Long-term stability of hypoglossal nerve stimulation for the treatment of obstructive sleep apnea in children with Down syndrome

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ABSTRACT

Importance: Obstructive sleep apnea (OSA) occurs in 55–97% of people with Down syndrome (DS). Even after adenotonsillectomy, residual OSA often persists into adulthood due, in part, to tongue base collapse. Implantable hypoglossal nerve stimulators are being investigated in children and young adults with DS and persistent, moderate to severe OSA. However, the long-term necessity for such an intervention—especially as patients mature and voltage adjustment becomes warranted—has not been previously reported in the pediatric DS population.

Objective: To assess the long-term need for implantable hypoglossal nerve stimulators and the necessity for voltage adjustment in children and young adults with Down syndrome.

Design: This is a case series from an ongoing clinical trial assessing safety and efficacy of hypoglossal nerve stimulation among 42 children and young adults with DS and persistent OSA, despite adenotonsillectomy and trialed positive airway pressure (PAP) therapy. We focus here on the first 4 participants who have undergone implantation by age 13 and have completed at least 44 months of follow-up.

Participants: 4 participants (2 male, 2 female; ages 10–13 years) with DS and persistent, severe OSA (AHI > 10 events/h) underwent hypoglossal nerve stimulator implantation and were followed for 44–58 months.

Setting: Participants completed in-lab sleep studies at baseline (before implantation), 1 year postoperatively, and 44–58 months postoperatively. During their most recent follow-up, 2 participants completed split-night sleep studies in which assessment was done with the device both on and off.

Interventions: Hypoglossal nerve stimulator implantation.

Main outcomes and measures: Stability in titrated and untitrated OSA as measured by the apnea–hypopnea index (AHI); growth measures including BMI; and quality of life as measured by the OSA-18 questionnaire.

Results: Compared to baseline, all 4 participants maintained reductions of at least 50% in AHI over the course of follow-up. At recent follow-up, two participants had persistent, moderate OSA despite stimulation therapy. The other two participants achieved 100% reductions in AHI with stimulation therapy; when they underwent split-night sleep studies, the severe OSA persisted with the device turned off. Improvement in OSA-18 quality of life scores was observed in three of the four participants.

Conclusion: and Relevance: Hypoglossal nerve stimulation continues to effectively control OSA in children with DS as they mature, while their underlying untitrated OSA appears to persist into adulthood.

Trial registration: clinicaltrials.gov Identifier: NCT2344108.

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1. Background

Obstructive sleep apnea (OSA) presents in 55–97% of individuals with Down syndrome (DS) prior to adulthood, compared to 1–4% of the neurotypical pediatric population [1]. In children, OSA is associated with cardiopulmonary complications (e.g., arrhythmias, hypertension), behavioral and psychiatric problems (e.g., excessive daytime sleepiness, depression), neurocognitive dysfunction, and adverse quality of life [2, 3].

In addition to the higher prevalence of OSA among children with DS, treatment complexity and disease progression differ from the general pediatric population. Adenotonsillectomy (T&A) remains the first treatment of choice for children with OSA who have adenotonsillar hypertrophy, including those with DS. Although OSA often improves in children with DS after T&A, residual airway obstruction is common, due in part to tongue base collapse, lingual tonsil hypertrophy, macroglossia, maxillary hypoplasia, and hypotonia [4]. Up to 75% of these children require respiratory support for residual airway obstruction following T&A [5].

When airway obstruction persists despite T&A, secondary treatment options include positive airway pressure (PAP) therapy, supplemental oxygen, and/or tracheotomy. However, each of these is challenging for children with DS, up to half of whom are noncompliant with airway support therapy due to a high frequency of coincident sensory integration disorders [6]. Tracheotomy bypasses upper airway obstruction but is associated with complications in up to 19% of patients, including inadvertent decannulation, formation of suprastomal granulation tissue, and formation of tracheoinominate fistula [7,8].

