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Original Article

Respiratory response to proton pump inhibitor treatment in children with obstructive sleep apnea syndrome and gastroesophageal reflux disease

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ABSTRACT

Objective: Evaluation of the respiratory response to proton pump inhibitors (PPI) in children with obstructive sleep apnea syndrome (OSAS) and gastroesophageal reflux disease (GERD).
Methods: Of 131 children diagnosed with OSAS (Apnea Hypopnea Index, AHI >1/h), 37 children (6.9 years; 28.24%) with GERD symptoms (>3 times/week) were included. Overnight polysomnography with 24 h pH-metry was performed before and after 4–8 weeks of PPI treatment (omeprazole once a day, 1 mg/kg).
Results: Of 37 children, 21 were diagnosed with acid GERD where pre- and post-treatment reflux indexes were 14.09 ± 1.47 vs. 7.73 ± 1.36; ($p < 0.001$). The number of obstructive apneas and hypopneas decreased after PPI treatment, resulting in an AHI reduction from 13.08 ± 3.11/h to 8.22 ± 2.52/h; ($p < 0.01$). Respiratory response to PPI ranged from complete resolution of OSA (three children with mild OSA; AHI < 5/h; 10.31 years; 14.29%) to lack of significant AHI change (six children with severe OSA; AHI > 10/h; 3.62 years; 28.57%). Post-treatment AHI was predicted by pre-treatment reflux index (adjusted $R^2 = 0.487$; $p < 0.001$).
Conclusions: Reduction of obstructive respiratory events following short-term PPI treatment in children with both GERD and OSAS may suggest a causal relationship between apnea and reflux in some children. Questionnaire screening for GERD in children with OSAS may be of benefit.

1. Introduction

Obstructive sleep apnea (OSA) is caused by a combination of high upper airway resistance and increased pharyngeal collapsibility leading to intermittent partial or complete upper airway obstruction during sleep. Clinical and biochemical sequels of prolonged upper airway obstruction disrupting normal ventilation and sleep continuity are defined as obstructive sleep apnea syndrome (OSAS) [1]. It is suggested that OSAS can be, in some patients, influenced by gastroesophageal reflux (GER) mechanisms [2–4]. GER, the passage of gastric contents into the esophagus, is a physiological process occurring several times per day in healthy infants, children, and adults [5]. Most episodes of GER in healthy individuals last <3 min, occur in the postprandial period, and cause few or no symptoms. Gastroesophageal reflux disease (GERD) is a condition which develops when the reflux of gastric contents causes troublesome symptoms or complications [5]. The anatomical proximity of the upper respiratory and alimentary tracts as well as a sole functional barrier between them raises the question: how do they influence each other? Epidemiological data indicate that both OSAS and GERD are common childhood disorders. OSAS and GERD occur in approximately 1–2% and 4% of children, respectively [5–7]. Finding these two in one child is therefore not surprising and does not prove any functional link between reflux and apnea. There are many previously published observations both for and against an association between reflux and apnea. One such argument against a relation between GERD and OSAS is a lack of a direct temporal relationship between reflux episodes and obstructive apnea episodes recorded during polysomnography with pH-metry [8,9]. On the other hand there are observations that, in patients diagnosed with both OSAS and GERD, treatment with a PPI or continuous positive airway pressure (CPAP) reduces OSAS severity as well as nocturnal GERD [10,11]. Decreases in the number of GER episodes following CPAP treatment indicate a possible role of *physical factors* in a causal association between apnea and reflux (Fig. 1). Large negative intrapleural pressure oscillations during apnea may facilitate retrograde movement of gastric contents [9]. Increased respiratory effort during OSAS events may lead to enhancement of the pressure gradient across the lower esophageal

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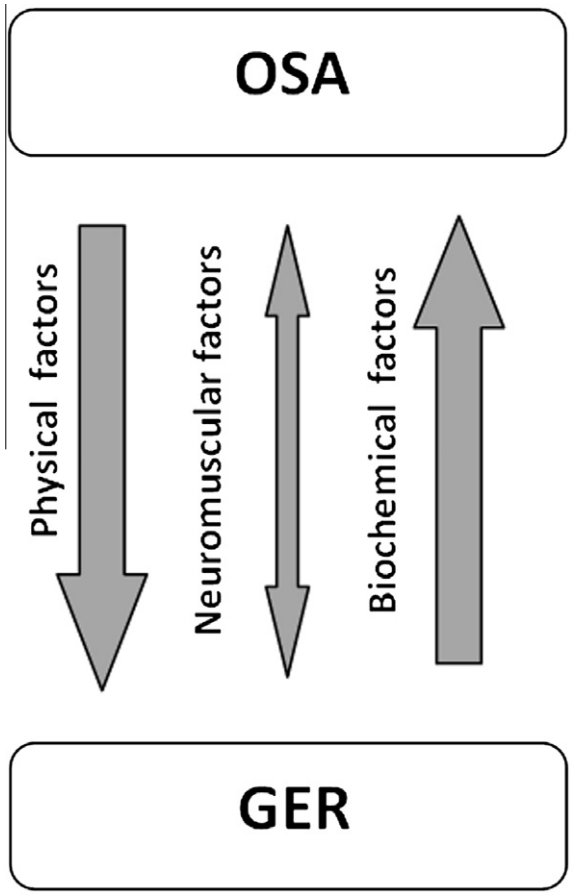

