

Sleep breathing disorders and nocturnal respiratory pattern in patients with Glycogenosis type II

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Patients affected by glycogenosis type II frequently present sleep-disordered breathing. The presence of symptoms suggestive of sleep breathing disorders was investigated, by a questionnaire, in 10 patients, affected by adult or juvenile forms of glycogenosis type II. Diurnal respiratory function, diaphragm weakness and nocturnal respiratory pattern were evaluated at the enrolment. In patients presenting sleep disordered breathing, the same parameters were re-evaluated after treatment with assisted non invasive ventilation. Out of 10 patients, 5 presented symptoms suggestive of sleep-disordered breathing at the baseline, 2 a pattern of sleep apnea syndrome and 3 nocturnal hypoventilation. All patients presented diaphragmatic weakness. No correlation was found between forced vital capacity values (FVC) in sit position and nocturnal respiratory disorders. Five patients with respiratory disorders were treated with non invasive ventilation. All patients – after one month of treatment - showed an improvement in symptoms with reduced diurnal hypersomnia (ESS < 10), absence of morning headaches and nocturnal awakenings, and reduced nicturia regardless the modality of ventilation. We recommend that all patients with glycogenosis type II, once diagnosed, are carefully monitored for the development of respiratory involvement, even in the absence of reduced FVC values and in the early stages of the disease, to receive appropriate therapy.

Key words: glycogenosis, apnoea, hypopnea, hypoventilation, non invasive ventilation

Background

Patients with glycogenosis type II, also known as Pompe disease, are susceptible to the development of sleep disordered breathing (SDB). Sleep, with its reduction in ventilatory responses (1, 2), represents a major stress to weakened respiratory muscles and an opportune

time to assess the ventilatory reserve. Sleep disordered breathing is found in 40-70% of patients with neuromuscular diseases (3, 4), but relates poorly to daytime functional variables (5). Recognition of nocturnal hypoventilation is of particular importance because it contributes to the development of respiratory failure (6). Unfortunately, a simple relationship between awake measurements of respiratory function and nocturnal breathing events has not been found (7-10). Symptoms suggestive of SDB are often underestimated, particularly in patients with neuromuscular diseases (4, 11). The presence of symptoms such as morning headaches and daytime hypersomnia may interfere heavily on the quality of life of these patients. The treatment of respiratory disorders can therefore have a strong impact on improving their quality of life (12-14).

Aims of the study were: 1) to evaluate respiratory function, nocturnal respiratory pattern and presence of symptoms suggestive of sleep-disordered breathing in a group of 10 patients, affected by Glycogenosis type II; 2) to investigate the relationship between diurnal respiratory function, diaphragmatic dysfunction and nocturnal breathing patterns; 3) to assess the improvement in symptoms after treatment with non invasive ventilation (NIV).

Patients and methods

Ten patients affected by adult or juvenile form of glycogenosis type II (Table 1) aged $41,2 \pm 13,3$ were progressively enrolled. All patients – at the enrolment – filled in a questionnaire on the presence of the following symptoms: a) excessive daytime sleepiness; b) choking or gasping

Table 1. Baseline characteristics of patients.

Patient	Age	FVC%	FEV1%	DW	SYM	CO2>45	AHI	T90
1	21	74	75	N	N	N	3	6
2	48	73	68	N	Y	N	14	8
3	28	67	70	N	N	N	4	1
4	50	62	61	Y	Y	N	6	32
5	49	61	61	Y	Y	Y	5	44
6	27	63	62	N	Y	N	16	9
7	31	66	66	N	N	N	4	0
8	57	58	58	N	N	N	2	6
9	43	49	49	Y	Y	Y	5	30
10	58	57	57	N	N	N	2	6

Legend
Y: yes; N: no; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; DW: diaphragm weakness; SYM: symptoms; AHI: Apnea/Hypopnea per hour; T90: % time with arterial oxygen saturation less than 90%

during sleep; c) recurrent awakenings from sleep; d) unrefreshing sleep; e) daytime fatigue; f) morning headaches; g) nicturia and h) impaired concentration.