Children with DS also differ from their neurotypical peers with respect to development and OSA progression. In the general pediatric population, remission from OSA is achieved in approximately 70% of individuals by adolescence or early adulthood, compared to about 26% of individuals with DS [9,10]. Developmental changes in upper airway anatomy may partially explain why most children "outgrow" OSA, whereas persistent tongue base collapse in children with DS may continue contributing to upper airway obstruction into adulthood [11].

The prevalence, persistence, and impact of OSA in children with DS warrants interest in alternative treatments. Since 2014, surgically implanted hypoglossal nerve stimulators have been approved by the Food and Drug Administration (FDA) for the treatment of OSA in neurotypical adults with an apnea–hypopnea index (AHI) less than 50 events/h, body mass index (BMI) less than 32 kg/m^2, and without circumferential airway collapse at the level of the velopharynx [12,13]. Prospective studies have shown that these devices remain safe and effective in adults up to three years after implantation [14].

The hypoglossal nerve stimulator (Inspire Medical Systems, Inc.) consists of three implanted components: an intercostal sensing electrode, a pulse generator, and a stimulation lead placed around the anterior branches of the hypoglossal nerve. On inspiration, the device electrically stimulates the hypoglossal branches, inducing tongue base protrusion and improving airway patency.

Recently, hypoglossal nerve stimulators have been investigationally implanted in 42 children and adolescents with DS for whom moderate to severe OSA persists despite T&A and for whom PAP therapy is not well tolerated. This pilot study remains ongoing, but preliminary reports suggest that hypoglossal nerve stimulators are safe and effective in this population, leading to a median reduction in AHI of 85% [7,15,16]. However, these studies have only evaluated device safety and efficacy in the first year after implantation. Growth throughout puberty poses a concern about displacement of the device's sensing and stimulation leads, and extended follow-up of these pediatric patients is needed in order to assess long-term device stability.

Here, we discuss 4 participants (2 male, 2 female) from the pilot study who underwent hypoglossal nerve stimulator implantation by the age of 13 and who have since been followed for at least 44 months. OSA severity was monitored according to the AHI at baseline (preoperative), 1 year postoperatively, and 44–58 months postoperatively. Changes in BMI and BMI percentile were also collected over this time.

2. Methods

The pilot study from which these participants were selected was approved by the Institutional Review Board (IRB) of Massachusetts Eye and Ear (Mass General Brigham, Boston, MA) and the US Food and Drug Administration, which issued an investigational device exemption (IDE). Participants were enrolled after obtaining written informed consent from subjects' legal guardians as well as verbal assent from the subjects themselves.

Eligibility criteria were modified from the criteria used in prior studies on the hypoglossal nerve stimulator in adults [13]. Specifically, participants required a baseline apnea–hypopnea index (AHI) between 10 and 50 events/hour, a central apnea contribution of less than 25%, a body mass index (BMI) under the 95th percentile, and an inability to tolerate PAP therapy or dependency on tracheotomy. Families were advised of the device's incompatibility with magnetic resonance imaging (MRI), and participants were excluded if they had medical conditions necessitating future MRI. Additionally, legal guardians were required to attest in writing to their child's ability to cooperate with study procedures and communicate discomfort.

Polysomnography (PSG) was performed to verify inclusion criteria if participants had not already undergone PSG within 6 months of enrollment. Participants meeting all other eligibility criteria underwent drug-induced sleep endoscopy (DISE) to evaluate upper airway anatomy at the level of the tongue base, oropharynx, hypopharynx, and velopharynx using the VOTE (velopharynx, oropharynx including palatine tonsils, tongue, and epiglottis) classification scheme [17]. Participants were excluded if their DISE revealed circumferential collapse at the level of the velopharynx. Three physicians (one otolaryngologist and two sleep medicine physicians) independently reviewed the DISE results, and recommendation for device implantation was required from at least two of them.