Fig. 1. Three potential pathways involved in the link between obstructive sleep apnea (OSA) and gastroesophageal reflux (GER): (i) obstruction of the upper respiratory tract affects the upper alimentary tract mainly through physical actions (i.e. pressure gradient changes), (ii) reflux of stomach contents exposes the upper respiratory tract to chemical factors (i.e. acid, pepsin), (iii) neuromuscular factors can be involved equally in OSA as in GER (i.e. impaired swallowing reflexes).

sphincter and trigger the reflux episode [11]. According to a new study, however, a compensatory increase of pressure in the upper esophageal sphincter (UES) and gastroesophageal junction (GEJ) during OSAS may be protective against GER [12]. A second possible pathway of the hypothetical apnea–reflux association involves *chemical factors* and the refluxate contents (acidic, alkaline, and neutral contents as well as gas) as possible triggers of apnea. Acidification of the proximal or distal esophagus as the mechanism of OSAS has been suggested in both children and adults [8,13,14]. A third potential pathway may involve *neuromuscular factors*. GER can alter laryngeal or pharyngeal neuromuscular activity either as a result of the direct toxic effect of acid or because of neural reflex activity [15]. Impaired swallowing reflexes present in patients with OSA may be significant because of prolonged exposure to acid [16]. Prolonged exposure of the respiratory tract to stomach contents may result in local edema and increased secretion of respiratory mucus as well as induce lymphoid tissue enlargement [17]. The subglottic mucosa and the vocal folds may be easily damaged when pepsin from the stomach is present in the larynx [18].

According to the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN), and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN), apnea is listed as an extraesophageal sign of GERD. However, the diagnosis and management of possible extraesophageal complications of GERD are not well established [5]. To test the hypothesis concerning the relation between apnea and reflux we evaluated the respiratory response in children with evidence of both OSAS and GERD to short-term treatment with a proton pump inhibitor (PPI). The main outcome measures were pre- and post-treatment polysomnographic respiratory indices: the number of obstructive apneas and the number of hypopneas, as well as saturation indices and number of arousals.

2. Methods

2.1. Study design and participants

The study protocol followed ethical guidelines and was approved by the Bioethics Committee of the Medical University of Białystok. Informed written consent was obtained from the parents and from the subjects prior to participation.

A short-term treatment regimen with a PPI was applied to relieve symptoms of GERD in children diagnosed with OSAS. Respiratory response to PPI treatment was evaluated based on results of both pre- and post-treatment polysomnography with pH-metry. Participants were recruited among patients of the Pediatric Sleep Laboratory of the Children's University Hospital between April 2008 and June 2010. The recruited subjects ranged from two to 16 years of age. OSAS symptoms according to Brouillette et al., as described in our previous article, were indications for polysomnography [19,20]. Children diagnosed with OSAS (Apnea Hypopnea Index, AHI, >1/h of sleep) and positively screened for symptoms of GERD (occurring >3x/week during the last month) were included.

2.1.1. Clinical assessment of GERD

Clinical assessment of GERD consisted of both a pre- and post-treatment reflux questionnaire (17 items). Due to the lack of a validated questionnaire for children at the time of patient enrollment in 2008 we created one ourselves. The type and frequency per week of specific signs/symptoms were analyzed. Gastrointestinal or respiratory GERD symptoms occurring more than three times a week during the last month prior to the study were considered for GERD and pH-metry was performed simultaneously with polysomnography. The questionnaire included the following gastrointestinal (GI) symptoms: (1) pain symptoms: abdominal pain, epigastric pain, heartburn, odynophagia; (2) signs of reverse peristalsis: vomiting, regurgitation followed by swallowing of the refluxate, munching and swallowing during sleep, halitosis; and (3) food refusal or increased thirst. The list of respiratory symptoms included: (1) soreness or redness of the throat; (2) hoarseness and grunting; and (3) coughing and wheezing (positional/exercise induced).

