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SLEEP BREATHING PHYSIOLOGY AND DISORDERS • SHORT COMMUNICATION

Successful upper airway stimulation therapy in an adult Down syndrome patient with severe obstructive sleep apnea

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Abstract

Purpose The aim of this study was to report on the successful application of upper airway stimulation (UAS) therapy in an adult Down syndrome (DS) patient with severe obstructive sleep apnea (OSA) and continuous positive airway pressure (CPAP) intolerance.

Methods Baseline polysomnography (PSG) in a 23-year-old male OSA patient (body mass index (BMI) 24.4 kg/m^2) revealed an apnea/hypopnea index (AHI) of 61.5 events/h and oxygen desaturation index (ODI) of 39.7 events/h. Based on the clinical examination, PSG and drug-induced sleep endoscopy, the patient fulfilled the formal inclusion criteria for UAS therapy: AHI between 15 and 65 events/h, BMI < 32 kg/m^2, and no complete concentric collapse at the level of the velopharynx.

Results Implantation of the hypoglossal nerve stimulator in the adult patient with DS resulted in a substantial subjective as well as objective improvement of OSA (63 to 81% decrease in AHI and 77% decrease in ODI), translating into an overall satisfactory outcome.

Conclusion Research on the long-term effectiveness of UAS therapy in a larger group of patients with DS is needed. However, based on the available literature and our presented case, respiration-synchronized electrostimulation of the hypoglossal nerve using UAS therapy may have a potential value in well-selected OSA patients with DS who are non-compliant to CPAP therapy.

Keywords Sleep-disordered breathing · Hypoglossal nerve stimulation · Treatment · Surgery · Down syndrome

Introduction

Down syndrome (DS) is the most common genetic disorder with an incidence of 1 in 691 births [1]. Patients with DS are predisposed to a number of health problems affecting their development and quality of life. Among them, obstructive sleep apnea (OSA) is very common, occurring in up to 66% of the children, and in the vast majority of the adults [2, 3]. The development of OSA in the DS population is a result of the physiologic and anatomical differences such as a reduced muscular tone, midfacial and mandibular hypoplasia, a small upper airway, relative macroglossia (due to crowding of the oropharynx), adenotonsillar hypertrophy, a shortened palate, generalized hypotonia, hypothyroidism, and more frequently reported laryngomalacia, subglottic stenosis, and tracheomalacia in the DS population [2]. These patients usually suffer from a more severe OSA with significant hypoxemia as compared to individuals without DS [3]. Consequently, patients with DS are more susceptible to cognitive difficulties and neurodegeneration [4]. Lal et al. have described the impact of OSA on patients with DS in a comprehensive literature review [5]. Early recognition and adequate treatment of OSA may improve their quality of life substantially. Behavioral modifications such as weight loss by exercise and dietary programs or avoidance of noxious fumes

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might help decreasing the OSA severity [5]. If these simple measures are not applicable or sufficient, other or additive treatment options are necessary. Continuous positive airway pressure (CPAP) is the gold standard treatment for adults, with or without DS, with moderate to severe OSA [5, 6]. Even though proper treatment is of utmost importance, only few treatment options have been investigated in adults with DS and OSA, namely CPAP and oral appliance therapy (the latter in only 2 patients) [3, 7]. Electrical neurostimulation of the hypoglossal nerve—using the Inspire II system (Inspire Medical Systems Inc., Maple Grove, MN, USA)—referred to as upper airway stimulation (UAS) therapy, has been recently approved for commercial use in selected patients with OSA [8–10]. Despite the significant amount of studies that have been published on UAS in the general population, only few studies have evaluated the effect of this treatment in DS patients with OSA [11–13]. These studies recommended UAS as a potential therapeutic option for patients with DS. However, all the studies published up to date were reporting on a pediatric and adolescent population with DS. So far, no studies were published on the application of UAS in adult patients with DS.

This paper presents, to the best of our knowledge, a case report of the first hypoglossal nerve stimulator ever implanted in an adult patient with DS and OSA.