Candidates meeting all eligibility criteria then underwent hypoglossal nerve stimulator implantation using previously described techniques [18,19,26]. (Fig. 1). Once implanted, devices were intraoperatively turned on to confirm tongue base protrusion and were then deactivated. Postoperative posterior-anterior and lateral chest radiography was performed for all participants to confirm proper device positioning and the absence of pneumothorax or pneumomediastinum. Participants were discharged after one night of observation, and devices were left deactivated.

One month after implantation, devices were activated and voltage was titrated during an overnight PSG. Participants returned for overnight PSGs and subsequent voltage titrations 2, 6, and 12 months after implantation. All PSGs were scored according to the American Academy of Sleep Medicine (AASM) pediatric standards [20]. Device usage questionnaires were also administered and compared against device usage data generated by the device itself. Beyond the 12-month follow-up period of the study, all 4 participants continued to be followed by their pediatric otolaryngologist and continued undergoing periodic PSG.

These 4 participants were selected because they underwent device implantation at relatively young ages and completed extended follow-up thereafter. All 4 participants underwent follow-up PSG between 44 and 58 months after implantation, at which time BMI was also measured. BMI percentiles were calculated using growth curves per the Centers for Disease Control and Prevention (CDC) [21,22].

Quality of life was assessed using the OSA-18 questionnaire, which has demonstrated test-retest reliability, internal consistency, and construct validity [23]. The OSA-18 questionnaire consists of 18 items which assess frequency of symptoms or problems associated with sleep disordered breathing. Participants are asked to indicate symptom frequency on a scale of 1 (indicating never) to 7 (indicating always). The
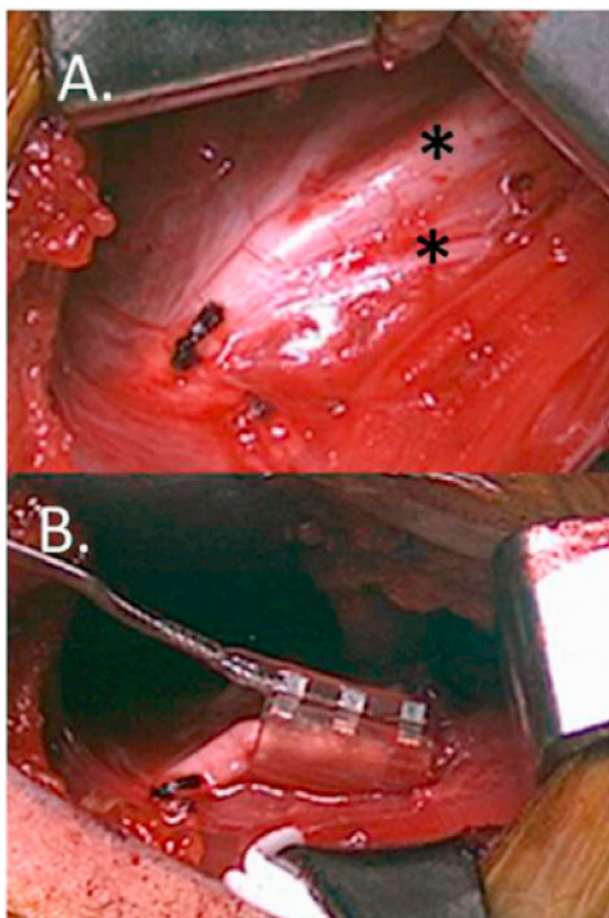
Fig. 1. Intraoperative electrode placement.
Fig. 1 A. The hypoglossal nerve is dissected anteriorly to expose its lateral and anterior branches, marked with asterisks (*).
Fig. 1 B. The stimulating electrode cuff is placed around the hypoglossal anterior branches. Reused from Diercks et al., 2016 [Ref. 26].

summed total score from these responses ranges from 18 to 126, with scores under 60 suggesting "minimal impact" of symptoms; scores between 60 and 80 suggesting "moderate impact" of symptoms; and scores above 80 suggesting "severe impact" of symptoms. In addition, the OSA-18 includes an overall quality of life subscore, which ranges from 0 (worst quality of life possible) to 10 (best quality of life possible). The OSA-18 was administered at baseline, 1 year postoperatively, and near the time of participants' most recent sleep study.