2.1.2. Physical examination

All children underwent a physical examination. Body mass index (BMI) (weight in kilograms divided by height in meters squared) was calculated and converted to a *z*-score. Children with BMI *z*-score values above 1.65 (>95th percentile) were classified as obese. Tonsil size was graded from 0 to 4+ according to the Brodsky scale [21].

2.1.3. GERD treatment

Omeprazole, a PPI, was recommended in a once daily dose 15–30 min before the first meal of the day (1 mg/kg) [5]. Four to eight weeks of GERD treatment was planned depending on the scheduled date of surgery (adenotonsillectomy, A&T). Parents monitored medication compliance with a daily journal. As A&T is the first-line treatment of OSAS, the wait-time to surgery was utilized as the period of observation and treatment with omeprazole in an attempt to ameliorate coexisting symptoms of GERD. NASPGHAN and ESPGHAN positional recommendations (side sleeping position and elevation of the head of the bed) and dietary

recommendations (eating smaller meals and avoiding fatty or sweet foods before bedtime) were additionally advised [5].

None of the patients had previously been diagnosed and treated for OSAS or GERD and none were receiving acid suppressive medications or prokinetics. All children were Caucasian. The exclusion criteria included: (1) infectious diseases, (2) craniofacial anomalies, (3) genetic and metabolic disorders, (4) endocrine disorders, and (5) neurological impairment.

2.2. Polysomnography and 24-h pH-metry

Pre- and post-treatment overnight multichannel polysomnography (Alice 4, Respironics USA), in addition to a 24-h pH probe, were performed. Throughout the test the child was accompanied by a parent in a quiet room and trained personnel constantly supervised the test. No sedatives or other medications were used. The following parameters were recorded: electroencephalogram (C4/A1 and C3/A2), bilateral electro-oculogram, chin electromyogram, and nasal and oral airflow measured using a thermistor (Healthdyne USA); snoring was detected by means of a microphone at the suprasternal notch, and chest and abdominal wall movements were measured by respiratory impedance. Heart rate was measured by an electrocardiogram, hemoglobin oxygen saturation (SpO_2) was assessed by pulse oximetry (Nellcor, Pleasanton, CA, USA) with simultaneous recording of the pulse wave form, actimeter, and digital time-synchronized video.

Sleep studies were interpreted according to standard criteria [14,22–24]. Sleep was analyzed in 30 s epochs, each of which were possible to categorize as rapid eye movement (REM) sleep or non-rapid eye movement (NREM) sleep [23]. Obstructive apnea (OA) was defined as the absence of airflow with continued chest or abdominal wall movements for a duration of at least two respiratory cycles [25]. Obstructive apnea index (OAI) was defined as the number of OA per hour of total sleep time (TST). Hypopnea (H) was defined as a reduction in the airflow signal amplitude of at least 50% compared to baseline in the presence of paradoxical chest/abdominal wall motion and associated with an SpO_2 desaturation $\geqslant$4%, or with an EEG arousal [22]. Central apnea was defined as the cessation of air flow in the absence of respiratory effort associated with an arousal or fall of $\geqslant$4% in SpO_2. Mixed apnea with obstructive and central components was counted as obstructive. The obstructive Apnea Hypopnea Index (AHI) was defined as the number of obstructive apneas and hypopneas as well as mixed apneas per hour of total sleep time (TST). An AHI > 1 was a diagnostic criterion of OSA [1]. OSAS was classified as follows: mild OSAS: 1 < AHI < 5/h, moderate OSAS: 5 $\leqslant$ AHI < 10/h, severe OSAS: AHI $\geqslant$ 10/h. Mean SpO_2, the SpO_2 nadir, and the oxygen desaturation index (ODI, events per hour of sleep) were recorded. Arousals were defined as per ASDA recommendations: respiratory-related arousals occurring immediately after apnea, hypopnea, or snoring were expressed as the total number of arousals per hour of sleep time (AI) [14].