Case report

A 23-year-old male, diagnosed with DS and severe OSA, was referred to our center. Unlike many adults with DS, this patient did not have other serious health conditions. He did not undergo any previous surgery except for a cholecystectomy. In the past, CPAP treatment was introduced with favorable results: a reduction in daytime sleepiness with some improvement in cognitive function. However, the parents deemed this treatment unfeasible since they had to readjust the nasal mask several times each night resulting in severe sleep fragmentation (also for the parents). Other CPAP masks were fitted without any success. Before considering a non-CPAP treatment, a new baseline polysomnography (PSG) was performed. The PSG showed a supine-dependent OSA with an apnea/hypopnea index (AHI) of 61.5 events/h and an oxygen desaturation index (ODI) of 39.7 events/h (Table 1). A sleep position trainer (SPT) was prescribed hereafter in view of the positional dependency [14]. Theoretically, the AHI could have been reduced from 61.5 events/h to 22.7 events/h (61% reduction) in the absence of supine sleep. However, after a 1-month trial, the SPT treatment was discontinued due to intolerance [15]. In order to assess the surgical treatment options, a series of further investigations were performed. Ear, nose, and throat examination revealed a normal nasal passage, grade 2 palatine tonsils, a normal sized uvula, and a Mallampati score of 4. The body mass index (BMI) was 24.4 kg/m^2. Drug-induced sleep endoscopy (DISE), performed under sedation with midazolam and propofol [16], demonstrated a complete anteroposterior collapse of the velopharynx and tongue base, and a partial laterolateral collapse of the oropharynx and epiglottis. No collapse was present at the level of the hypopharynx. Subsequently, direct laryngoscopy excluded laryngeal anomalies. Based on the results of the clinical examination, the PSG and the DISE, the patient fulfilled the formal inclusion criteria for UAS therapy: AHI between 15 and 65 events/h, BMI < 32 kg/m^2, and no complete concentric collapse at the level of the palate during DISE. Implantation of the device (Inspire II system, Inspire Medical Systems Inc., Maple Grove, MN, USA) occurred uneventfully under continuous electromyogenic monitoring of the hypoglossal nerve. The surgical technique has been described previously [17]. A postoperative chest radiograph confirmed the position of the pulse generator and excluded postoperative pneumothorax. Postoperative titration and clinical follow-up took place according to a predefined protocol [18]. One month after implantation, the UAS device was activated without discomfort at a stimulation amplitude of 1.0 V. Final titration occurred 1 month after activation during a titration PSG to optimize therapeutic efficacy and patient tolerance by applying different stimulation levels. There was a clear difference in airflow and oxygen saturation with stimulation off compared to stimulation on (Fig. 1). Based on this titration PSG, with a residual AHI of 11.5 events/h (81% decrease compared to baseline), the stimulation amplitude was elevated to 1.2 V. Average device usage amounted to 9.4 h each night. Six months after implantation, an additional titration PSG was performed. However, no changes were made because the patient did not tolerate any elevated voltage. The follow-up PSG showed a persistent response (Table 1) with a 63% reduction in AHI and a 77% reduction in ODI.

Discussion

Down syndrome predisposes to OSA due to multiple anatomical variations, such as midfacial hypoplasia, relative macroglossia, glossoptosis, lingual tonsillar hypertrophy, hypotonia, and lower airway stenosis [2]. Adults with DS have even more predisposing factors as they are more likely to develop obesity or hypothyroidism. DISE, performed in children with DS, revealed a multilevel collapse in 85% of patients [19]. As a consequence, these patients often require a combined approach including multilevel, surgical, or non-surgical treatments. One study described improvements in daytime functioning and excessive sleepiness in CPAP-compliant adults with DS and OSA [3]. However, no surgical treatments have been investigated so far in this population.

Respiration-synchronized UAS, using electrical neurostimulation of the hypoglossal nerve, reduces the collapsibility of the upper airway by activation of the genioglossus muscle [20]. This procedure may provide a multilevel effect

Table 1 Comparison of polysomnographic studies before and after device implantation.