Here, we compare AHI values and quality of life measures at three time points: (1) baseline, or preoperatively; (2) 1 year postoperatively; and (3) the time of participants' most recent PSG (abbreviated "recent" in figures). For 2 of the 4 participants exhibiting AHIs of zero at the time of their most recent PSG, split-night sleep studies were performed with the device turned off in order to evaluate whether OSA remained present in the absence of stimulation therapy. Statistical analyses were not done due to small sample size.

3. Results

The two male and two female participants ranged in age from 10.2 to 13.9 years at the time of implantation, and from 13.8 to 18.6 years at the time of their most recent PSG. The interval from implantation to most recent PSG ranged from 44 to 58 months. Between the 1 year and recent PSGs, optimal device voltage increased in all 4 participants by 0.1–1.3 V (Table 1).

At baseline, AHIs ranged from 21.0 to 30.7 events/h, indicative of severe OSA in all 4 participants. One year after implantation, AHIs ranged from 2.9 to 11.0 events/h at therapeutic device voltage, while individual reductions in AHI from baseline ranged from 48% to 88%. One year after implantation, and with device usage, one participant exhibited severe OSA (AHI = 11.0 events/h), one participant exhibited moderate OSA (AHI = 5.0 events/h), and two participants exhibited mild OSA (AHI = 2.9, 3.8 events/h).

After 44–58 months of device therapy, AHIs remained within ±3.8 events/h of that observed 12 months after implantation. AHIs from the most recent PSGs ranged from 0.0 to 5.2 events/h at therapeutic device voltage, while individual reductions in AHI ranged from 51% to 100% compared to baseline (Fig. 2).

At the time of their most recent PSG, two participants exhibited no OSA (AHI = 0.0 events/h) and two participants exhibited moderate OSA (AHI = 5.2, 9.5 events/h). In the same PSG session, the two participants showing complete OSA resolution (AHI = 0.0 events/h) underwent a split-night PSG in which AHI was also measured while the device was turned off. Both of these participants exhibited severe, residual OSA with AHIs of 11.2 and 109.7 events/h when the device was turned off (Fig. 3).

Age- and sex-adjusted BMIs ranged from 19.2 to 24.6 kg/m^2 (36th to 92nd percentile) at baseline, and from 19.8 to 34.6 kg/m^2 (57th to 99th percentile) at the time of the most recent PSG. In 3 participants, BMI percentile increased with age (Fig. 4).

Quality of life scores as measured by the OSA-18 questionnaire improved over the course of follow-up in three of the four participants (Fig. 5A and B). Changes in OSA-18 total scores (which are between 18 and 126) ranged from −40 to +5 from baseline to 1 year; −17 to +48 from 1 year to the time of most recent follow-up; and −57 to +12 from baseline to the time of most recent follow-up. At the time of most recent follow-up, three of the four (75%) participants' total OSA-18 scores were indicative of "minimal impact of OSA" as defined by scores under 60 (Fig. 5A).

Overall quality of life subscores (0–10) also improved over the course of the study in three of the four participants. Changes in OSA-18 overall subscores ranged from +2 to +3 between baseline and 1 year; −5 to +3 between 1 year and the time of most recent follow-up; and −3 to +5 between baseline and the time of most recent follow-up (Fig. 5B). Two participants showed improvements of +5, and one showed an improvement of +4, in overall quality of life subscores from baseline to the time of most recent follow-up.

Table 1
Participant Summary: sex, age, BMI and BMI percentile, and optimal voltage setting.