Twenty-four hour pH-monitoring was performed simultaneous with polysomnography. A pH antimony electrode was introduced transnasally and placed in the distal esophagus using Strobel's equation [26]. The reference electrode was attached to the anterior chest wall. The acid gastroesophageal reflux index (RI), which represents the proportion of the total time of the recording for which the esophageal pH is less than 4.0, was calculated and expressed as a percentage value. An RI $\geqslant$ 7% was the cut-off value for the diagnosis of acid GER [5]. A detailed pH-metric study included the following indices: acid reflux index in supine position (norm $\leqslant$ 2.5%), total number of episodes where pH was less than 4.0 for at least 10 s (normal range is up to 50 episodes/24 h), number of episodes longer than 5 min (norm $\leqslant$ 2 min), and duration of the longest episode (norm $\leqslant$ 9 min, 540 s). Exposure of the esophageal mucosa to a strong alkaline pH was assessed by calculating the time duration of pH > 8 within the esophagus (in percent) (alkaline reflux index $_{pH>8}$).

2.3. Statistical analysis

Verification of the hypothesis that pre- and post-treatment measurements did not differ was performed using two tests; the Wilcoxon matched-pairs signed rank test was applied to compare pairs of variables representing pre- and post-treatment measurements which had abnormal distributions (respiratory indices OA, H, AHI, AI, SpO_2) while a Student's *t*-test was used for normal distributions (pH-metry indices). The Shapiro–Wilk test was applied to verify the statistical shape of the tested variable. The chi-square (χ^2) test for independence was applied to compare the qualitative and categorized variables (symptoms of GERD). The Mann–Whitney *U*–test was applied to compare variables of non-parametric distribution. Multiple regression analysis was performed to assess factors predicting respiratory response to PPI treatment. Data are presented as mean ± SEM with statistical significance taken at the $p < 0.05$ level.

Two-tailed probability values of less than 0.05 were considered significant. Analyses were performed with StatSoft (STATISTICA data analysis software system, version 9.0 www.statsoft.com) and GraphPad Prism v 5.03 software (GraphPad Software Inc., San Diego, CA, USA, www.graphpad.com).

3. Results

3.1. Patient characteristics

Out of a total of 131 patients diagnosed with OSAS, 17 children (12.98%) with co-morbid disorders met the exclusion criteria, 73 of 114 (64.04%) were negatively screened for GERD symptoms, and 41 of 114 (35.96%) children with GERD symptoms met the inclusion criteria, of which 37 children (32.46%) underwent both polysomnography and 24 h pH-metry. Four patients dropped out of the study (three of whom dropped out due to a febrile infection and one because parents did not follow therapeutic recommendations). Out of 37 patients who completed the study, 21 were diagnosed with acid GER and were submitted to analysis. They ranged in age from two to 14 years (mean age 4.3 years) and the male/female ratio was 15/6 (71.4%/28.6%; $p = 0.76$). Three children were overweight or obese and constituted 14.3% of the acid GER population and their BMI $-z$ score was 1,92; 1,94; 2.48 (Table 1).

The duration of PPI treatment ranged from 28 to 58 days (mean time 47 ± 7.7 days). Compliance, in terms of days where treatment

Table 1
Pre-treatment participant characteristics.

Characteristics		Participants ($n = 21$)	95% CI
Male, *n* (%)		15 (71.43)	
Age, years		4.31 ± 0.75	2.74–5.88
BMI *z*-score		0.48 ± 0.24	−0.02–0.98
Overweight/obese children, *n* (%)		3 (14.29)	
Acid reflux index,%,		14.09 ± 1.47	11.01–17.16
AHI, *n*/h		13.08 ± 3.11	6.53–19.62
OSA severity			
Mild	1 < AHI < 5, *n* (%)	7 (33.33)	
Moderate	5 $\leqslant$ AHI < 10, *n* (%)	5 (23.81)	
Severe	AHI $\geqslant$ 10, *n* (%)	9 (42.86)	
Tonsil size			
	Grade 1, No. (%)	0 (0.00)	
	Grade 2, No. (%)	8 (38.10)	
	Grade 3, No. (%)	12 (57.14)	
	Grade 4, No. (%)	1 (4.76)	

Data are presented as mean ± SEM.
BMI, body mass index; SEM, standard error of the mean; 95% CI, 95% confidence interval; AHI, Apnea Hypopnea Index; OSA, obstructive sleep apnea.

was maintained compared to recommendations, was 93.1%. Treatment with omeprazole was well tolerated and no side effects were registered.

3.1.1. Patient characteristics according to clinical symptoms

The most prevalent pre-treatment GI symptoms were daytime: morning food refusal ($n = 11$; 52.38%) and pain symptoms ($n = 6$; 28.57%) and nighttime: regurgitation ($n = 13$; 61.90%). The most prevalent respiratory symptoms, apart from OSA symptoms (difficulty breathing, apnea during sleep, and snoring), were daytime: hoarseness ($n = 9$; 42.86%) and exercise induced coughing ($n = 7$; 33.33%) and nighttime: coughing or wheezing ($n = 8$; 38.10%). After PPI treatment, GI and respiratory symptoms persisted in four (19.05%) and five (23.81%) children respectively.