	Baseline PSG	Follow-up PSG at 6 months
Sleep overview		
Total sleep time	6 h 38 min	7 h 27 min
Sleep efficiency (%)	75.6	84.5
REM sleep (% sleep time)	15.7	5.6
N1 (% sleep time)	3.8	11.4
N2 (% sleep time)	64.7	57.5
N3 (% sleep time)	15.8	25.5
Respiration		
AHI (events/h)	61.5	23.0
AI	33.3	1.7
HI	28.2	21.2
REM sleep	46.1	12.0
NREM sleep	64.4	23.6
Arousal index (events/h)	50.1	31.7
Snoring index (events/h)	331.2	113.6
SaO_2		
ODI (events/h)	39.7	9.3
Mean SaO_2 (%)	94.7	96.0
Minimal SaO_2 (%)	71.0	86.0
Position dependency		
AHI supine (events/h)	92.7	41.2
AHI non-supine (events/h)	22.7	20.2
Supine position (% sleep time)	58.2	13.0

PSG polysomnography, *REM* rapid eye movement, *NREM* non-REM, *N1–3* sleep stages 1 to 3, *AHI* apnea/hypopnea index, *AI* apnea index, *HI* hypopnea index, *ODI* oxygen desaturation index, *SaO_2* oxygen saturation

without changing the anatomy [9]. Three components are implanted during the surgical procedure: an infraclavicular implantable pulse generator, a submandibular stimulation cuff-electrode around the protruding branches of the hypoglossal nerve (cranial nerve XII), and an intercostal sensing lead [18]. Since the hypoglossal nerve innervates both protrusion (genioglossus) and retraction (hyoglossus and styloglossus) tongue muscles, only the protruding medial branches are included in the stimulation

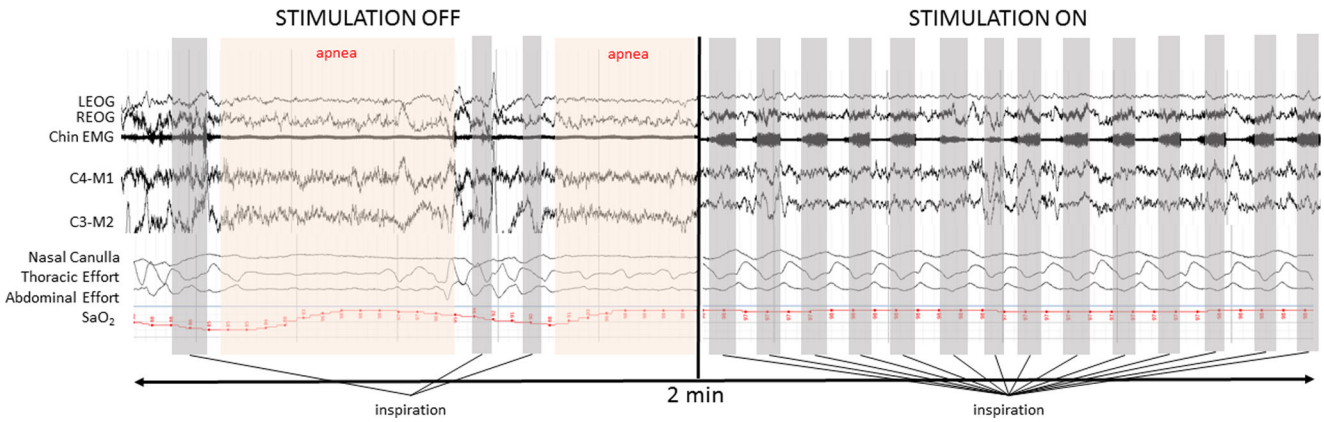

Fig. 1 Representative signal recording during polysomnography comparing UAS off (left panel) and UAS on (right panel) in het reported patient. Electrical neurostimulation of the hypoglossal nerve, synchronized with respiration, corresponds to the increase in the EMG signal. This example recording clearly illustrates UAS leading to a normalization of both airflow and oxygen saturation. LEOG, left electrooculography; REOG, right electrooculography; UAS, upper airway stimulation, EMG, electromyography; EOG, electrooculography; EEG, electroencephalography; SaO_2, oxygen saturation

electrode. Selective nerve monitoring facilitates the intraoperative identification of these different branches. By sensing the pleural pressure, the device generates a respiration-synchronized stimulation of the hypoglossal nerve while sleeping. Long-term effectiveness and adherence of UAS therapy are well documented with the 5-year results of the stimulation therapy of apnea reduction (STAR) trial recently published [8, 21]. Serious adverse events are uncommon and side effects are generally well tolerated. Nevertheless, selecting suitable patients remains of paramount importance. Only patients who are non-compliant to CPAP treatment with moderate to severe OSA (AHI between 15 and 65 events/h) are considered good candidates for UAS therapy. Exclusion criteria are as follows: obesity (BMI > 32 kg/m^2), central sleep apnea (> 25% of total AHI), and complete concentric collapse at the level of the velopharynx during DISE [8, 10, 18, 22].