Participant	Sex	Age (years)		Interval (months)	BMI (Percentile)[a]		Optimal Voltage (V)	
		Baseline	Recent		Baseline	Recent	1 Year	Recent
Subject 1	M	13.9	18.6	56	24.6 (92)	34.6 (99)	1.9	2.2
Subject 2	M	13.6	18.5	58	19.2 (55)	26.1 (85)	1.5	2.8
Subject 3	F	11.9	16.8	58	20.2 (75)	22.4 (68)	1.5	1.8
Subject 4	F	10.2	13.8	44	16.2 (36)	19.8 (57)	2.1	2.2

[a] BMI and BMI percentiles were calculated per CDC growth curves for the neurotypical pediatric population [21,22].
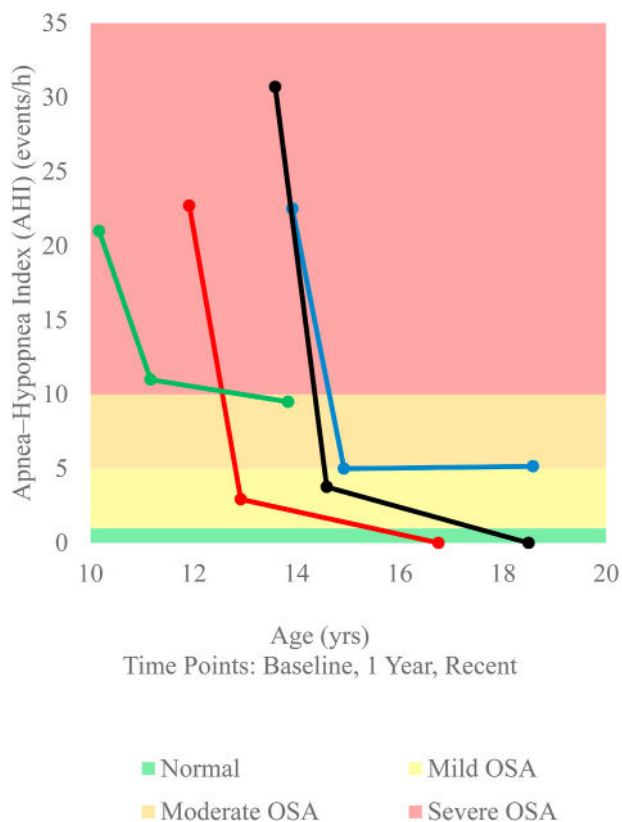
Fig. 2. Change in apnea–hypopnea index (AHI).

Fig. 2. Apnea–hypopnea indexes (AHIs) obtained from polysomnography at baseline (without stimulation therapy), 1 year after implantation, and at the time of their most recent follow-up. Interpretation of OSA severity is indicated by background color and defined according to AHI: normal (<1 event/h), mild OSA (1 to < 5 events/h), moderate OSA (5 to < 10 events/h), severe OSA (≥10 events/h). In all figures, color coding of participants is kept consistent: subject 1 = blue, subject 2 = black, subject 3 = red, subject 4 = green.
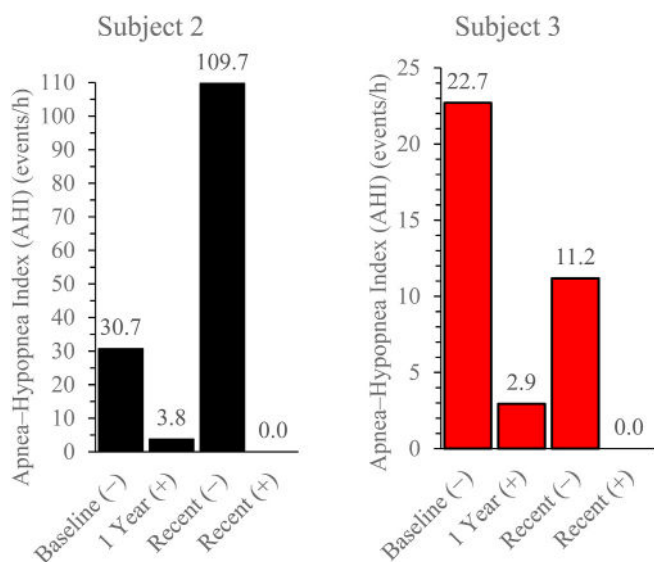
Fig. 3. Split-night sleep studies: AHI in the absence of stimulation therapy.

