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Obstructive sleep apnea syndrome in children with type II mucopolysaccharidosis (Hunter syndrome)

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17 children received cardiorespiratory monitoring in order to evaluate spread and dynamics of changes in the primary obstructive sleep apnea syndrome (OSAS) parameters at type II mucopolysaccharidosis. Mild OSAS [apnea/hypopnea index (AHI) – 1.5-5] was diagnosed in 4 patients (23.5%), moderate OSAS (AHI – 5-10) – in 4 patients (23.5%), severe OSAS (AHI>10) – in 2 patients (11.8%). Average AHI at Hunter syndrome was 5.3±6.9/hour. Mild OSAS (AHI – 0.8±0.3/hour) was prevalent in the group of younger children (1-3 years of age); severe OSAS was prevalent in the group of adolescents (AHI – 10.9±9.4/hour); average blood oxygen saturation (SpO_2) was 87.5±10.6%, desaturation index – 10.4±13.3/hour. In total, OSAS was observed in 58.8% of children and aggravated in direct proportion to aggravation of the disease course.

Thus, cardiorespiratory monitoring is necessary to reveal children with moderate and severe OSAS course with subsequent prevention of life-threatening conditions, which may appear at this syndrome.

Keywords: *obstructive sleep apnea syndrome, Hunter syndrome, cardiorespiratory monitoring, children.*

INTRODUCTION

Obstructive sleep apnea/hypopnea syndrome (OSAS) is a rather widespread form of sleep breathing disorders in patients with mucopolysaccharidoses (a group of lysosomal accumulation diseases developing due to congenital enzyme deficiency catalyzing degradation of glycosaminoglycans). Type II mucopolysaccharidosis (Hunter syndrome) is an extremely rare pathology (X-linked recessive inheritance mode) as frequent as 0.3-0.71 cases per 100,000 on live neonates [1]. Congenital deficit of lysosomal enzyme iduronate-2-sulfatase results in accumulation of glycosaminoglycans (dermatan sulfate, heparan sulfate) with progressive multi-organ lesion.

The first disease symptoms manifest themselves after 1 year of age and include frequent respiratory viral infections, recurrent otites, rhinites and abdominal hernias. Thickening of nostrils and lips, macroglossia and growth inhibition develop after 2 years of age. The disease is often characterized by macrocephaly, short neck and body. The child's face acquires coarse features (Hurler syndrome). Motion incoordination develops at 3-4 years of age along with behavior changes and development of aggressiveness. Deafness, joint stiffness, contractures and large and small joints, atypical pigment retinitis and corneal opacity appear at an older age [2-4]. The ongoing cellular accumulation of glycosaminoglycans results in affection of vital organs and their progressive functional deterioration: development of secondary cardiomyopathy,

incompetence and/or stenosis of mitral and aortic valves, obstructive respiratory tract diseases (including obstructive sleep apnea syndrome furthered by tonsillar and adenoidal hypertrophy, tracheal lumen narrowing, tracheomalacia, thickening of vocal cords, macroglossia), hepatosplenomegaly; psychoverbal development delay with subsequent mental retardation. The rate and degree of progression may vary [5-7].

The disease may be mild or severe. Severe form is characterized by all symptoms with profound deterioration of cognitive and mental functions; the patients die in the second decade of life. Mild form may be characterized by late disease onset (in adolescence); mental retardation is insignificant or absent; the patients often live up to 30 years of age.

Only few data on the spread and severity of OSAS at mucopolysaccharidoses have been published as yet [8]. Polysomnography is recommended for assessing condition of patients with type I mucopolysaccharidosis; it is the main criterion for determining efficacy of enzyme replacement therapy (ERT) at type I mucopolysaccharidosis [9, 10]. However, spread and peculiarities of OSAS course in children with type II mucopolysaccharidosis have been studied extremely insufficiently as yet. Still, the data accumulated throughout the last decade indicate that obstructive sleep apnea increases risk of mortality of cardiovascular complications and may be an independent risk factor of sudden cardiac death in this category of patients [11-13].

The aim of our trial was to determine spread of OSAS and dynamics of its course changes depending on the severity of affection of different organs in children with type II mucopolysaccharidosis.

