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Upper Airway Stimulation for Children and Adolescents with Down Syndrome: Long-Term Follow-Up

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Objective(s): Hypoglossal nerve stimulation (HGNS) is safe and effective for patients with Down syndrome (DS) and severe persistent obstructive sleep apnea (OSA). Long-term outcomes for this patient population have not been evaluated.

Methods: A prospective single-group multicenter cohort study with 1-year follow-up was conducted between 2015 and 2021 among 42 adolescent patients with DS and severe persistent OSA. Here, we evaluate long-term outcomes in this patient cohort. Patients were evaluated with polysomnogram (PSG) at three timepoints: pre-implantation (timepoint 1), 1-year post-implantation (timepoint 2), and long-term follow-up (timepoint 3).

Results: Long-term follow-up data were available for 33 of 42 patients. Mean (SD) of timepoint 3 was 4.0 (1.9) years after implantation. Using a therapy response definition of a 50% decrease in Apnea Hypopnea INdez (AHI) from timepoint 1, the response rate was 69.7% (23/33) at timepoint 2 and 87.9% (29/33) at timepoint 3. From timepoint 1, there was a mean (SD) decrease in AHI of 12.7 (13.4) events/h at timepoint 2 and 15.7 (13.1) events/h at timepoint 3. The mean percentage change in AHI between timepoints 1 and 2 was −51.1% (95% CI: −32.8% to −69.3%) and between timepoints 1 and 3 was −59.6% (95% CI: −42.0% to −77.3%).

Conclusion: Patients with DS and severe persistent OSA who undergo HGNS implantation may continue to experience improvement in PSG parameters at long-term follow-up. Future studies are needed to assess additional long-term outcomes in this patient population, including neurocognition and quality of life.

Key Words: Down syndrome, hypoglossal nerve stimulation, obstructive sleep apnea, upper airway stimulation.

Level of Evidence: 3

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INTRODUCTION

Obstructive sleep apnea (OSA) is more common in children with Down syndrome (DS), affecting up to 80% of individuals compared to <5% of the general pediatric population.[1] Untreated OSA can lead to numerous downstream consequences, contributing to worse quality of life and adverse cardiopulmonary outcomes.[2,3] Studies indicate that untreated OSA in this patient population can have a negative impact on neurocognition, with one study documenting a lower verbal IQ by approximately nine points when comparing children with DS with and without OSA.[2,4] Comprehensive treatment of OSA is therefore critical in preventing lifelong consequences in this vulnerable patient population.

Adenotonsillectomy is the first-line treatment for OSA; however, only 16%–33% of children with DS experience resolution of OSA after this initial intervention.[5,6] Anatomic differences in patients with DS, including reduced muscular tone, macroglossia, lingual tonsil hypertrophy, and maxillary hypoplasia, lead to higher rates of persistent disease even after adenotonsillectomy.[7,8] Drug induced sleep endoscope (DISE)-directed second-line

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Dr. Skotko occasionally consults on the topic of Down syndrome through Gerson Lehrman Group. He receives remuneration from Down syndrome nonprofit organizations for speaking engagements and associated travel expenses. In the past 2 years, Dr. Skotko received 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 2 years, he has received research funding from AC Immune and LuMind IDSC 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 nonpaid 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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surgical options include tongue base reduction or suspension, palatal surgery, supraglottoplasty, and epiglottopexy. However, >50% of patients in this population experience persistent OSA even after DISE-directed second-line surgery.[9,10] Positive airway pressure, a minimally invasive therapy, can have limited effectiveness in patients with DS due to reduced tolerability.[11,12]

Hypoglossal nerve stimulation (HGNS) is a novel technique that involves an implantable device designed to sense respiratory patterns and deliver electrical impulses to the hypoglossal nerve during inspiration, resulting in tongue protrusion.[13] This device has been shown to be effective in treatment of neurotypical adults with moderate to severe OSA.[14] HGNS techniques have also been optimized for implantation in the pediatric population.[15,16] More recently, HGNS has been shown to be safe and effective for treatment of adolescent patients with DS and severe persistent OSA who are unable to tolerate positive airway pressure therapy.[17] The results of these preliminary studies, used in clinical trials to achieve FDA approval for device use in the pediatric population, were reported at 1 year post-implantation. The primary aim of this article is to describe the long-term outcomes of HGNS for this initial patient cohort.

