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The Incidence of Late-Onset Pompe Disease in Subjects with Obstructive Sleep Apnea: A Cross-Sectional Study

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Abstract

Objectives: Current treatment options for obstructive sleep apnea syndrome often work to the satisfaction of the patient, but in certain cases may not yield the required results for reasons that remain unclear. Late-onset Pompe disease may be a contributing factor in these circumstances. The aim of the present study was to determine the incidence of late-onset Pompe disease in a population diagnosed with obstructive sleep apnea. Material and Methods: The study had a cross-sectional, explorative design to assess the prevalence of late-onset Pompe disease in subjects with an established diagnosis of obstructive sleep apnea syndrome. In two different study mid to large size sleep clinics in Europe patients have been asked to donate a blood sample for the detection of acid-glucosidase enzyme activity. Results: Of a total of 544 patients with mild to severe obstructive sleep apnea, none had an acid maltase deficiency. Conclusions: Screening for Pompe disease in newly or recently detected OSA patients in mid to large size sleep clinics is not clinically effective. It should be confined to those subjects with OSA when upright forced vital capacity during spirometry is only moderately abnormal, because of the disproportionate diaphragmatic involvement.

Keywords

Kidney, Transplant, Dialysis

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1. Introduction

Breathing during wakefulness and sleep depends on a mutual balance between central nervous system and muscle activation including diaphragm, costal, auxiliary and dilating muscles in the upper airway. This is ensured by a balance between dilating muscles in upper airway to avoid collapse due to inspiratory negative pressure combined with the effort of the respiratory muscles. They call for a balance of neural and anatomic factors maintain pharyngeal patency during sleep to allow efficient breathing. With sleep onset and during sleep, neural drive to the upper airway muscles falls, muscle tone is reduced, and pharyngeal resistance may increase even in individuals who do not snore and may contribute to obstructive sleep apnea (OSA) [1].

In patients susceptible to apnea, increased activity of upper airway muscles may overcome and compensate, partially or completely, for the added anatomic load induced by apnea and thus these muscles maintain normal ventilation for varying periods of sleep [2] [3]. Orchestration of diverse types of pressures generated by muscle activity is important in subjects with obstructive sleep apnea syndrome [4] [5]. Current treatment options during OSA like mandibular reposition application and continuous positive air pressure (CPAP) non-invasive ventilation intend to reduce obstruction of the upper airways [6]. They often work to the satisfaction of the patient, but in certain cases may not yield the required results for reasons that remain unclear. Late-onset Pompe disease may be a contributing factor in these circumstances.

Pompe disease, also referred to as acid maltase deficiency, is a rare genetic lysosomal storage disorder caused by an absence or deficiency of the lysosomal enzyme acid -glucosidase (GAA) [7] and leads to progressive accumulation of glycogen in many tissues but predominantly affects cardiac, skeletal, and smooth muscle [8]. The clinical presentation includes a range of phenotypes, commonly classified into infantile- and late-onset forms [9]. By definition, the late-onset form (also known as adult-onset) is a more slowly progressive form that is characterized by substantial involvement of skeletal muscle, which leads to progressive muscle weakness and respiratory insufficiency [9]. The clinical presentation of late-onset Pompe disease is markedly heterogeneous, making an accurate and timely diagnosis difficult [10].

The aim of the present study was to determine the incidence of late-onset Pompe disease in a population diagnosed with obstructive sleep apnea.

2. Study Population

The study had a cross-sectional, explorative design to assess the prevalence of late-onset Pompe disease in subjects with an established diagnosis of obstructive sleep apnea syndrome (OSAS) in large to midsize sleep clinics. In two different study centers in Europe (Leiden (mid size sleep clinic) and Copenhagen (large size sleep clinic), patients have been asked between January 2011 and October 2013 to donate a blood sample for the detection of acid-glucosidase enzyme activity. The Ethics Committee of both study centers approved the study protocol.

Patients were eligible for this study when their age was over 18 years, had a diagnosis of OSAS no older than 5 years confirmed by polysomnography. In the Leiden site, the apnea-hypopnea index (AHI) had to be higher than 15/h, whereas in the Copenhagen site it had to be higher than 5/h. We excluded patients when they had severe left-sided heart failure, an active psychiatric-diagnosed mental disorder or a clinical suspicion on vascular cerebral accident located in the ventral medulla of the brain stem.

In Leiden, all newly detected OSA patients were requested to participate in the study. In Copenhagen, patient information sheets were mailed to all patients registered in an OSAS database of the clinic, with an OSAS diagnosis established by criteria of the American Society for Sleep Medicine [11]. After informed consent was obtained, the medical record of each patient was checked if the in- and exclusion criteria of this study were met.

3. Testing Procedures

Blood was administered to standardized filter paper and allowed to dry for 24 h at ambient temperature. A fluorometric assay as a swift and reliable diagnostic tool [12] was employed to assess acid α-glucosidase in the Metabolic Laboratory, Hamburg University Medical Center, Germany. A tandem mass spectrometry [13] was only performed for borderline results or when confirmation was required.

4. Statistical Methods

All values are expressed as mean ± SD.

5. Results

In the Leiden site all 200 newly detected patients volunteered to participate in the study. Patient characteristics are shown in **Table 1**. The mean AHI was 34.3 ± 7.8/h.

