting paradoxical abdominal movement during inspiration, which is most easily seen by examining the patient in the supine or near supine posture. Measurement of VC at the bedside in the sitting and supine postures is likely to demonstrate a greater than 20% decline in VC in the supine posture.

Standard respiratory function tests can miss diaphragm weakness as a cause of breathlessness because they are conducted with the patient seated. Supine and erect VC is a useful screening test for diaphragm weakness. VC decreases in the supine posture by about 7% in health. This is because of displacement of gas by redistribution of blood to the lungs and reduced mechanical advantage of respiratory muscles. In patients with diaphragm weakness, decreases in VC can be ameliorated by compensatory activation of other respiratory muscles. This compensation is more effective in the erect than the supine posture. In diaphragm weakness, a greater than 20% decrease in VC from erect to supine is usually observed. Both our patients had declines

in VC in the supine posture of more than 50% implying severe diaphragm weakness.

MIPS and MEPS can be normal in diaphragm weakness. As illustrated by our cases, patients with severe diaphragmatic weakness may be able to generate normal maximum respiratory pressures using other respiratory muscles. Fluoroscopic sniff test can also be deceptively normal in bilateral diaphragm weakness because paradoxical movement of one hemidiaphragm relative to the other is absent in bilateral diaphragm weakness. The gold standard test for diaphragm weakness is measurement of maximum transdiaphragmatic pressures but this is invasive and only available at specialist respiratory laboratories.

When isolated diaphragm weakness is confirmed, it is useful to consider whether the pathology lies in the phrenic nerves or the respiratory muscles. Phrenic nerve function can be assessed non-invasively using electrical or magnetic stimulation of the nerve as it traverses the anterior aspect of the neck, eliciting a compound muscle action potential detected by surface electrodes placed on the skin over each hemidiaphragm. Magnetic stimulation has the advantages of more easily stimulating the nerve due to its wide field and causing less discomfort (Figure 3).

In both cases presented, phrenic nerve stimulation demonstrated marked slowing in nerve conduction velocities suggesting demyelination of both phrenic nerves. The abnormality was isolated to the phrenic nerves. No other causes for phrenic nerve damage were identified from detailed imaging and blood tests. Specialist neurology reviews suggested isolated idiopathic inflammatory phrenic neuropathies and both patients were treated with IVIG. Case 1 presented 5 years after Case 2 and was treated with a higher dose of IVIG. This may reflect differences in clinical practice that have changed over time, nevertheless resulting in a similar clinical outcome. In Case 1, this was associated with near-complete symptom resolution and normalization of nerve conduction velocities, diaphragm strength, ventilatory capacity and lung volumes at follow-up after 2 years. Thus far, Case 2 has had an incomplete recovery.

There are sporadic case reports of isolated bilateral diaphragmatic nerve palsy in the literature.[1–3] Most are described on the spectrum of acute brachial neuritis even in the absence of upper limb weakness because of concurrent severe shoulder pain on presentation.[4] In the absence of a known cause, there are few treatment options for bilateral diaphragm palsy, except for ventilatory support during recumbency and sleep. Surgical plication to prevent paradoxical diaphragm movement only has a role in unilateral palsy. Phrenic nerve pacing requires an intact phrenic nerve. Experimental treatments are described in the literature including IVIG, which was given to one patient on the basis of albumin-cytologic dissociation in cerebral spinal fluid.[5] A case series of three patients with unilateral diaphragm weakness, diagnosed using a sniff test without assessment of the phrenic nerves, found a favourable response to a single week's course of valacyclovir suggesting a viral aetiology.[6] Our cases suggest a role for immunotherapy in selected patients.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTION

All listed authors contributed to the article.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors declare that appropriate written informed consent was obtained for the publication of this manuscript and accompanying images.

ORCID

Sarbroop Dhillon https://orcid.org/0000-0003-2859-4480

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How to cite this article: Dhillon S, Abeyweera P, Kosky C, Harrison L, Isaac A, Noffsinger W, et al. Isolated diaphragm weakness and the diagnostic value of phrenic nerve stimulation. Respirology Case Reports. 2022;10:e0915. https://doi.org/10.1002/rcr2.915