Obstructive sleep apnea in Prader-Willi syndrome: risks and advantages of adenotonsillectomy

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Abstract

Obstructive sleep apnea is a well-known clinical manifestation of Prader-Willi syndrome. The aim of our study is to evaluate the efficacy of adenotonsillectomy for the treatment of the disorder as well as the improvement of their post-operative quality of life. Five patients with moderate to severe obstructive sleep apneas and adenotonsillar hypertrophy of grade III-IV underwent adenotonsillectomy. Pre- and post-operative apneas and *Quality of Life* were assessed respectively with a polysomnography with multi-sleep latency test and with the pediatric *Quality of Life* questionnaire, performed before and 6 months after surgery. A decrease of apnea/hypopnea index values has been detected between pre- and post-surgery (t=2.64, P=0.005), as well as oxygen desaturation index values (t=5.51, P=0.005), multi-sleep latency test (t=4.54, P=0.01), and of the values of pediatric *Quality of Life* questionnaire. No correlation has been detected between body mass index and apnea/hypopnea index, oxygen desaturation index and multi-sleep latency test values pre- and post-adenotonsillectomy. A correlation has been found between multi-sleep latency test and oxygen desaturation index values post-surgery (P=0.04). No post-operative complications were observed. Our data underline the efficacy of surgery in Prader-Willi patients with adenotonsillar hypertrophy in order to improve their quality of life.

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Conflict of interest: the authors declare no potential conflict of interest.

Key words: Prader-Willi syndrome; Obstructive sleep apnea; Adenotonsillar hypertrophy; Adenotonsillectomy; Polysomnography.

Received for publication: 4 March 2015.
Accepted for publication: 14 August 2015.

La Pediatria Medica e Chirurgica 2015; 37:107
doi:10.4081/pmc.2015.107

Introduction

Prader-Willi syndrome (PWS) is a disorder linked to a genetic defect involving the paternal chromosome 15; methylation test and fluorescent *in situ* hybridization test demonstrated to be useful in diagnosis.[1] The prevalence is estimated in 1 on 10,000-25,000 live births.[2,3] Even though the diagnosis is mainly clinical, the features are relatively non-specific, varying with age.[2] Prader-Willi syndrome is characterized by neonatal hypotonia (affecting 94% of subjects), hypogonadism (95%), hyperphagia (94%), childhood obesity, small hands and feet, short stature, mental retardation, central nervous system abnormalities and others behavioural disorders.[4] Emotional lability and cognitive impairment are the constant features in adolescence. Sleep disorders are commonly reported in children with PWS, including obstructive sleep apneas leading to daytime hypersomnolence, restless sleep, hyperactivity, alveolar hypoventilation and restrictive lung disease.[5]

Prader-Willi syndrome always causes a generalized hypothalamic insufficiency leading to a dysregulation of the hypothalamic-pituitary axis [including growth hormone (GH), thyroid function, and possibly regulation of the adrenal cortex], increased appetite, increased prevalence of Mellitus Diabetes type II (MDTII), dysregulation of thermoregulation and respiratory control.

Growth hormone therapy in infants, children and adults with PWS has been demonstrated to be useful. Growth hormone replacement therapy improves linear growth velocity and ultimate height, body composition (increased lean body mass and decreased fat mass), muscle function, and level of activity. There is evidence of improvement in the respiratory drive and function. When treatment occurs from infancy, facial appearance and body habitus normalize above all when therapy is associated with a regular dietary management. Rare side effects of human growth hormone therapy include pedal edema, hastening of scoliosis, slipped capital femoral epiphysis and risks to develop pseudotumor cerebri.[2]

The most important risk factors for developing sleep-disordered breathing are hypotonia, obesity and adenotonsillar hypertrophy; snoring and obstructive sleep apnea syndrome (OSA) are most frequent in childhood, mostly around 3-6 years of age.[5,6]