3.1.2. Patient characteristics according to pH-metry results

An RI $\geqslant$ 7% (acid GER confirmed) was found in 21/37 children. PPI treatment resulted in RI decreasing from 14.22 ± 1.54% (95% CI 10.99–17.45) to 7.42 ± 1.39% (4.50–10.34) ($p = 0.001$) (Fig. 2). Pre-treatment intraluminal esophageal acidification in the studied children was characterized by an equally distributed reflux index between the daytime and nighttime, 12.94% vs. 12.66%, respectively (Table 2). Total number of episodes of pH < 4.0 was within the normal range in both the daytime and the nighttime. The number of episodes longer than 5 min was slightly increased in both daytime and nighttime, 3.83 vs. 3.11 respectively. The mean times of the longest GER episodes substantially surpassed the norm of 9 min and were 22.51 min vs. 33.54 min for daytime and nighttime respectively. PPI treatment resulted in a significant reduction of the reflux index and shortening of the duration of the longest GER episode.

There were six children who did not respond to the PPI with a mean post-treatment reflux index of 12.93%. They were classified belonging to the "resistant to treatment acid GER subgroup" (RT subgroup) in contrast to the "susceptible to treatment acid GER subgroup" (ST subgroup) with a final post-treatment RI < 7% (Table 3). None of the children in the RT subgroup were overweight or obese and all had oversized tonsils (one child with grade 4 and five children with grade 3).

Exposure of the esophageal mucosa to alkaline pH > 8 was noted only in one of 21 children (pre-treatment alkaline reflux index was 3.97%, post-treatment 0.00%). Antisecretory treatment did not result in an increased alkaline RI in all but one patient whose pre-treatment index value was 0.00% and post-treatment RI – 3.39%.

Table 2
Detailed pre- and post-treatmentpH-metric measurements in children with Acid GER and OSAS.

	Pre- treatment	Post- treatment	*p*-Value[a]
Reflux index (%)			
	14.09 ± 1.47 (11.01–17.16)	7.73 ± 1.36 (4.89–10.57)	0.001
Reflux index (%)			
Daytime	12.94 ± 1.76 (9.24–16.65)	8.34 ± 2.14 (3.78–12.90)	0.039
Nighttime	12.66 ± 2.75 (6.87–18.46)	5.92 ± 2.24 (1.42–10.69)	0.008
Total No. of episodes pH < 4.0 (>10 s)			
Daytime	22.67 ± 2.77 (16.77–28.57)	20.25 ± 3.22 (13.38–27.12)	0.408
Nighttime	15.11 ± 4.32 (6.00–24.22)	10.88 ± 3.38 (3.70–18.05)	0.190
No. of episodes longer than 5 min			
Daytime	3.83 ± 0.71 (2.34–5.32)	2.50 ± 0.74 (0.93–4.08)	0.136
Nighttime	3.11 ± 0.75 (1.53–4.69)	2.31 ± 0.78 (0.64–3.98)	0.388
Duration of longest episode			
Daytime	1335.11 ± 281.89 (740.37–1929.85)	816 ± 234.92 (315.40–1316.85)	0.026
Nighttime	2012.61 ± 488.77 (981.40–3043.82)	1059.88 ± 326.78 (363.35–1754.40)	0.023

Data are expressed as mean ± SEM.
Data in parentheses indicate 95% confidence interval (95% CI).
[a] The Wilcoxon par test.

Table 3
Reflux index (RI) and Apnea Hypopnea Index (AHI) by GER subgroup in children with OSAS.

Characteristics	Acid GER		*p*
	Susceptible to treatment (ST) $n = 15$	Resistant to treatment (RT) $n = 6$	
Age (years)	5.60 ± 1.05	3.62 ± 1.65	0.494
RI pre-treatment (%) (95% CI)	12.07 ± 5.22[a] (9.17–14.96)	19.13 ± 7.95 (10.78–27.48)	0.063
RI Post-Treatment (%) (95% CI)	5.65 ± 1.21 (3.19–8.11)	12.93 ± 1.92 (9.03–16.82)	**0.004**
AHI pre-treatment (*n*/h) (95% CI)	9.75 ± 2.65[b] (4.79–14.70)	22.52 ± 4.32 (13.75–31.28)	0.248
AHI post-treatment (*n*/h) (95% CI)	5.10 ± 2.15 (0.69–9.43)	17.47 ± 3.28 (10.79–24.14)	0.083

Data presented as mean ± SEM.
[a] $p < 0.01$compared with post-treatment RI.
[b] $p < 0.01$compared with post-treatment AHI.