PATIENTS AND METHODS

The trial involved 17 children of 1.5-15 years of age (boys; average age – 12.5±3.9 years) undergoing scheduled examination and treatment at the FSBI SCCH research institute of preventive pediatrics and medical rehabilitation in 2009-2012. Hunter syndrome was mild in 7 children, severe – in 10 children. The division into forms was based on preservation of intellect.

5 out of 7 children with mild form of the disease (75% of the patients with circulatory deficiency (CD) I) and 10 out of 10 children (60% of patients with CD II) with severe form of the disease were diagnosed with cardiovascular system's alterations in the form of cardiac valvular incompetence by the beginning of the trial. Absence or mild form of respiratory disorders was revealed in an equal number of patients (25 and 25%, respectively) with mild form of the disease. Moderate and severe respiratory disorders were prevalent at the severe form of the disease (33.3 and 44.4%, respectively). Adenoidal hypertrophy was revealed in every 2 patients with mild or severe form of the disease.

Clinical presentation of mild and severe forms of type II mucopolysaccharidosis in the examined patients is given in tb. 1.

Table 1. Clinical description of mild and severe Hunter syndrome in the examined children

Therapeutic parameters	**Clinical forms**	
	Mild (n=7)	**Severe (n=10)**
1-3 years of age	5	-
4-7 years of age	1	6
>7 years of age	1	4
CVSC	**5**	**10**
CD 0	-	-
CD I	4	4
CD II	1	6
RD	**5**	**9**
Absence	2	1
Mild	2	2
Moderate	3	3
Severe	-	4
Adenoidal hypertrophy	**4**	**5**

Note. CVSC – cardiovascular system's changes, RD – respiratory disorders, CD – circulatory deficiencies.

Apart from the common study methods (including ECG, Echo-CG, ENT consultation), all children underwent cardiorespiratory monitoring of diurnal and nocturnal sleep using polysomnographic complex Embla N7000, portable cardiorespiratory device ApneaLink and pulse oximeter MIROxi.

The main cardiorespiratory parameters

In order to assess severity of sleep respiratory disorders, we used the following main concepts of nocturnal sleep monitoring: 1) apnea – respiratory standstill with complete termination of air flow in the respiratory flow for at least 10 seconds;

2) hypopnea – breathing airflow decrease by 50% or more accompanied by blood oxygenation decrease by 4% or more;

3) apnea/hypopnea index – number of significant apnea/hypopnea episodes per 1 hour of sleep;

4) desaturation index – number of episodes of blood oxyhemoglobin oxygenation decrease associated with episodes or respiratory disorders by more than 4% per 1 hour of sleep.

The OSAS severity degree was assessed using apnea/hypopnea index (AHI). We distinguished between 3 OSAS severity degrees: mild form (AHI – 1.5-5 per hour), moderate form (AHI – 5-10 per hour) and severe form (AHI – more than 10 per hour) [14].

RESULTS

AHI parameters – blood oxygenation (SpO_2) and desaturation index (DI) – were studied in 17 children with type II mucopolysaccharidosis (Hunter syndrome). Obstructive sleep apnea syndrome (AHI>1.5) was diagnosed in 10 cases (58.8%): mild form (AHI – 1.5-5) – in 4 patients (23.5%), moderate form (AHI – 5-10) – in 4 patients (23.5%), severe form (AHI>10) – in 2 patients (11.8%). The average AHI at Hunter syndrome was 5.3±6.9 per hour. OSAS was not present in 7 children (41.2%). The average body mass index (BMI) was 19.6±3.6 kg/m^2 (12.9-28.2). The average blood oxygenation (SpO_2) value was 87.5±10.6%, DI – 10.4±13.3 per hour; the number of patients with SpO_2<95% - 76.4% (13 children).

OSAS was absent in children of 1-3 years of age; mild OSAS was prevalent in the group of children of 4-7 years of age (43%, 3 out of 7). Moderate OSAS was revealed in 60% of children over 7 years of age (3 out of 5), severe OSAS – in 40% of children (2 out of 5; tb. 2).