Fig. 3. Apnea–hypopnea indexes (AHI) for the two subjects who underwent split-night sleep studies with the device both on (+) and off (−).

4. Discussion

Preliminary results of this pilot study have demonstrated that hypoglossal nerve stimulation is both safe and effective for the treatment of T&A-refractory, moderate to severe OSA in children with DS who do not tolerate PAP therapy [7,15,16]. Here, we expand on those results with the goal of assessing long-term device stability in patients implanted by the age of 13 years. The 4 participants presented here demonstrate sustained, clinically significant reductions in AHI after 44–58 months of device therapy.

Two of these four participants showed 100% reductions in AHI at their most recent follow-up, suggesting that OSA remission is possible with adherence to device therapy. This was a *bona fide* treatment effect as both of these participants exhibited severe, underlying OSA when the devices were turned off during their recent split-night sleep studies. These data are consistent with a previous study that has shown OSA to persist into adulthood for a majority of children with DS [9].

Optimal device voltage increased modestly for all 4 participants following their 1 year sleep study. The recent therapeutic voltage settings in these participants were similar to long-term optimal voltage settings reported in adults [24]. BMI percentiles also increased for 3 of the 4 participants, which may partially explain the need for additional voltage titration.

The quality of life measures provided by the OSA-18 questionnaire suggest that meaningful improvements in quality of life can be experienced by participants following device use. Two of the four participants who exhibited "moderate symptom impact" scores at baseline showed sustained improvements 1 year after surgery and at recent follow-up suggesting "minimal symptom impact." Strikingly, three of the four participants showed improvements of at least 4 points out of 10 in their OSA-18 overall quality of life subscores.

One participant showed improvement in OSA-18 questionnaire scores 1 year after surgery, followed by worsening of quality of life measures at their recent follow-up. It is possible that the questionnaires at these time points were completed by different parents or guardians, which could help explain the inconsistency.

For many children with DS, OSA becomes a chronic medical problem for which suitable treatment options remain limited. While the cumulative impact of OSA on these patients' long-term health is not yet fully understood, OSA is associated with an increased risk for multiple comorbidities and diminished quality of life. Furthermore, Breslin et al. have reported that verbal IQ is, on average, 9 points lower in children with DS and an AHI >1.5, demonstrating a relationship between OSA and cognitive outcome in this population [25].

When implanted during childhood, hypoglossal nerve stimulators may offer patients with DS long-term relief from this potentially lifelong condition. However, the residual, moderate OSA observed in 2 of the 4 participants after long-term device usage suggests that adjunct therapy may still sometimes be warranted after hypoglossal nerve stimulator implantation, especially when considering the significant impact on verbal IQ reported by Breslin et al. in children with DS and AHI >1.5 [25]. These 2 participants were noncompliant with PAP therapy due to sensory integration disorders; and as such, AHI with both hypoglossal nerve stimulation and PAP therapy was not available. Therefore, the combined effects of hypoglossal nerve stimulation and PAP or other adjunct therapies on AHI would be a valuable topic for future studies.