3.2. Respiratory response to PPI treatment

In the studied group of 21 children before PPI treatment, seven children were diagnosed with mild OSA, five with moderate OSA, and nine with severe OSA. After a course of PPI treatment the AHI was reduced from 13.08 ± 3.11/h to 8.22 ± 2.52/h ($p = 0.004$) (a decrease of 37.16%), of which the total number of obstructive apneas decreased from 42.05 ± 13.11 to 16.22 ± 6.63 ($p < 0.001$) (a decrease of 68.82%) and the total number of hypopneas decreased from 71.00 ± 28.32 to 46.26 ± 19.02 ($p < 0.017$) (a decrease of 34.85%) (Fig. 3). PPI treatment did not change the SpO_2 mean, SpO_2 nadir, the total number of CA, or the number of arousals (respiratory or spontaneous). Pre-treatment AHI values correlated with pre-treatment RI values ($r = 0.592$, p=.008). No correlation was found between AHI and values other than RI pH-metric characteristics, including the number of GER episodes and the duration

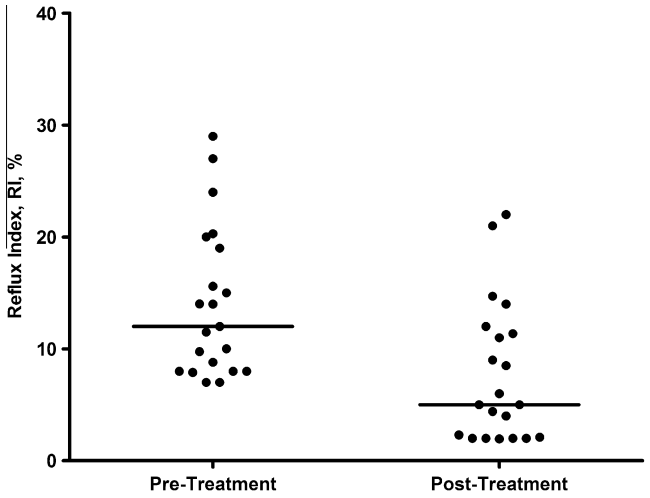

Fig. 2. Scatter plot for the pre- and post-treatment reflux index in the acid GER group (horizontal bars indicate median values, $p < 0.001$).

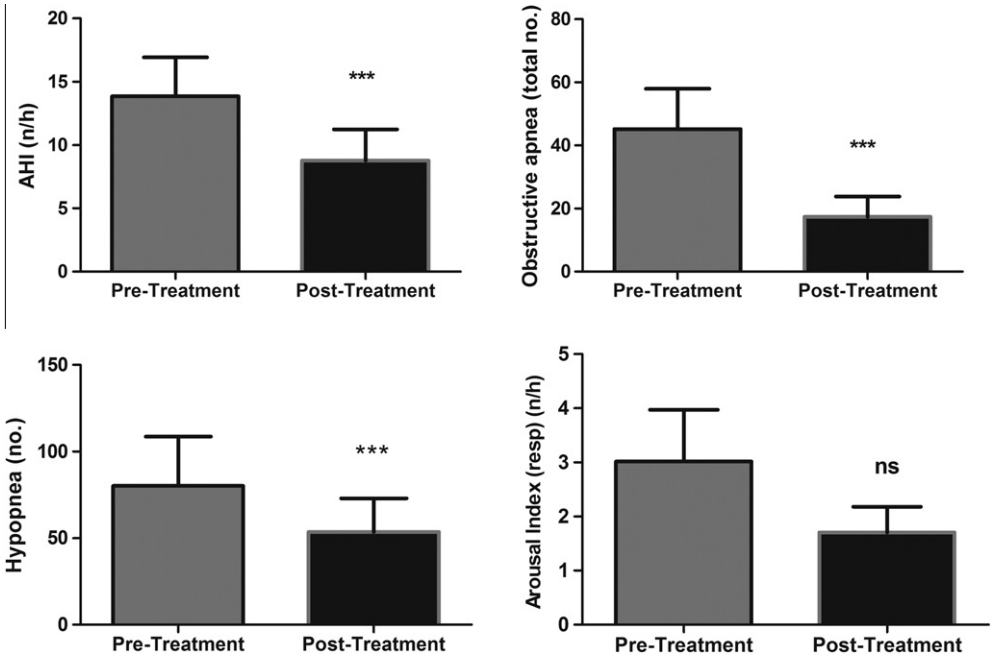

Fig. 3. Respiratory polysomnographic parameters recorded before and after PPI treatment. AHI, Apnea Hypopnea Index. Statistical significance in comparison to pre-treatment indices: $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$; ns, not statistically significant.