All patients underwent a respiratory investigation including pneumological examination, measure of ventilator capacity, arterial blood gas determination and polysomnography. Ventilatory capacity was investigated by vital capacity (VC), forced vital capacity (FVC) and forced expiratory volume in one second (FEV1), measured by a hand-held spirometer (SpirolabIII, MIR). Measurements were obtained both in sitting and supine positions to evaluate diaphragm weakness. The best of three consistent efforts (< 5% variability) was used. The reduction in lung function was classified according to ATS/ERS criteria. The defect was considered *mild* for values of FEV1 > 70% of the expected, *moderate* for values between 60 to 69%, *moderately-severe* for values between 50 to 59%, *severe* for values between 35% to 49%, and *very severe* for values < 35% of the expected, according to age, height and weight. Arterial blood gas tension was determined in the arterial blood of the earlobe, by automated blood gas analyzer (OMNI 6 MODULAR SYSTEM AVL).

Overnight polysomnography was performed in all patients, without oxygen supplementation. Sleep stages, electroencephalogram, electro-oculogram, submental electromyogram, electrocardiogram, oro-nasal flow and respiratory movement sensors, as far as oxyhemoglobin saturation were recorded using a computerized work station (SOMNO lab, Weinmann). Sleep stages and respiratory parameters were scored manually. Analyses were performed using the American Academy Sleep Medicine scores. The sleep disorders breathing was sub-classified into two distinct syndromes, namely, 1) obstructive sleep apnea-hypopnea syndrome (OSAHS), and 2) sleep hypoventilation syndrome (SHVS). OSAHS was diagnosed when sleep monitoring demonstrated 5 or more apneas/hypopneas epi-

sodes/hour during sleep (AHI > 5). SHVS was diagnosed in presence of PaCO₂ values > 10 mmHg on waking in the morning, compared with awake supine values, and/or in presence of sustained hypoxemia with arterial oxygen saturation [SaO₂] < 90% for more than 30% of the registration period, during sleep (T90 > 30%), not related to apnea or hypopnea episodes. Patients showing SDB were addressed to ventilatory assistance and treated by continuous positive airway pressure (CPAP autosep spirit, ResMed) or non invasive ventilation (NIV with VSIII ResMed) in pressure support, with synchronised tidal volume. Parameters were set individually. Nasal masks were preferentially used, unless special needs of the patient. In this case, a facial mask was used. These patients were re-evaluated by the same parameters, 30 days after the treatment. No patient was in enzyme replacement therapy (ERT).

Results

Diurnal respiratory function

All patients presented restrictive ventilatory defect. Two had a mild reduction of respiratory capacity; 4 patients presented a moderate reduction; 3 a moderate-severe, and 1 had a severe reduction. Diaphragm weakness (DW, postural drop of VC ≥ 20 %) was present in 3/7 patients.

Arterial blood gas analysis

Two patients presented diurnal hypercapnia > 5,9 kPa (45 mmHg).

Sleep disordered breathing

Five patients presented hypersomnia (ESS > 10), morning headaches, sleep disturbance, nicturia and im-

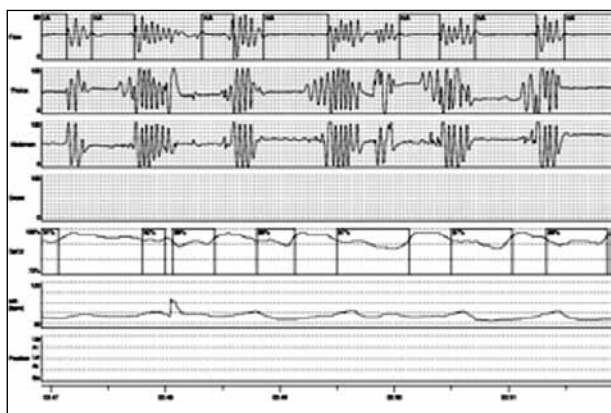


Figure 1. Apnea.