The average AHI value in the group of children over 7 years of age was 10.9±9.4 per hour; it significantly ($p<0.05$) exceeded the average AHI value in the younger age group (1-3 years of age) – 0.8±0.3 per hour. The average AHI value in the preschool group (4-7 years of age) was 4.3±4.8 per hour (see tb. 2).

We did not reveal significant differences between the average SpO_2 values and the average number of blood oxyhemoglobin oxygenation decrease episodes and DI in these age groups (tb. 3). The average SpO_2 values in all the age groups were lower than 95% at that (1-3 years of age – 92.0±5.4%; 4-7 years of age – 89.2±4.7%; >7 years of age – 80.6±17.3%).

The average AHI values in children mild and severe Hunter syndrome forms were 1.9±1.9 per hour and 7.6±8.1 per hour, without significant differences between the groups ($p>0.05$; tb. 4). However, it ought to be mentioned that patients without OSAS were prevalent in the group of children with mild form of the disease (57.1%; 4 out of 7), whereas patients with moderate and severe OSAS were prevalent in the group of children with severe form of the disease (30%, 3 out of 10; 40%, 4 out of 10, respectively; see tb. 4).

The average SpO_2 (mild form – 91.2±4.7%, severe form – 89.2±4.7%) and DI (mild form – 4.3±3.9 per hour, severe form – 89.2±4.7 per hour) values were not significantly different in the two groups (tb. 5). The overwhelming majority of patients of both groups had SpO_2 lower than 95% (mild form – 71.4%, 5 out of 7; severe form – 80%, 8 out of 10).

We defined the average AHI, SpO_2 and DI values in children with different tracheobronchial tree lesions (tb. 6, 7). OSAS was absent in all children without respiratory disorders. Equal number of patients without OSAS (50%, 2 out of 4) and with mild OSAS (50%, 2 out of 4) was observed in

the group of children with mild respiratory disorders. 50% of children with moderate respiratory disorders developed moderate OSAS (50%, 3 out of 6), whereas 50% of patients with severe respiratory disorders (2 out of 4) developed mild OSAS.
The average SpO_2 values ca. 95% were observed only in the group of children without respiratory disorders (95.2±3.6%), whereas in other groups they were 91.5±2.9; 88.7±4.7; 76.0±17.1% (mild, moderate and severe respiratory disorders, respectively; see tb. 7). The average DI values increased in direct proportion to the severity of respiratory disorders (see tb. 7).

Table 2. Apnea/hypopnea index (AHI) index in children with type II mucopolysaccharidosis of different age groups

AHI value	**1-3 years of age (n=5)**	**4-7 years of age (n=7)**	**>7 years of age (n=5)**	***p***
Average value	0.8±0.3 (0.6-1.3)	4.3±4.8 (0.0-13.3)	10.9±9.4 (4.4-27.5)	pA>0.05 pB<0.05 pC>0.05
Norm, in %	100	29.0	-	-
Slightly over the norm, in %	-	43.0	20.0	-
Moderate over the norm, in %	-	14.0	60.0	-
Considerably over the norm, in %	-	14.0	20.0	-

Note. A – *p* values for the comparison of smaller patients with preschool patients; B – *p* values for the comparison of smaller patients with patients over 7 years of age; C – *p* values for the comparison of preschool patients with patients over 7 years of age.

Table 3. SpO_2 (in %) and desaturation index (DI) in children of different age groups with type II mucopolysaccharidosis.

Average value	**1-3 years of age (n=5)**	**4-7 years of age (n=7)**	**>7 years of age (n=5)**	***p***
SpO_2	92.0±5.4 (84.0-97.6)	89.2±4.7 (85.5-97.0)	80.6±17.3 (51.0-92.0)	pA>0.05
				pB>0.05
				pC>0.05
DI	5.0±4.5 (0.1-10.5)	13.8±18.2 (0.0-43.0)	10.8±11.4 (3.0-30.7)	pA>0.05
				pB>0.05
				pC>0.05

Note. A – *p* values for the comparison of smaller patients with preschool patients; B – *p* values for the comparison of smaller patients with patients over 7 years of age; C – *p* values for the comparison of preschool patients with patients over 7 years of age.