4.1. Limitations

There are some limitations inherent to the study design that should be noted. This was a small sample size of 4 participants, which will need to be expanded once other recipients have completed longer follow-up. Additionally, although the apnea–hypopnea index (AHI) remains a diagnostic gold standard, it fails to capture the complete clinical profile of OSA. Additional long-term studies would be helpful to further evaluate device effectiveness and OSA progression through measures of gas
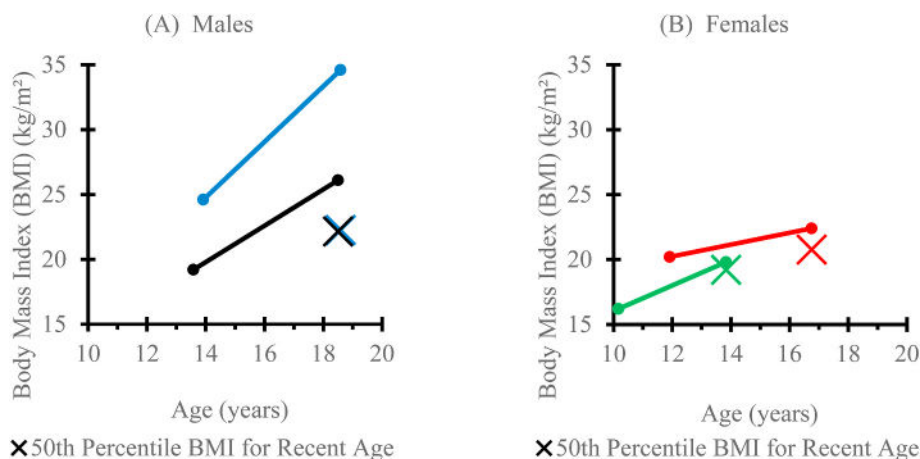
Fig. 4. Change in BMI and BMI percentile.

Fig. 4 A–B. Change in body mass index (BMI) from baseline to the time of the most recent sleep study. The ✕ symbols mark the 50th percentile BMIs among individuals of the same age and sex [22].

Fig. 4 C. Change in body mass index (BMI) percentile from baseline to time of the most recent sleep study. BMI percentiles were calculated per CDC growth curves for the neurotypical pediatric population [21]. Interpretation of BMI percentile is represented by background color: overweight (85th < percentile ≤ 95th); obese (percentile > 95th).
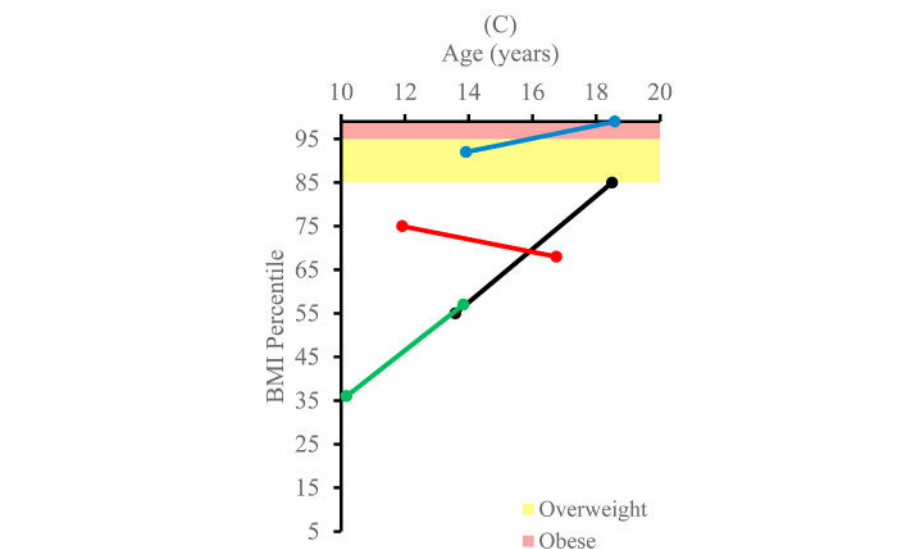
Fig. 5. Change in OSA-18 quality of life scores.

Fig. 5 A. OSA-18 total scores at baseline, 1 year postoperatively, and at the time of participants' most recent follow up. Interpretation of OSA symptom impact on quality of life is indicated by background color and defined according to total score: minimal impact (total score < 60), moderate impact (60 < total score < 80), severe impact (total score > 80). In all figures, color coding of participants is kept consistent: subject 1 = blue, subject 2 = black, subject 3 = red, subject 4 = green.