of the longest GER episode. Finally, after PPI treatment, full resolution of OSA occurred in three of 21 (14.29%) children (age 10.31 years), all with mild (AHI 1.6–2.1/h) pre-treatment OSA and with a mean pre-treatment RI of 9.97%. In the remaining group of 18 children the number of patients with severe OSA decreased from nine to five and with moderate OSA from five to four while those with mild OSA increased from 4 to 9.

3.3. Factors predicting respiratory response to PPI treatment

A multiple regression model was used to assess all the pre-treatment pH-metric findings in order to find any variables predicting the outcome of the main post-treatment respiratory index (AHI). Only one pre-treatment pH-metric finding, reflux index, was a significant predictor of the post-treatment respiratory variable. The result, presented in Table 4, indicates that the post-treatment AHI was predicted by the pre-treatment RI value in about 50% of children.

3.4. Follow up

One year follow-up included 19 out of a total of 21 children: 13 from the ST subgroup and six from the RT subgroup. Out of 19 children, 14 were treated with A&T, all of whom were children from the RT subgroup. One boy with a transient improvement of OSA symptoms lasting up to a month after A&T further required a Nissen fundoplication. Parents of two children with mild OSAS decided against A&T and their children remained under observation by a laryngologist. Three children successfully treated with a course of PPI did not require surgery.

Table 4
Pre-treatment reflux index as a predictor of post-treatment AHI in multiple regression model.

Post-treatment	*b*	*SE*	*R*	Adjusted *R* square	*p*
AHI	0.608	0.139	0.717	0.487	0.000

4. Discussion

This study examined the respiratory response to acid suppression in children diagnosed with both OSAS and symptoms of GERD. The study results show that PPI treatment applied for treating GERD symptoms can decrease objective processes of upper airway obstruction, but this decrease is not ensured. The respiratory response to the PPI ranged from complete resolution of OSA in three school aged children with mild OSA (10.31 years) to lack of a significant AHI change in six preschool aged children with severe OSA (3.62 years).

The subset of children resistant to PPI was characterized by having the most advanced OSAS (mean AHI – 22.5/h), the highest RI (mean 19.13%), and oversized tonsils (Grade 4 to 3) prior to treatment. They were also preschool aged (when oversized tonsils are the most common cause of OSAS). All were eligible for elective A&T, which is the first-line surgical treatment for OSAS secondary to lymphoid tissue hypertrophy. This subset of studied children was additionally characterized by a lack of normalization of pH-metric indices (reflux index) after antisecretory treatment. None of the children from this group were overweight or obese. For this reason, obesity as a predictor of a weak respiratory and a pH-metric response to treatment was excluded in these patients [27]. Lack of normalization of the RI despite pharmacological acid suppression in the patients with the most severe OSAS may suggest that enlarged tonsils and adenoids played a role in sustaining the GER mechanism in those children. An association between GERD and enlarged tonsils and adenoids has been discussed, though not confirmed [5]. In a retrospective study by Carr, 88% of children under two years of age requiring adenoidectomy had GERD. However, criteria for diagnosing GERD were based on different methods (24 h pH monitoring, scintigram, barium swallow, esophageal biopsy) [13]. In a small study by Keles et al. children with adenoid hyperplasia had a higher frequency (OR – 9.6) of pharyngeal reflux than healthy children of the same age [28]. GERD was also diagnosed in 41.1% of OSAS children aged from 6 to 12 years by Noronha et al. [8].

Resolution of OSAS after PPI treatment was noted in three (14.29%) children (10.31 years) with mild OSAS in contrast to the