Table 4. Apnea/hypopnea index (AHI) levels in children with mild and severe type II mucopolysaccharidosis

AHI value	**Mild form (n=7)**	***p***	**Severe form (n=10)**
Average value	1.9±1.9 (0.4-5.8)	>0.05	7.6±8.1 (0.0-27.5)
Norm, in %	57.2	-	20.0
Slightly over the norm, in %	23.5	-	10.0
Moderate over the norm, in %	14.3	-	30.0
Considerably over the norm, in %	28.5	-	40.0

Table 5. SpO_2 levels (in %) in children with mild and severe type II mucopolysaccharidosis

Average value	Mild form (n=7)		Severe form (n=10)
SpO_2	91.2±4.7 (84.0-97.6)	0.05	85.0±13.0 (51.0-97.0)
DI	4.3±3.9 (0.1-10.5)	0.05	14.6±16.0 (0.0-43.0)

Table 6. Apnea/hypopnea index (AHI) levels depending on severity or absence of respiratory disorders in children with type II mucopolysaccharidosis

AHI value	Norm (n=3)	Mild (n=4)	Moderate (n=6)	Severe (n=4)
Average value	0.9±0.3 (0.6-1.3)	2.1±2.0 (0.0-4.4)	6.2±4.8 (0.4-13.3)	10.4±11.9 (2.2-27.5)
Norm, in %	100	50	33.3	-
Slightly over the norm, in %	-	50	-	50
Moderate over the norm, in %	-	-	50.0	25
Considerably over the norm, in %	-	-	16.7	25

Table 7. SpO_2 (in %) and desaturation index (DI) levels depending on severity and absence of respiratory disorders in children with type II mucopolysaccharidosis

Average value	Norm (n=3)	Mild (n=4)	Moderate (n=6)	Severe (n=4)
SpO_2	95.2±3.6 (91.0–97.6)	91.5±2.9 (88.0–95.0)	88.7±4.7 (84.0–96.6)	76.0±17.1 (51.0–88.0)
DI	0.6±0.8 (0.0–1.6)	2.5±1.2 (1.4–95.0)	7.3±2.9 (3.2–10.5)	30.2±14.2 (10.2–43.0)

Our research demonstrated significant differences ($p<0.05$; tb. 8) between:

- AHI and SpO_2 values in groups of children without respiratory disorders or with moderate respiratory disorders;
- DI values in groups of children without or with mild, moderate or severe respiratory disorders (the average DI value – 0.6±0.8 per hour; 2.5±1.2 per hour; 7.3±2.9 per hour; 30.2±14.2 per hour, respectively).

We studied the effect of adenoidal hypertrophy on AHI, SpO_2 and DI values in children with Hunter syndrome. OSAS was revealed in 5 out of 9 (55.6%) children with adenoidal hypertrophy: mild – in 2 patients (22.2%), moderate – in 2 patients (22.2%), severe – in 1 patient (11.1%) (tb. 9). OSAS was not present in 4 out of 9 children with adenoidal hypertrophy (44.5%). The average AHI value in this group was 6.7±9.0 per hour (see tb. 9).

OSAS was not present in 37.5% of children (3 out of 8) without adenoidal hypertrophy; the equal number of children (25% each (2 out of 8)) had mild and moderate OSAS; the average AHI value in that group was 3.9±4.4 per hour (see tb. 9). The average SpO_2 and DI values were determined for each group as well: 89.3±4.8% and 13.4±14.5 per hour; 85.6±15.0% and 7.0±10.1 per hour (with/without adenoidal hypertrophy, respectively; tb. 10).

Comparison of average AHI, SpO_2 and DI values did not reveal effect of adenoidal hypertrophy on the OSAS severity (approximately the same percentage of mild, moderate and severe OSAS in all the groups); we did not reveal significant differences in SpO_2 and DI values in all the groups either ($p>0.05$; see tb. 10).

CD I or II A (in the event of concomitant therapy) did not aggravate OSAS (the average AHI value at CD I was 6.2±9.2 per hour, at CD II A – 4.6±4.7 per hour), SpO_2 decrease (the average SpO_2 values at CD I was 84.5±14.6%, at CD II A – 89.3±4.3%) or DI increase (the average DI

value at CD I was 9.3±9.2 per hour, at CD II A – 13.8±18.2 per hour) in children with secondary cardiomyopathy (tb. 11, 12).