The application of UAS in DS patients has been described more recently in a pediatric and adolescent population [12]. The same inclusion and exclusion criteria as described above were maintained in the DS population. Even though the follow-up PSG showed a residual OSA in all 6 patients, a decrease in OSA severity was achieved every time, with a 56 to 85% reduction in AHI compared to the baseline PSG. In addition, a mean use of 5.6 to 10.0 h/night was reported. The quality of life of the patients also improved after implantation. In our case, the AHI decreased significantly from 61.6 to 23.0 events/h during follow-up PSG and even to 11.5 events/h in the optimal settings during titration PSG (63 to 81%). Treatment with CPAP might have resulted in a greater decrease in AHI. However, the greater efficacy of CPAP is offset by inferior adherence in our case, resulting in a higher true clinical effectiveness of UAS therapy as compared to CPAP in the described case.

In our case, follow-up polysomnography showed a residual supine-dependent OSA, with an AHI in supine position of 41.2 events/h, compared to 92.7 events/h at baseline. In non-supine position, the AHI only changed marginally (22.7 events/h to 20.2 events/h). The prevalence of positional OSA has been described in a population undergoing UAS implantation before and after surgery showing a high prevalence of 61% before and after UAS implantation [23].

In our patient, the amount of sleep in supine position was widely different between the baseline and follow-up PSG. In order to compare the AHI values of these examinations, a correction for the time in supine position during the baseline PSG was done, showing a significant decrease of 47.3% (instead of 62.6%) with UAS.

In addition, the AHI in both REM as NREM sleep was decreased drastically during follow-up PSG, showing an improvement in OSA severity over the entire course of the night.

Importantly, the amount of apneas decreased significantly in our case, as mostly hypopneas occurred during UAS therapy (54.2% apneas during baseline vs. 7.6% apneas during follow-up PSG) (Table 2). Moreover, the decrease in ODI (77% as compared to baseline) was more pronounced than the decrease in AHI. Nevertheless, the effect of UAS treatment in our DS patient could have been higher, if he would have been able to tolerate higher stimulation voltages and/or SPT treatment.

The parents reported a significant improvement in daytime sleepiness and cognitive performance of their son and even expressed their gratitude and satisfaction in a letter to the interdisciplinary medical team. Since the activation of the device, the patient slept soundly at night and enjoyed his activities once again during the day.

In summary, the results in the reported patient are in concordance with the results described in literature on UAS in the pediatric and adolescent population with DS. Our results clearly illustrate the potential value of UAS therapy in well-selected DS patients with OSA refractory to conventional treatments such as CPAP. However, because of the lack of large cohort studies, further research on hypoglossal nerve stimulation in patients with DS is warranted.

Table 2 Comparison between number of apneas and hypopneas per hour in supine and non-supine position: before (baseline polysomnography) and after (follow-up polysomnography at 6 months) device implantation

	Before implantation	After implantation
Supine		
AI	56.5	1.0
HI	36.3	40.2
AHI	92.7	41.2
Non-supine		
AI	1.4	1.8
HI	21.2	18.4
AHI	22.7	20.2

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Compliance with ethical standards

Conflict of interest Olivier Vanderveken has the following potential conflicts of interest: research support and lecture fees from Inspire Medical Systems, research grant from and consultancy for Philips Respironics, research grant and lecture fees from Somnomed, consultancy for Nyxoah, consultancy for Galvani, research support from ReVent, research support from Nightbalance. The other authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical approval All procedures performed were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Patient consent statement The patient guardian has consented to the submission of the paper for submission to the journal.

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Comment

This case highlights the potential for hypoglossal nerve stimulation in treating patients with Down's syndrome, who may otherwise have difficulty tolerating CPAP and other therapeutic modalities. This patient's response suggests that hypoglossal stimulation can overcome defects in upper airway anatomy and neuromuscular control commonly found in this condition.

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