When adenotonsillar hypertrophy is the predominant factor contributing to OSA, adenotonsillectomy is the treatment of choice.[7] A high risk for postoperative complications in children with OSA is well known,[8,9] and the rate of complications after adenotonsillectomy ranges around 0-32%.[10,11] For this reason, preoperative sleep studies and postoperative overnight observation are mandatory.[9]

Because of respiratory obstruction leading to unexpected deaths during the early periods of growth hormone treatment, sleep polysomnography and assessment of ENT disorders leading to apnea

(enlarged tonsils and adenoids) are recommended before beginning of treatment and 6-8 weeks after starting.

The aim of our study is i) to evaluate the efficacy of adenotonsillectomy for the treatment of OSA in children with PWS and evaluate the increase in their quality of life; and ii) to report the postoperative complications rate in our sample.

Materials and Methods

The Pediatric Unit of our Hospital is a reference Centre for PWS for northern and centre Italy with a total number of 126 followed patients. From January 2007 to June 2010, all patients (126) diagnosed with PWS, established by genetic analysis, underwent ear, nose and throat (ENT) examination including anterior rhinoscopy, oroscopy and nasal endoscopy with a flexible fiberscope. The ENT examination was always done before starting GH therapy and we evaluated the presence of clinical symptoms as obstructive sleep apneas and adenotonsillar hypertrophy.

Patients were classified in 4 grades of adenotonsillar hypertrophy. Tonsil hypertrophy grade I when tonsils occupy less than 25% of the oropharynx, grade II when more than 25% and less than 50%, grade III occupying more than 50% and less than 75% of the oropharynx, and grade IV occupying more than 75% of the oropharynx. Grades III and IV were considered to be pathological. Adenoid size was measured by estimating the percentage of the posterior choanal area that was occluded by adenoid tissue. Adenoid hypertrophy of grades III (obstructing more than 50% and less than 75% of the choana) and IV (obstructing more than 75% of the choana) were considered to be pathological.

We selected 20 patients (16 male and 4 female) with pathological adenotonsillar hypertrophy (grade III-IV) and presence of clinical symptoms as obstructive sleep apneas. These 20 patients underwent overnight polisomnography (PSG) examination and multi sleep latency test (MSLT) in the Sleep Medicine Centre of our Hospital. The apnea/hypopnea index (AHI) was defined as the number of mixed/obstructive apnea/hypopnea per hour of sleep.[12] Oxygen desaturation index (ODI) was defined as the number of desaturations (drop in SaO_2>4% of baseline value) per hour of sleep.

Multi sleep latency test is the gold standard test to measure the physiologic sleep propensity. The MSLT consists of four/five nap opportunities performed at two-hour intervals. The initial nap opportunity begins 1.5 to 3 hours after termination of the nocturnal recording. The conventional recording montage for the MSLT includes central electroencephalography (EEG) (C3-A2, C4-A1) and occipital (O1-A2, O2-A1) derivations, left and right eye electrooculograms (EOGs), mental/submental electromyogram (EMG), and electrocardiogram (EKG). Sleep onset for the clinical MSLT is determined by the time from lights out to the first epoch of any stage of sleep, including stage 1 sleep. Sleep onset is defined as the first epoch of greater than 15 sec of cumulative sleep in a 30-sec epoch. The absence of sleep on a nap opportunity is recorded as a sleep latency of 20 minutes. This latency is included in the calculation of mean sleep latency (MSL).[13]

Multi sleep latency test score was considered normal when MSL>12 min, borderline when between 8 and 12 min, and pathological when <8 min.[14] Sleep was scored according to the AASM Manual.[12] Nine patients out of 20 with moderate to severe OSA confirmed by sleep study and adenotonsillar hypertrophy grade III and IV, underwent adenotonsillectomy in general anesthesia, surged by the same surgeon. All patients performed antibiotic and antihemorrhagic therapy. Patients remained in the Pediatric Unit for two days after adenotonsillectomy.