By the time of the first trial 4 children with Hunter syndrome had been undergoing enzyme replacement therapy for 7-12 months (drug Elaprase, Shire Human Genetic Therapies, Inc., USA); in 13 children the first trial had taken place before ERT: we did not reveal any significant differences between AHI, SpO_2 and DI values observed in different groups ($p>0.05$); it may have been caused by insufficient ERT duration (tb. 13).

Two children with severe Hunter syndrome underwent the second trial 2 years after beginning of ERT. The first patient (9 years of age at the beginning of the study, 11 years – the second trial) had considerable positive dynamics of AHI, SpO_2 and DI values (before the therapy AHI was 4.4, SpO_2 – 88%; after 2 years AHI was 0.6, SpO_2 – 95.6%); no significant dynamics was observed in the second patients due to absence of OSAS before or in the setting of the ERT (before the therapy AHI was 0.8, SpO_2 – 97%; after 2 years AHI was 0.0, SpO_2 – 95%).

Positive effect of enzyme replacement therapy was demonstrated in the 6-minute-long walk test and by pulmonary function assessment. Improvement of physical stress tolerance was partially related to the improvement of respiratory function.

Treatment of respiratory disorders in the setting of a respiratory infection involves application of steroids in order to decrease degree of inflammation. It is often necessary to perform aden- or tonsillectomy. In severe cases, such operations are impossible due to potential complications arising of anesthesia or surgical intervention [15].

Severe sleep respiratory disorders may be treated with continuous positive airway pressure (CPAP), when high-pressure air is pumped in the mask; this prevents airway collapse during respiration, improves sleep quality, reduces dyspnea and normalizes blood gas concentration [16, 17].

Table 8. Comparison of apnea/hypopnea index (AHI), SpO_2 (in %) and desaturation index (DI) levels depending on severity and absence of respiratory disorders in children with type II mucopolysaccharidosis

Parameter	**Norm**	**Mild**	**Moderate**	**Severe**	***p***
AHI	0.9±0.3	2.1±2.0	6.2±4.8	10.4±11.9	pA>0.05
					pB<0.05
					pC>0.05
					pD>0.05
					pE>0.05
					pF>0.05
SpO_2	95.2±3.6	91.5±2.9	88.7±4.7	76.0±17.1	pA>0.05
					pB<0.05
					pC>0.05
					pD>0.05
					pE>0.05
					pF>0.05
DI	0.6±0.8	2.5±1.2	7.3±2.9	30.2±14.2	pA<0.05
					pB<0.05
					pC<0.05
					pD>0.05
					pE>0.05
					pF>0.05

Note. A – *p* values for the comparison of patients without respiratory disorders with patients with mild respiratory disorders; *p* values for the comparison of patients without respiratory disorders with patients with moderate respiratory disorders; C - *p* values for the comparison of patients without respiratory disorders with patients with severe respiratory disorders; D - *p* values for the comparison of patients with mild respiratory disorders with patients with moderate respiratory disorders; E - *p* values for the comparison of patients with mild respiratory disorders with patients with severe respiratory disorders; F - *p* values for the comparison of patients with moderate respiratory disorders with patients with severe respiratory disorders.

Table 9. Apnea/hypopnea index (AHI) levels depending on presence or absence of adenoidal hypertrophy in children with type II mucopolysaccharidosis

AHI value	**No hypertrophy (n=8)**		**2-3 grade hypertrophy (n=9)**
Average value	3.9±4.4 (0.0-27.5)	0.05	6.7±9.0 (0.4-13.3)
Norm, in %	37.5		44.5
Slightly over the norm, in %	25.0		22.2
Moderate over the norm, in %	25.0		22.2
Considerably over the norm, in %	12.5		11.1

Table 10. SpO_2 (in %) and desaturation index (DI) levels depending on presence or absence of adenoidal hypertrophy in children with type II mucopolysaccharidosis

