

Bilateral Diaphragmatic Paralysis: A Rare but not to be Neglected Cause of Dyspnea

Ana R. Nogueira MD^{1,5}, Sumit Chatterji MD FRCP², Tiberiu Shulimzon MD² and Yehuda Shoenfeld MD FRCP (Hon) MaACR^{1,3,4}

¹Zabludowicz Center for Autoimmune Diseases, and ²Pulmonary Institute, Sheba Medical Center, Israel

³Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

⁴Laboratory of the Mosaics of Autoimmunity, Saint Petersburg University, Saint Petersburg, Russian Federation

⁵Faculty of Medicine of the University of Coimbra, Coimbra, Portugal

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The diaphragm is a dome-shaped structure that separates the thoracic from abdominal cavities and is the principal muscle of respiration. It is innervated by the phrenic nerves that arise from the C3 to C5 nerve roots, and is composed of fatigue-resistant slow-twitch type I and fast-twitch type IIa myofibers. Bilateral diaphragmatic paresis (incomplete paralysis) or total paralysis are rare causes of dyspnea, but should not be overlooked as this can lead to considerable delays in treatment [1]. Multiple etiologies are recognized, with the potential for recovery better for patients with post-traumatic or infectious causes, and worse for those with high-spinal lesions or neuromuscular disorders. Treatment options are limited but frequently involve nocturnal respiratory support due to the prevalence

of respiratory failure and sleep-disordered breathing in this population [1].

PATIENT DESCRIPTION

A 68-year-old male presented with progressive symptoms of orthopnea that had developed over 3 years. He reported feeling suffocated and unable to sleep unless in a seated position. His sleep was fragmented due to waking breathless several times at night and, consequently, he suffered from daytime fatigue, memory problems and concentration difficulties. Mild exertion breathlessness was also reported. He denied cough, wheeze, peripheral edema, or history of pulmonary infections. His medical history included essential arterial hypertension, atrial fibrillation, mixed hyperlipidemia, and hypothyroidism. There was no history of surgical procedures, cervical trauma, or neurological or rheumatological disease. The general physical examination was unremarkable; his body mass index was 32 kg/m².

A chest X-ray revealed reduced lung volumes bilaterally and minor atelectasis in the lower lobes. Polysomnography showed a significant progressive nocturnal hypoxemia (SpO₂ 91% to 70%) with absence of central or obstructive apnea. Moreover, the patient had trans-cutaneous paco₂ levels of 37 mmHg during the day.

Pulmonary function tests revealed a restrictive defect (total lung capacity of 62.2%) with a diffusion capacity of the lung for carbon monoxide of 66%. Ultrasound of the diaphragm confirmed the diagnosis of bilateral diaphragmatic paralysis. A repeat ultrasonography 18 months later showed mild improvement in diaphragmatic movement bilaterally on M-mode assessment, with a low diaphragm thickening fraction of 9% ([thickness at end inspiration (mm) - thickness at end expiration (mm)] / [thickness at end expiration (mm)] x100). However, significant muscle atrophy remained (using > 2.1 mm as a normal cutoff). These findings are shown in Figure 1.

Figure 1. Diaphragmatic ultrasonography performed after 18 months

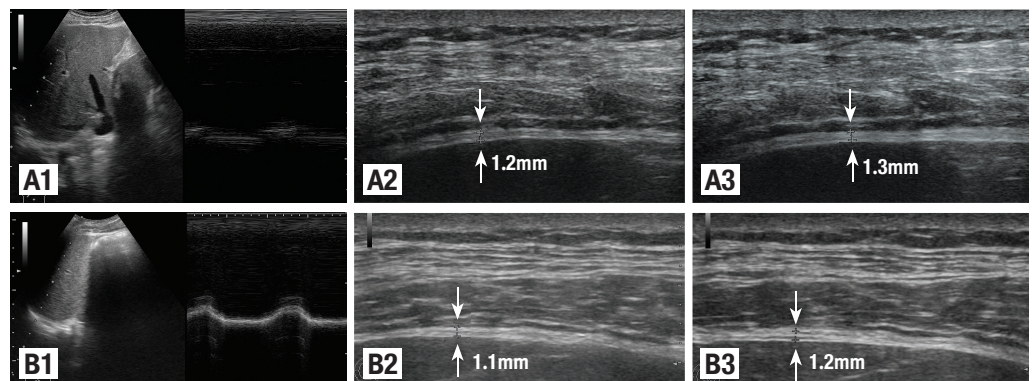
[A] Right hemidiaphragm

[B] Left hemidiaphragm

(1) M-mode imaging during full inspiration showing 1–3 cm cranio-caudal movement (normal ≥ 4.5 cm)