MATERIALS AND METHODS

A phase 1, prospective, single-group, multicenter cohort study with 1-year follow-up was conducted between 2015 and 2021 among a sample of 42 adolescent patients with DS and severe persistent OSA to evaluate the safety and effectiveness of HGNS. Details of study eligibility and design are outlined in the previously published report.[17] In summary, patients with DS between ages 10 and 22 with persistent severe OSA were eligible for inclusion. Persistent severe OSA was defined as an AHI of 10 events/h or more after adenotonsillectomy with either inability to tolerate positive airway pressure or nighttime tracheostomy dependence. Baseline age, sex, body mass index, and polysomnogram (PSG) were recorded. Eligible patients then underwent DISE, and if anteroposterior base of tongue collapse was noted without circumferential palatal collapse, patients underwent HGNS implantation using previously described techniques.[15]

Patients were recruited from five academic centers: Massachusetts Eye and Ear ($n = 25$), Cincinnati Children's Hospital Medical Center ($n = 8$), Children's Healthcare of Atlanta ($n = 4$), Children's Hospital of Pittsburgh ($n = 3$), and Children's Hospital of the King's Daughters ($n = 2$). Patients underwent implantation between April 1, 2015 and July 31, 2020. PSG was obtained 1-year post-implantation. Notably, the 1-year post-implantation PSG was a non-titration PSG, meaning that the majority of the night was spent at a single voltage.

In the current study, we evaluated long-term outcomes of this original 42-patient cohort. Repeat PSG was obtained at a long-term follow-up timepoint approximately 3–5 years after implantation. Three timepoints were compared: pre-implantation (timepoint 1), one-year post-implantation (timepoint 2), and long-term follow-up (timepoint 3). All data analysis was performed with Microsoft Excel. p-values were calculated using Microsoft Excel's TTEST function, applying a one-tailed, two-sample t-test assuming equal variances. The project met criteria for exemption after review by the Mass General Brigham Institutional Review Board (IRB).

RESULTS

Patient Characteristics

Of the 42 patients originally enrolled in the study, long-term follow-up data were available for 33 patients. Of the patients for whom follow-up data were unavailable, four patients were unable to tolerate a repeat sleep study secondary to patient behavioral intolerance of the study, three patients were lost to follow-up and/or parents elected not to pursue another sleep study, one patient developed severe cardiopulmonary disease unrelated to but precluding device use, and one patient developed severe epilepsy unrelated to but precluding device use. Only two patients of the original 42 patient cohort were confirmed to no longer be using their device at the time of publication.

For the 33 patients for whom follow-up data were available (20 male [60.6%]), mean (SD) age at time of follow-up was 19.0 (3.6) years. Five patients (15.2%) required implantable pulse generator (IPG) replacement during the follow-up period. Of these five patients, one required IPG *and* sensor lead replacement after sustaining blunt trauma to the device in a motor vehicle accident, and four required IPG replacement due to battery depletion. No patients experienced adverse effects from the device itself. Characteristics of the 33 patients are shown in Table I.

TABLE I.
Demographic Characteristics of Patients.

Characteristics	No.	%
Sex		
Male	20	60.6
Female	13	39.4
Age at time of implant, years		
10–13	12	36.4
13–17	14	42.4
18–21	7	21.2
Age at time of follow-up, years		
10–13	2	6.1
13–17	8	24.2
18–21	14	42.4
21+	9	27.3
Site of implantation		
MEE	20	60.6
CCHMC	5	15.2
CHOA	4	12.1
CHP	2	6.1
EVMS	2	6.1
IPG replaced?		
Yes	5	15.2
No	28	84.8

CCHMC = Cincinnati Childrens Hospital Medical Center; CHOA = Children's Healthcare of Atlanta; CHP = Children's Hospital Pittsburgh; EVMS = Eastern Virginia Medical Center; IPG = implantable pulse generator; MEE = Mass Eye and Ear.

Long-Term Polysomnogram Outcomes

Mean (SD) of the long-term follow-up PSG, designated timepoint 3, was 4.0 (1.9) years after HGNS implantation. In this study, AHI includes both central and obstructive events. Mean (SD) AHI at timepoints 1, 2, and 3 was 23.8 (10.0), 11.1 (14.3), and 8.1 (8.4) events/h, respectively. In this study, patients with >50% postoperative decrease in AHI were considered therapy responders. At timepoint 2, 23 of 33 patients (69.7%) were classified as therapy responders. At timepoint 3, 29 of 33 patients (87.9%) were classified as therapy responders.