Average value	**No hypertrophy (n=8)**	***p***	**2-3 grade hypertrophy (n=9)**
SpO_2	85.6±15.0 (51.0-97.6)	0.05	89.3±4.8 (84.0-97.0)
DI	7.0±10.1 (0.1-30.7)	0.05	13.4±14.5 (0.0-43.0)

Table 11. Apnea/hypopnea index (AHI) levels in the event of secondary cardiomyopathy in children with type II mucopolysaccharidosis

AHI value	**CD I (n=8)**	**CD II A (n=7)**
Average value	6.2±9.2 (0.0-27.5)	4.6±4.7 (0.6-13.3)
Norm, in %	50.0	28.6
Slightly over the norm, in %	12.5	42.8
Moderate over the norm, in %	25.0	14.3
Considerably over the norm, in %	12.5	14.3

Note. CD – circulatory deficiency.

Table 12. SpO_2 (in %) and desaturation index (DI) levels in the event of secondary cardiomyopathy in children with type II mucopolysaccharidosis

Average value	**CD I (n=8)**	**CD II A (n=7)**
SpO_2	84.5±14.6 (51.0-96.6)	89.3±4.3 (85.6-97.0)
DI	9.3±9.2 (1.0-30.7)	13.8±18.2 (0.1-43.0)

Table 13. Comparison of apnea/hypopnea index (AHI), SpO_2 and desaturation index (DI; M±σ) levels in patients with Hunter syndrome in the event of presence or absence of enzyme replacement therapy at the time of the first trial

Therapy	**AHI**	**SpO_2**	**DI**
Therapy "+", n=13	6.2±7.5	85.7±11.5	12.4±14.5
P	>0.05	>0.05	>0.05
Therapy "+", n=4 (7-12 months)	2.2±1.6	93.4±4.2	3.90±3.9

CONCLUSION

Obstructive sleep apnea syndrome has been revealed in more than a half of the children (58.8%) with type II mucopolysaccharidosis; equal numbers of such children had mild and moderate OSAS (23.5% each), AHI being 5.3±6.9 per hour. In most aspects, our data correspond with data of the previously published studies by S.E. Leighton et al. [11], who had been observing course of severe OSAS among patients with type I mucopolysaccharidosis.

Mild OSAS (AHI – 0.8±0.3 per hour) was prevalent in the group of smaller children (1-3 years of age), whereas severe OSAS (AHI – 10.9±9.4 per hour) was prevalent in the group of adolescents. OSAS course aggravated with age, possibly, due to progression of the disease itself,

which may be caused by numerous factors, including spread of glycosaminoglycan deposition in the tracheobronchial tree's mucous tunic.
OSAS severity also depended on:

- the form of disease (patients without OSAS were prevalent at the mild form – 57.2%, moderate and severe OSAS were revealed at the severe form – 30 and 40%, respectively);
- the severity of respiratory disorders (absence of respiratory disorders matched absence of OSAS (AHI – 0.9±0.3 per hour); moderate OSAS was revealed in case of moderate disorders (AHI – 6.2±4.8 per hour; $p<0.05$)).

SpO_2 in children with type II mucopolysaccharidosis was 87.5±10.6% (number of patients with SpO_2<95% - 76.4%); its average value was within the norm only in the group of children without respiratory disorders – 95.2±3.6%. Minimal DI values were observed in that same group – 0.6±0.8 per hour; they were significantly different from DI values in groups of patients with mild, moderate and severe respiratory disorders (2.5±1.2 per hour; 7.3±2.9 per hour; 30.2±14.2 per hour).
In our trial, progression of circulatory deficiency in children with secondary cardiomyopathy resulted in the lesser number of children without apnea (AHI<11.5 at CD I – in 50% of cases, at CD II A – in 28.6% of cases); however, it did not determine differences regarding frequency of severe OSAS (AHI>10 at CD I – in 12.5% of cases, at CD II A – in 14.3% of cases).
Thus, high frequency of respiratory disorders in patients with mucopolysaccharidosis, their severity degree and manifestation in the onset of the primary disease proves importance of timely assessment and subsequent observation. Cardiorespiratory monitoring is necessary for revealing children with moderate and severe OSAS and subsequent prevention of life-threatening conditions, which may arise in the event of this disorder.

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