Fig. 5 B. OSA-18 overall quality of life subscores at baseline, 1 year postoperatively, and at the time of participants' most recent follow up. Overall subscores are reported exactly as answered on the OSA-18 instrument by participants or their parent/guardian. The instrument defines the range in score from zero to ten as follows: zero (0) indicates "worst quality of life possible; " five (5) indicates "average, between worst and best; " and ten (10) indicates "best quality of life possible.".

exchange, neurocognitive outcomes, and quality of life. Participants in this study were also supported by families who were motivated to facilitate acclimation and adherence to device therapy. The suitability of this device may differ in pediatric patients with DS who are less communicative or whose caregiver support is less involved. Finally, our results indicate that hypoglossal nerve stimulator implantation between the ages of 10 and 13 is associated with sustained reductions in AHI for at least 44 months; however, additional research is needed to better

inform decisions regarding optimal age at implantation. Furthermore, the interpretation of these results cannot be extrapolated to the neuro-typical pediatric population.

4.2. Conclusion

OSA in children with DS represents a significant public health problem due to its high prevalence, long-term persistence despite standard treatments, and broad associations with comorbidity. When implanted during childhood, hypoglossal nerve stimulators offer potentially long-lasting therapeutic benefit to patients with DS whose OSA persists into adulthood and is insufficiently managed by standard treatments. However, larger scale studies are needed to more rigorously evaluate long-term efficacy, safety, and impacts on other health domains, especially neurocognitive and cardiovascular wellbeing.

Author contributions

Stenerson had full access to the dataset and assumes responsibility for the integrity of these data. Stenerson was also responsible for drafting this manuscript. All authors contributed to the study concept and design, acquisition and interpretation of data, and critical revision of the manuscript for intellectual content. Hartnick acted as chief supervisor for this manuscript.

Funding/support

Inspire Medical Systems, Inc. provided technical support and provided the nerve stimulators used in this study free of charge. The staff and faculty of Massachusetts Eye and Ear (Boston, MA) waived professional, facility, and operating room fees involved in this study.

Role of the funder/sponsor

The funders had no role in the design or conduct of this study. The funders were not involved in data collection, study management, manuscript preparations, or the decision to submit this manuscript for publication.

Additional information

The US Food and Drug Administration approved of this study and issued an investigational device exemption (IDE): G140209.

Question

What are the long-term sleep and developmental outcomes of hypoglossal nerve stimulation in children with Down syndrome and persistent obstructive sleep apnea (OSA)?

Findings

OSA resolved completely with device usage in 2 of the 4 participants, both of whom exhibited persistent, severe OSA when the device was turned off. Moderate OSA remained present after implantation in the other 2 participants; however, severity was reduced by over 50% compared to baseline.

Meaning

OSA in children with DS appears to persist into adulthood; but significant and ongoing OSA control can be achieved with modest increases in voltage applied to the hypoglossal nerve.

Declaration of competing interest

Dr. Skotko occasionally consults on the topic of Down syndrome through Gerson Lehrman Group. He receives remuneration from Down syndrome non-profit organizations for speaking engagements and associated travel expenses. Dr. Skotko receives annual royalties from Woodbine House, Inc., for the publication of his book, Fasten Your Seatbelt: A Crash Course on Down Syndrome for Brothers and Sisters. Within the past two years, he has received research funding from F. Hoffmann-La Roche, Inc., AC Immune, and LuMind Research Down Syndrome Foundation to conduct clinical trials for people with Down syndrome. Dr. Skotko is occasionally asked to serve as an expert witness for legal cases where Down syndrome is discussed. Dr. Skotko serves in a non-paid capacity on the Honorary Board of Directors for the Massachusetts Down Syndrome Congress and the Professional Advisory Committee for the National Center for Prenatal and Postnatal Down Syndrome Resources. Dr. Skotko has a sister with Down syndrome.

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