Patients' parents were asked to complete the pediatric *Quality of Life* questionnaire (PedsQL4.0). The 23-item PedsQL 4.0 Generic Core Scales encompass: i) *physical functioning* (8 items); ii) *emotional functioning* (5 items); iii) *social functioning* (5 items); and iv) *school functioning* (5 items). Parents performed the questionnaire in the week before the surgery and 6 month after. For each question, 5 possible responses are given (never, almost never, sometimes, often and almost always), scoring respectively 100-75-50-25 and 0 points.[15] Four patients were lost at follow up, because they did not attend the check-ups and they were not considered in the results. Our final sample included 5 children (3 male and 2 female) with PWS. None of the patients received growth hormone treatment before intervention. Six months after adenotonsillectomy patients underwent a PSG and MSLT control. Three children presented adenotonsillar hypertrophy grade III and two children presented grade IV and moderate-to-severe OSA.

Statistical analysis

The significance of any difference in continuously distributed variables between pre- and post-surgery parameters was examined by t-test for independent samples. Correlation between parameters was studied with a Pearson chi-square test and correlation coefficients between variables.

Results

The mean age at surgery was 5.8 years (range 5-7 years). The mean BMI (Kg/m2) was 28.6 (range 20-39). One patient presented MDTII, and 3 patients were obese. Clinical features of subjects are summarized in Table 1. The mean value of pre operative AHI score was 11±3.4, while ODI was 9.8±3.7; post-operative AHI was 4.6±2.4 and ODI 3.6±1.5. MLST preoperative mean score was 5±2 and post-operative 8.4±2.5. Results are reported in Table 2.

A statistical significance has been detected between AHI values pre- and post-surgery (t=2.64, P=0.005), ODI values (t=5.51, P=0.005) and MSLT (t=4.54, P=0.01). No correlation has been detected between BMI and AHI, ODI and MSLT values pre- and post-tonsillectomy. A correlation has been found between MSLT and ODI post-surgery (P=0.04).

After adenotonsillectomy all parents reported an improvement in snoring and perception of apneas during sleep. The values of PedsQL demonstrated an improvement of quality of life of these subjects after

Table 1. Clinical features of subjects.

Patients	BMI	GH therapy	Age at surgery	Comorbidity
L.J.	21	No	6	None
A.G.	28.1	No	6	Obesity
L.R.	35	No	5	Obesity
M.D.	20	No	5	None
R.J.	39	No	7	MDTII, obesity

BMI, body mass index; GH, growth hormone; MDTII, mellitus diabetes type II.

the adenotonsillectomy. Mean values, standard deviations and statistics are summarized in Table 3. No postoperative complications have been observed in a 15 days follow-up.

Discussion

The major risk factors for developing sleep disorders in PWS subjects include hypotonia, obesity and the presence of adenotonsillar hypertrophy and these findings often coexist.[5] Untreated sleep-disordered breathing in children has been reported to be related with various problems such as attention deficit/hyperactivity disorder, poor academic achievement, and behavioral problems.[16,17] For all these reasons and with the purpose of improving their quality of life, the reduction of OSA in PWS children is recommended.

Some studies suggest that adenotonsillectomy represents the treatment of choice in PWS children when adenotonsillar hypertrophy is present, and the positive results in reducing OSA are reported around 75% of cases, even in obese children, and only in poor responsive children continous positive pressure ventilation (CPAP) is useful.[7,18,19]

