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Central drive and ventilatory failure in late-onset Pompe disease: At the gates of a new phenotype

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Abstract

Subjects with late-onset Pompe disease (LOPD) typically present as slowly progressive proximal muscle weakness. Respiratory muscle weakness and diaphragmatic paralysis are common features, and may be the initial manifestation of the disease. There is often a poor correlation between the severity of limb and respiratory muscle weakness. Early clinical observations about disproportionate hypercapnia to the respiratory muscular weakness in late-onset Pompe disease were recognized and will be discussed with special reference to blunted respiratory drive, and the connections between early clinical observations, respiratory functional studies and anatomical findings. According to new evidence about blunted respiratory drive in Pompe disease, it is necessary to rethink what is meant by "asymptomatic Pompe disease" and propose a new phenotype with its therapeutic implications. The conceptual model of the mechanisms leading to respiratory failure in this disease could be considered according to these new findings. It may broaden the diagnostic spectrum of the adult forms and warrants a closer interaction between neurologists and pulmonologists. The recognition of this new phenotype of predominant central alveolar hypoventilation in Pompe disease will improve the understanding of the underlying mechanisms of ventilatory failure and could lead to improved future therapeutic strategies.

Keywords: Late-onset Pompe disease; Control of breathing; Hypercapnic respiratory drive; Central chemoreception; Hypercapnia; Respiratory underresponsiveness to hypoxia and hypercapnia.

1. Introduction

Pompe disease (PD) is an infrequent metabolic autosomal recessive disorder produced by the lack or deficiency of the acid alpha-glucosidase lysosomal enzyme in tissues of involved individuals. Late-onset Pompe disease (LOPD) is a multisystem condition, with a heterogeneous clinical presentation that mimics other neuromuscular disorders (NMD) [1].

Subjects with late-onset Pompe disease (LOPD) typically present with respiratory muscle weakness, and diaphragmatic paralysis may be the initial manifestation of disease [2,3]. Early clinical observations about disproportionate hypercapnia to the respiratory muscular weakness in LOPD were recognized and will be discussed with special reference to blunted respiratory drive.

2. Control of ventilation in neuromuscular diseases and late-onset Pompe disease

In early clinical observations, patients with NMD may present with CO_2 retention out of proportion to the degree of respiratory muscle weakness and alterations of lung mechanics. Some physiologic studies have reported a blunted central respiratory drive as the culprit for chronic hypercapnia [4–6]. However, prior clinical and functional studies focusing on the hypercapnic respiratory drive response in subjects with NMD have reported conflicting results [7].

It has been invoked that evaluation of the respiratory drive response in patients with NMD can be difficult in the presence of restrictive thoracic disorders and respiratory muscle weakness. Before 1975, central breathing response

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was based on the ventilatory response, a parameter influenced by respiratory system resistance, compliance and respiratory muscle weakness, which may cause variations in ventilation that do not reflect variations in the activity of the respiratory centers. Since then, determination of occlusion pressure at the first 0.1 s ($P_{0.1}$) has allowed the clinical assessment of central chemosensitivity. In fact, $P_{0.1}$ represents an useful index of the output of the respiratory centers. It can be obtained quickly and simply by a noninvasive technique and has proven to be a valuable tool for both physiological and clinical scenarios [8,9].

Early clinical descriptions of respiratory compromise in Pompe disease noticed the presence of unclear hypercapnia.

Bellamy et al. published a case report of a 34-year-old man with clear features of primary alveolar hypoventilation who was finally found to have LOPD. His vital capacity (VC) was only slightly reduced, and the ventilatory response to CO_2 (ml/min/mmHg) was virtually absent [10].

Rosenow and Engel published their clinical experience with 10 patients with LOPD. Three subjects presented with chronic hypercapnia disproportionate to VC [11].

Braun et al. studied 53 patients with proximal myopathy. Six of them suffered from LOPD. In two, hypercapnia was not related to very low values of VC and it was attributed to coexistent lung disease or abnormality of ventilatory control, or both [12]. As seen, anomalies of the control of ventilation in LOPD were suspected decades ago. Recently, the CO_2 rebreathing response in subjects with LOPD was assessed. They have a blunted central respiratory drive to hypercapnia induced by rebreathing, compared with controls. Those patients had chronic hypercapnia that appeared disproportionate to the degree of respiratory muscle weakness and mechanical defect, supporting a blunted central respiratory drive, as predicted on clinical basis [13,14].

3. What is the cause of the central depressed CO_2 response?

Motor problems in Pompe disease, including impaired ventilation, have historically been attributed to muscular pathology. However, the genetic mutation in Pompe disease is not restricted to muscle tissues, and accordingly central nervous system (CNS) pathology must be considered. Several studies have found glycogen deposition in the brain of subjects with the infantile form of Pompe disease [15–20]. But the most dramatic glycogen accumulation was present in the motor neurons of the ventral horn in the spinal cord, and interestingly, in all the motor nuclei of the brain stem [16], where the respiratory centers are located [21–23]. Because of the clinical characteristics of these patients, the functional correlate on control of ventilation deserve further research. These data agree with observations obtained in animal models [14,24]. Moreover, animal models of Gaa-/- showed impaired ventilatory CO_2 response when compared to the wild type controls [15].