treatment resistant group, which was characterized by a younger age of patients and a severe form of OSAS. Complete resolution of OSAS resulting from esomeprazole treatment was previously described by Friedman in two of 29 (6.9%) adult patients [4]. Additionally, Orr and Steward observed subjective clinical improvement in daytime sleepiness but did not observe a significant reduction in the AHI in adult patients with OSAS after PPI treatment [29,30]. This may be due to the different OSAS mechanisms in adults as opposed to pediatric patients. In both previously mentioned studies the mean BMI of patients with OSAS was above 30 kg/m^2 and a possible role of obesity in upper airway obstruction should be first considered as a cause of unchanged AHI despite PPI treatment in such patients. In our group of cured children, parents reported non-inflectional recurrences of OSA symptoms during a one year follow up. These reports were noted when the advised dietary recommendations were not adhered to. Parents mentioned late eating, sweet and fatty foods, and drinks such as apple juice or cola as provoking snoring, difficulty breathing, and apnea. Respiratory symptoms resolved either after changing dietary habits or after antireflux therapy. This type of sleep-disordered breathing can be described as "diet-related reversible OSA". Based on this observation we could suspect that, apart from PPI treatment, non-pharmacological management of GERD such as diet change and physical positioning may have had a role to play in decreasing the number of obstructive events and the reduction of AHI in children with susceptibility to treatment of OSA in our study. However, neither sleep position recording nor a diet diary was maintained during the treatment.

Analyses of initial pH-metric characteristics of acid GER in children with OSAS indicate high nighttime acid exposures. However, reflux index was equally distributed between the daytime and the nighttime (12.94% vs. 12.66%). There are different norms of the reflux index for the daytime (upright RI) and the nighttime (recumbent RI). These norms are 7.0% and 2.5%, respectively. This may indicate that increased esophageal acidification in the supine position has a crucial role to play in sleep-disordered breathing. An increased RI was not the result of an increased number of episodes with pH < 4.0, which were within normal ranges. Single long-term acid GER episodes, lasting even up to 33 min, were probably most crucial in the process of esophageal acidification.

GER is also likely to be important in the pathogenesis of arousals [9,31]. Suzuki et al. suggested various types of arousals depending on the severity of OSAS [32]. In this study, PPI treatment did not significantly change the number of arousals. These results are not consistent with a previous study by Oztruk and are contrary to a study by Ing, who found that antireflux therapy reduced the AI in adult patients with OSAS [9,33]. According to Orr, arousal response to reflux may be beneficial and critical in an acid clearing process [15]. We suppose that lymphoid hypertrophy, the chief factor responsible for maintaining upper respiratory tract obstruction, may have been responsible for the lack of arousal change in the studied children.

The change in AHI as a result of PPI treatment was positively predicted by the acid RI in multiple regression analysis. Based on the adjusted *R* square value in multiple regression analysis we can estimate the impact of pH value on AHI at about 50% in the studied group. In children with OSAS one should take into account that GER is not the only factor that may affect the AHI value.

There are some limitations to this study. One of these limitations is the fact that intra-esophageal pH monitoring is insensitive to weakly acidic, alkaline/non-acid or gaseous reflux events; alkaline episodes of GER, however, can be detected by intraluminal impedance monitoring [5]. Therefore false-negative GER diagnoses in children with symptoms of GERD but negative pH-metry results are possible. Another limitation is the fact that a non-validated questionnaire was used. Relying on extensive gastrological experience, the children were qualified for the study on the basis of bothersome GERD symptoms recorded in a detailed original questionnaire. We would like to point out that, as of 2011, a validated questionnaire has been made available which also takes into account two separate age groups, one for toddlers and children (1–10 years) and one for adolescents (11–17 years) [34].We used the before-and-after design of the study to assess preliminary evidence for treatment intervention effectiveness. The results of this study should be confirmed in an experimental, randomized study.

5. Summary

The study was designed to test the hypothesis concerning the relation between sleep obstructive apnea and gastroesophageal reflux. An evaluation of the respiratory response to short-term treatment with a proton pump inhibitor (PPI) in children with evidence of both OSAS and GERD was performed. This study demonstrated that a short course of a PPI may ameliorate OSAS, as shown by a decrease in the Apnea Hypopnea Index following antisecretory treatment. The reduction of obstructive events suggests a mutual relationship between apnea and reflux. Respiratory response to the PPI ranged from complete resolution of OSAS in children with mild OSAS to lack of significant AHI change in children with severe OSAS. The varied distribution of results is understandable as the pathophysiological mechanisms underlying OSAS and GERD are multifactorial and various mechanisms are possible in different individuals. The most significant respiratory response to PPI treatment was observed in three school-aged children with evidence of mild OSAS and GERD secondary to dietary habits. Such a positive response to PPI treatment should not be expected in preschool-aged children with severe OSAS and oversized tonsils. However, antisecretory treatment leading to a reduction in the number of obstructive events may be advantageous as a pre-operational preparation for adenotonsillectomy.

In conclusion, both a high coexistence and a possible mutual relationship between apnea and reflux suggest that questionnaire screening for GERD in children with OSAS may be of clinical benefit.

Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: doi: 10.1016/j.sleep.2012.04.016.

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