Few works focused on treatment suggestions, and all of them report small samples. Nixon and Brouillette[5] described the case of a 9-year-old PWS girl treated with adenotonsillectomy. The surgery led to a reduction in AHI to 2.8 events/hr with an improvement in her daytime sleepiness and behaviour. Wong and colleagues[20] described in a recent case report a 13-year-old girl with PWS who underwent surgical treatment for OSA. She obtained an improvement not only on her OSA but in her quality of life score as well. Schluter and colleagues[21] described two patients with PWS affected by adenotonsillar hypertrophy and treated with adenotonsillectomy, but persistent irregular findings were described after surgery. Pavone and colleagues[22] studied five PWS patients, evaluating the efficacy of adenotonsillectomy and postoperative complications. A sleep study performed 16 months after adenotonsillectomy showed a significant decrease in AHI. Four out of five children showed at least one postoperative complication, one difficult awakening from anesthesia, two subjects presented hemorrages, and one respiratory complications requiring reintubation. DeMarcantonio and colleagues[23] studied pre- and post-operative AHI in five patients with PWS and OSA in order to review the effectiveness and safety of surgical intervention for obstructive sleep apnea in PWS. The authors could not demonstrate statistically significant changes after surgery. Tanna and colleagues[24] showed postoperative results in three cases of PWS patients with OSA. Resolution of OSA after adenotonsillectomy was variable. The patient with the highest body mass index and tonsil size had a residual OSA after adenotonsillectomy. No perioperative complications or adverse events were observed by the authors.

According to the majority of literature, our results showed a statistical significance between AHI values pre- and post-surgery (P=0.005), ODI values (P=0.005) and MSLT (P=0.01). Results of post-operative PSG demonstrated the presence of a small number of apneas and hypopneas, and the presence of central apneas may be the possible causal factor.[25] In addition, we focused on children quality of life. Prader-Willi syndrome children often suffer from impaired social and emotional context and in our opinion in these patients an effective treatment of OSA is mandatory. We observed a statistically significant improvement in each item of post-operative PedsQL questionnaire. These findings suggest an important role of surgical treatment in order to improve their physical, emotional, social and scholar quality of life.

Literature reported a very high peri- and post-operative complication rate. In summary, potential complications of adenotonsillectomy include anaesthetic complications, post-operative problems, hemorrhages and respiratory complications including worsening of OSA.[8,10] Reider reported a case of death in the immediate postoperative period.[26] Although limited to five patients, we did not find peri- and post-operative complications. Neverteless adenotonsillectomy in patients with PWS is not a riskless surgery. Thus we suggest the need for monitoring of all pediatric patients with PWS after surgery. We recovered the patients for at least two days and they were operated with a particular care to hemostasis, giving a special pre- and post-surgery anesthesiological support.

The true prevalence of OSA in PWS is unknown.[5] Early diagnosis of sleep disordered breathing, in particular OSA, in PWS patients may help prevent complications such as cor pulmonale. Finally, it is important to re-evaluate OSA in children with PWS and to assess the effective improvement.

Table 2. Pre- and post-operative sleep parameters.

Patients	AHI pre	AHI post	ODI pre	ODI post	MSLT pre	MSLT post
L.J.	12	6	12	3	3	9
A.G.	16	2	6	2	4	6
L.R.	9	4	9	3	4	6
M.D.	11	3	8	4	6	9
R.J.	7	8	10	6	8	12

AHI, apnea hypopnea index; ODI, oxygen desaturation index; MSLT, multi sleep latency test.

Table 3. Values of pediatric *Quality of Life* questionnaire before and after 1 month of surgery.

	Before	After	Statistics
Physical subscale	200±58	300±40	t=4.2; P=0.01
Emotional subscale	105±45	290±38	t=8.P=0.001
Social subscale	135±29	215±22	t=4.3; P=0.01
School subscale	85±14	235±42	t=8.5; P=0.001
Total score	525±95	1035±63	t=8.8; P=0.001

Conclusions

Our data support the hypothesis that adenotonsillectomy is useful in PWS children with apneas in order to reduce their sleep disorders, leading to a better quality of life. Surgical complications should be carefully evaluated; nonetheless, a strict post surgery follow-up may considerably reduce complications. We suggest a post-operative evaluation of sleep disorders and quality of life in these subjects performing a PSG and PedsQL questionnaire.

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