Is this blunted response due to muscular (diaphragm and others respiratory muscles), or neuronal (motor nuclei of the brain stem or the motor neurons of the ventral horn of the spinal cord) malfunction? Results in animal models suggest that spinal motoneuron pathology, and in particular phrenic motoneuron pathology, is likely to make a substantial contribution to diaphragm motor deficits in Pompe disease [25].

Hobson-Webb et al. attempted to provide correlation between reported histological and clinical findings in a female patient and reviewed the literature on autopsy findings in LOPD patients [26]. The lack of arterial blood gases, maximal static pressures at the mouth and supine testing of VC preclude any speculation about the central control of ventilation. She was obese, and her cause of death was believed to be “positional asphyxia”. Sections of the medulla and spinal cord were likewise unremarkable. There was no evidence of glycogen deposition in the pons [27].

There is roughly agreement between clinical respiratory manifestations, pulmonary function test and histologic/autopsy findings. This is true for instances for diaphragmatic paralysis. Early clinical descriptions of ventilatory failure in LOPD suggesting blunted central drive are now supported by physiologic studies [13,14]. However, the small number of autopsies in LOPD prohibits any clinical, functional and pathological correlate.

4. What does asymptomatic Pompe disease mean?

Asymptomatic Pompe disease could be defined as patients with normal clinical examination, pulmonary function tests, and echocardiography. They may present with at least one subclinical abnormality, including hyperCKemia, vacuolar myopathy and muscle magnetic resonance imaging abnormalities. This also applies to patients screened because they have a relative diagnosed with Pompe disease. A few years ago, Echaniz-Laguna asked to the medical community: Should patients with asymptomatic Pompe disease be treated? [27]. The clinical spectrum of LOPD is expanding. As more patients are diagnosed and monitored around the world, it is becoming apparent that LOPD causes more than proximal myopathy and respiratory failure [26,28,29].

Considering that many subjects with LOPD have chronic alveolar hypoventilation because of blunted respiratory drive [13,14], it becomes relevant to ask what is meant by asymptomatic Pompe disease? The conceptual model of the mechanisms leading to respiratory failure in Pompe disease proposed by Fuller et al. could be considered in the light of these new findings [25]. This is true regarding the first critical period that represents the “asymptomatic” stage. Perhaps a new phenotype should be identified.

5. Chronic alveolar hypoventilation associated with inadequate central impulse?

In clinical practice, abnormalities of breathing control are often overlooked. They should be considered at any level of respiratory muscle weakness, restriction or obstruction level, or abnormalities of gas exchange that cannot

explain hypercapnia. The presence of morning headaches, hypersomnia, wheezing (gasping) or restless sleep are indicative of sleep-related breathing disorders (abnormalities of ventilation control tend to manifest earlier at night). Other findings can be polyglobulia not explained by diurnal hypoxemia and pulmonary hypertension without a clear cause. A history of unusually high breath holding time is also suggestive of alterations in the central impulse (apnea diving). It is important to maintain a high index of suspicion in cases of unexplained alveolar hypoventilation, delayed recovery of spontaneous breathing after sedation or anesthesia, or in the event of severe respiratory infection [30]. When present, any of these clinical findings warrant further testing with $P_{0.1}/CO_2$ challenge. A flat response confirms the diagnosis.

In summary, respiratory manifestations in LOPD are the consequence of a variable combination of inspiratory muscles weakness (in particular of the diaphragm), of the expiratory muscles, of the muscles of bulbar innervation, of the respiratory disorders during sleep, and the alterations in respiratory control. This route is not only a "*physiologic preciosity*" when planning early strategies for respiratory support.

Practical knowledge of how to detect, monitor and manage respiratory muscle involvement is crucial for optimal patient care. A multidisciplinary approach combining the expertise of neurologists, pulmonologists, and intensive care specialists is needed [3,31].

Even if peripheral and respiratory muscle function is improved via enzyme replacement therapy (ERT), glucosidase alfa (human recombinant GAA) does not enter the CNS. Declines in central drive from the respiratory neurons may still eventually lead to hypercapnic ventilatory failure and need noninvasive ventilation. ERT with modified forms of recombinant GAA and gene therapy approach can be a valid alternative in these situations and be paired with rational ventilatory support and rehabilitation programs. The different response to ERT depends on several factors, mainly on timing of treatment and cross reactive immune material [32]. The trajectories of hypercapnic ventilatory failure with ERT may well be different if the main mechanism is severe respiratory muscle weakness or blunted respiratory drive. The recognition of this new phenotype of predominant central alveolar hypoventilation in LOPD will improve the understanding of the underlying mechanisms of ventilatory failure and could lead to improved future therapeutic strategies.

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