In the Copenhagen site, 344 of 840 patients volunteered to participate and their mean AHI was 37.5 ± 23.1/h. Patient disposition is shown in **Figure 1**. Seventy-eight percent patients were currently receiving treatment with CPAP.

Of a total of 544 patients with mild to severe OSA, none had an acid maltase deficiency that would have been detected by enzyme assay using dry-blood-spot samples.

Table 1. Patient characteristics*.

	Leiden (n = 200)	Copenhagen (n = 344)
Age (yr)	56 ± 9	59 ± 11
Race	97% Caucasian	98.5% Caucasian
Gender (M/F (%))	62/38	80/20
Body Mass Index (kg/m^2)	28.2 ± 4.6	31.3 ± 6.3
AHI (/h)	34.3 ± 7.8	37.5 ± 23.1
On CPAP (%)	62	78

*all values are Mean ± SD

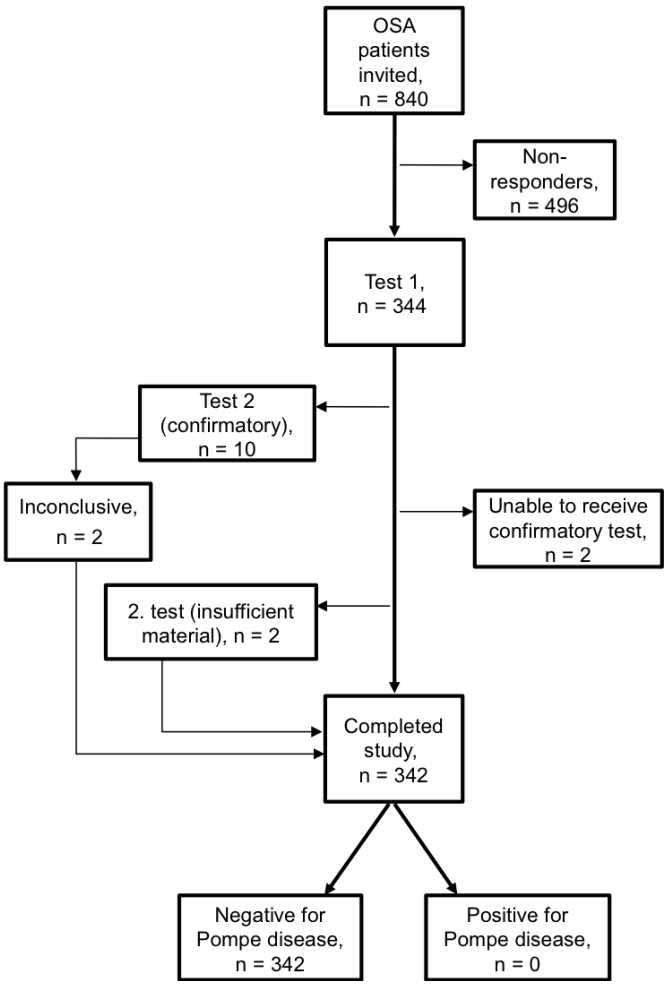

Figure 1. Disposition of Copenhagen patients.

6. Discussion

No case of Pompe disease was detected in this cohort of patients with established obstructive sleep apnea. This study was not designed to establish the prevalence of OSA in late-onset Pompe disease. To the best of our knowledge, the prevalence of late-onset Pompe disease in the general population has not been firmly established, but in subjects from European descent it is based on the gene frequency estimated to be 1:60,000 [14]. Our study population may have been enriched for late-onset Pompe disease due to possible muscle weakness as an additional cause of obstructive sleep apnea/hypopnea syndrome [15] [16]. Patients with OSA have, on average, a narrower and more collapsible upper airway relative to others. They may overcome the abnormal upper airway mechanics during wakefulness by increased activation of upper airway dilators but develop OSA in sleep because of a reduction in basal upper airway muscle activity and attenuation of the mechanisms involved in activating upper airway dilators in response to negative pressure. Therefore, we reasoned that OSA detected within the previous 5 years may facilitate the detection of late-onset Pompe disease when present in latency [17] [18].

Another reason for assessment of the presence of Pompe disease was that those OSA patients who experience some difficulties to benefit from CPAP or mandibulair reposition application may in fact suffer from late-onset of the former condition. Before this study started, one such example was detected in the Leiden clinic where a 79-year-old lady with normal body mass index had difficult to treat OSA. Spirometry showed a lower than predicted forced vital capacity with no other signs of respiratory disorders during full lung function assessment. Her serum acid α-glucosidase activity was markedly reduced and only after augmentation therapy of the enzyme deficiency her OSA was cured.

To our knowledge, this is the first targeted-population screening for late-onset Pompe disease in OSA patients. The two clinics involved in this study each receive 500 to 1000 newly referred patients for OSA diagnostic work up, annually. On the basis of our findings, the implementation of a standard screening program for late-onset Pompe disease in adult OSA patients in mid to large size sleep clinics cannot be recommended, but selected evaluation in high risk population, e.g. unexplained hypoventilations should be considered. Sleep physicians should nevertheless be aware of this rare condition, when a diagnosis of OSA has been rejected in patients presenting with hypoventilation and signs of mobility problems.

7. Conclusion

We conclude that screening for Pompe disease in newly or recently detected OSA patients is not clinically effective. It should be confined to those subjects with OSA when upright forced vital capacity during spirometry is only moderately abnormal, because of the disproportionate diaphragmatic involvement [19].

Acknowledgements

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