(2) High-frequency image of diaphragm thickness on full expiration (arrows indicate diaphragm thickness in mm)

(3) Full inspiration diaphragm thickness (arrows indicate diaphragm thickness in mm)



Non-invasive ventilation (BiPAP) was initiated at night with rapid resolution of fatigue, daytime somnolence and nocturnal hypoxemia. His compliance with the treatment was excellent, and he adapted easily to the equipment, describing it as having a positive impact on his quality of life and sleep [Figure 2].

COMMENT

The diaphragm is the primary muscle involved in inspiration, with contraction (downward displacement), resulting in the generation of higher negative intrapleural pressure (and hence trans-pulmonary pressure), which is the precursor to airflow into the lungs. Conversely, diaphragm relaxation during expiration is largely a passive process. Diaphragm paralysis can affect one or both hemidiaphragms. Bilateral dysfunction is rare and patients are usually symptomatic. It can appear following a thoracic trauma or surgery, infectious disease (for example, botulism), following a high-cervical cord injury, and in the context of metabolic or inflammatory disorders, myopathies or neuropathies [1]. Symptom onset varies according to the etiology – from sudden, with acute respiratory failure, to a more progressive course as in the case described here, which is often under-recognized or misdiagnosed [1]. Typical symptoms include dyspnea at rest, which is exacerbated by exertion, bending

or lying down. Submersion in water above the waist can also provoke breathlessness due to water pressure on the abdomen, preventing outward displacement of the abdomen due to relaxation of the abdominal wall muscles in inspiration – one of the strategies used to promote downward diaphragm movement and inspiratory airflow [3]. Nocturnal hypoventilation when supine, with progressive hypoxemia, low mean oxygen saturation, and episodes of worsening ventilation during rapid-eye movement (REM) sleep when thoracic muscular tone is diminished, are other characteristic findings.

A variety of techniques can be used to investigate the diaphragm function, with choices dictated by local availability and expertise. Plain chest radiographs show poor specificity for diagnosing bilateral palsy, with non-specific features like poor lung volumes or basal lung atelectasis [4]. Likewise, dynamic chest radiography (also referred to as fluoroscopy), such as the ‘sniff test’, demonstrates poor sensitivity in the context of bilateral paralysis and is no longer considered useful. Commonly accessible, useful and minimally invasive techniques such as lung function testing and diaphragm ultrasound are popular due to their good specificity and reproducibility. Bilateral diaphragm paralysis typically results in a moderate–severe restrictive defect (drop of total lung capacity to 30–50% predicted), and a similar reduction in supine vital capacity due to upward displacement of abdominal contents [1]. Maximal static and sniff inspiratory nasal pressures show reductions to less than 30% predicted, but the tests are less reliable, being more effort-dependent. Taken together, lung function testing is an essential tool in the investigation of restrictive lung disorders where diaphragm palsy remains a possibility.

Likewise, trans-thoracic ultrasound evaluation of diaphragm movement using B-mode and M-mode imaging techniques is sensitive and well-established [2]. Using a 12 MHz linear probe in the lower axilla, the diaphragm can be visualized in the ‘zone of apposition’ inferior to the costo-

phrenic angle, where it lies adjacent to the chest wall. The five diaphragmatic layers can be identified, and the resting muscle thickness, maximal inspiratory and maximal expiratory thickness is measured to determine if atrophy (< 2.1 mm thickness) or palsy (< 20% increase in thickness) is present [Figure 1]. This method can also be used to monitor the function recovery over time.

More invasive tests of function including trans-diaphragmatic pressure measurement with esophageal and gastric balloon catheters and electromyography are typically reserved for more difficult diagnostic cases, or if a distinction between neuro-pathic and myopathic causes is required. These tests are less comfortable for the patient and need specialist equipment and interpretation [1].