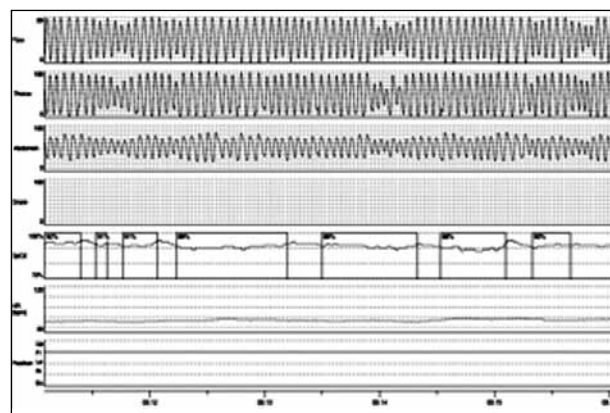


Figure 2. Desaturazione.

paired concentration. Of these, three patients complained awakenings and choking or gasping during sleep. *SDB* was found in five patients, three with diaphragm weakness, two without. Two subjects had findings consistent with sleep apnea syndrome (OSAHS: AHI > 5; T90 < 20%) (Fig. 1); in three patients with diaphragm weakness, REM sleep hypopneas with REM sleep hypoventilation and continuous sleep stage-independent hypoventilation (SHVS: AHI ≤ 5; T90 > 30%) were found (Fig. 2). The 5 patients presenting sleep disordered breathing, started therapy with non invasive positive pressure ventilation: 2 patients were well adapted with CPAP while 3 needed pressure support ventilation with target volume. After one month of treatment, all treated patients reported an improvement in symptoms with reduced diurnal hypersomnia (ESS < 10), absence of morning headache and nocturnal awakenings, reduced nicturia (Table 2), regardless of the modality of ventilation.

Discussion

The presence of sleep disordered breathing is too often overlooked in patients with neuromuscular diseases until the development of awake respiratory failure. Part of the problems lies in the difficulty of identifying symptoms associated with sleep breathing disorders in these

patients., as they may maintain a good daytime function with minimal symptoms, despite significant apneas and severe nocturnal oxygen desaturation (15).

In our series, 5 patients (50%), had symptoms suggestive of sleep disordered breathing confirmed by an altered nocturnal breathing pattern. Three patients had diaphragmatic weakness and presented nocturnal hypoventilation with a pattern of latent chronic respiratory insufficiency. Two patients had a nocturnal breathing pattern type apnea/hypopnea. The role of diaphragm in these disease is fundamental. If the diaphragmatic strength is preserved but the upper airway or intercostal muscles are weak, then obstructive events are likely to predominate. On the other hand, when patients have severe diaphragmatic dysfunction, suppression of intercostal and accessory muscles during sleep will produce hypoventilation and abnormalities in gas exchanges (14). The presence of sleep hypoventilation is particularly important to be diagnosed, because it usually precedes the development of diurnal respiratory failure (15). Furthermore, in patients with neuromuscular diseases OSAHS may be responsible for significant daytime disability such as excessive daytime sleepiness and cognitive dysfunction. To recognize an altered nocturnal breathing is of particular importance because it represents an early sign of respiratory dysfunction. Many factors such as obesity, scoliosis, ability to

Table 2. Mechanical ventilation in patients treated.

Patient	Mode of MV	Mask	Time of ventilation per day	Difference in ESS score
1	PSV/VT	Full Face	8	-8
2	PSV/VT	Nasal	8	-7
3	PSV/VT	Nasal	6	-5
4	CPAP	Nasal	6	-8
5	CPAP	Nasal	5	-7

PSV/VT: pressure-support ventilation with target volume; CPAP: continuous positive airway pressure; ESS: Epworth Sleepiness Scale.

arouse from sleep, and other compensatory mechanisms can contribute to influence the severity of SDB and gas exchange defects. In such cases an early investigation of presence of SDB and its monitoring after the beginning of therapy, is recommended. Failure to recognize and treat SDB may contribute to unnecessary disability or even to premature death in these patients (16, 17). Treatment with NIV, accepted by all patients with good compliance, is able to reduce symptoms reported by patients (morning headaches, nicturia) and also improve the quality of life of patients, while reducing the frequency of hospitalizations and increasing their life expectancy (18-22), even in patients not receiving ERT. Therefore we recommend that all patients with Glycogenosis type II or Pompe Diseases, once diagnosed, are carefully monitored for the development of respiratory involvement, even in the absence of reduced FVC values and in the early stages of the disease, to receive appropriate treatment.

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