Treatment of bilateral diaphragmatic palsy can be challenging since surgical options such as diaphragm plication or phrenic nerve transplantation are ineffective in this setting. Infective and metabolic conditions need to be managed, and patients usually benefit from nocturnal non-invasive ventilatory support typically with bi-level ventilators (BiPAP). These devices augment tidal volumes, improve oxygenation, and reduce nocturnal hypercapnia by delivering pressure-support to spontaneous ventilation in both inspiratory and expiratory phases. In severe cases a tracheostomy and invasive ventilation may be necessary. Finally, diaphragmatic pacing can be considered where the etiology is high-spinal cord injury [1]. The potential for recovery of diaphragm function depends on the underlying pathology, and it is necessary to follow cases associated with phrenic injury, and inflammatory, metabolic or infectious causes for several years (3 years is typically suggested) as approximately two-thirds of cases may recover spontaneously [5].

To conclude, bilateral diaphragmatic paralysis should be considered in patients with any of the following: unexplained dyspnea or ventilatory failure, orthopnea, a restrictive pattern on lung function testing, small lung volumes on chest imaging,

Figure 2. Patient receiving bi-level positive airway pressure (BIPAP) non-invasive ventilation via a full-face mask



or failure to wean from mechanical ventilation. Non-invasive ventilatory support can be extremely useful and efforts must be made to ensure that the mask and machine setup is comfortable in order to optimize patient compliance. Early diagnosis and intervention in this way can lead to significant improvement in a patient's quality of life.

Correspondence

Dr. Y. Shoenfeld

Zabludowicz Center for Autoimmune Diseases,
Sheba Medical Center, Tel Hashomer 5265601, Israel

Fax: (972) 353-2855

email: yehuda.shoenfed@sheba.health.gov.il

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Capsule

How natural selection affects mouse coat color

Evolution, at its core, involves changes in the frequency of alleles subject to natural selection. But identifying the target of selection can be difficult. **Barrett** et al. investigated how allele frequencies affecting pigmentation change over time. Wild-caught mice (*Peromyscus maniculatus*) were exposed

to avian predators against naturally occurring dark or light backgrounds. Natural selection yielded shifts in coloration owing to genetic variants in the mouse coat color *Agouti* gene.

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Eitan Israeli

Capsule

A wrench in the gears of life for tuberculosis

Tuberculosis is a global health crisis that threatens to become worse as resistance to existing drugs emerges. Identifying ideal targets for drug development requires knowledge of weak points in biochemical pathways that are specific for the pathogen but are absent in hosts. **Ballinger** et al. identified a small molecule that inhibits the enzyme phosphopantetheinyl transferase (PptT), which is crucial for biosynthesis of myco-

bacterial structural and virulence. Treatment resulted in selective killing of the bacteria in vitro and in a mouse model. The target pathways were made sensitive to PptT inhibition by a second enzyme, phosphopantetheine hydrolase, whose activity opposes that of the transferase.

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Eitan Israeli

Capsule

Structure-based selection of human metabolite binding P4 pocket of DRB1*15:01 and DRB1*15:03, with implications for multiple sclerosis

Binding of small molecules in the human leukocyte antigen (HLA) peptide-binding groove may result in conformational changes of bound peptide and an altered immune response, but previous studies have not considered a potential role for endogenous metabolites. **Mirsa** et al. performed virtual screening of the complete Human Metabolite Database (HMDB) for docking to the multiple sclerosis (MS) susceptible *DRB1*15:01* allele and compared the results to the closely related yet non-susceptible *DRB1*15:03* allele. They then assessed the potential impact on binding of human myelin basic peptide (MBP). The authors observed higher energy scores for metabolite binding to *DRB1*15:01* than *DRB1*15:03*. Structural comparison of docked metabolites with *DRB1*15:01* and *DRB1*15:03* complexed with MBP revealed that Pheny-

lalanineMBP92 allows binding of metabolites in the P4 pocket of *DRB1*15:01* but ValineMBP89 abrogates metabolite binding in the P1 pocket. They observed differences in the energy scores for binding of metabolites in the P4 pockets of *DRB1*15:01* vs. *DRB1*15:03* suggesting stronger binding to *DRB1*15:01*. This study confirmed that specific, disease-associated human metabolites bind effectively with the most polymorphic P4 pocket of *DRB1*15:01*, the primary MS susceptible allele in most populations. These results suggest that endogenous human metabolites bound in specific pockets of HLA may be immunomodulatory and implicated in autoimmune disease.

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Eitan Israeli