Among the 33 patients included in this study, from timepoint 1 to timepoint 2 there was a mean (SD) decrease in AHI of 12.7 (13.4) events/h (95% CI: −8.1 to −17.3 events/h). From timepoint 1 to timepoint 3 there was a mean (SD) decrease in AHI of 15.7 (13.1) events/h (95% CI: −11.1 to −20.2 events/h). The mean percentage change in AHI between timepoints 1 and 2 was −51.1% (95% CI: −32.8% to −69.3%) and between timepoints 1 and 3 was −59.6% (95% CI: −42.0% to −77.3%). Between timepoints 1 and 3, 31 of the 33 patients (93.9%) had at least some reduction in their AHI (percentage reduction range −15.6 to −100). Between timepoints 2 and 3, 18 of the 33 patients (54.5%) had a further reduction in their AHI. PSG results are shown in Table II. During the follow-up period there were no adverse effects reported from the device itself other than need for IPG replacement.

Massachusetts Eye and Ear Subgroup Analysis

To better understand the impact of HGNS therapy on PSG features of sleep-related breathing and sleep structure, subgroup analysis was performed for the 20 patients who underwent implantation at Massachusetts Eye and Ear. At timepoint 3, mean (SD) total sleep time (TST) at optimal voltage was 138 (128) min. The mean (SD) AHI at timepoint 1 was 27.1 (21.7) events/h, with a mean (SD) obstructive AHI (OAHI) of 25.3 (22.1) events/h and a mean (SD) central apnea index (CAI) of 1.7 (1.8) events/h. At timepoint 3, the mean (SD) residual AHI was 8.7 (10.9) events/h, indicating a 61.6% decrease in the AHI from timepoint 1 ($p = 0.002$). The mean (SD) residual OAHI was 7.9 (9.7) events/h, indicating a 58.7% decrease in the frequency of obstructive apneas and hypopneas from timepoint 1 ($p = 0.003$). The mean (SD) residual CAI was 0.7 (1.5) events/h, which was stable from pre-implantation diagnostic PSG ($p = 0.08$).

Analysis of sleep architecture revealed that mean (SD) percentage rapid eye movement (REM) sleep at timepoint 1 was 13.0% (8.4) and mean (SD) percentage REM sleep at timepoint 3 was 21.7% (24.7), reflecting improvement in percentage TST spent in REM sleep (see Chart 1).

Of the 20 patients who underwent implantation at Massachusetts Eye and Ear, six underwent an advanced titration protocol (i.e., optimization of stimulation and sensing lead settings) between timepoints 2 and 3. Nine patients in this subgroup have the updated IPG that allows for remote monitoring of device usage via SleepSync. Of these nine patients, mean (SD) duration of therapy is 7 h and 58 min (2 h 32 min), and, on average, patients are using the device more than 4 h 67% of nights.

DISCUSSION

This study represents the first report of long-term outcomes of HGNS implantation in adolescent patients with DS and severe persistent OSA. Evaluation of long-term outcomes for this patient population is crucial to assess safety and durability of effectiveness beyond 1-year follow-up. Our data suggest that when using the therapy response definition of a 50% decrease in AHI, the response rate was 69.7% (23/33) at 1-year post-implantation and 87.9% (29/33) in long-term follow-up. Subgroup analysis suggests improvement in at least one PSG measure of sleep quality, the proportion of TST spent in REM (%REM).

Selecting appropriate outcomes for long-term follow-up studies poses a considerable challenge due to the multifaceted nature of health interventions. When evaluating long-term outcomes of pediatric HGNS, multiple therapy response definitions have been utilized, including AHI

TABLE II.
Polysomnogram Outcomes.

Characteristic	Mean (SD) [95% CI]	Range	% AHI Less Than 10	% AHI Less Than 5	% AHI Less Than 2
AHI					
Timepoint 1	23.8 (10.0)	10.0–48.8	0	0	0
Timepoint 2	11.1 (14.3)	0.6–61.1	72.7	36.4	9.1
Timepoint 3	8.1 (8.4)	0.0–45.0	78.8	39.4	18.2
Change in AHI					
Timepoint 1 to 2	−12.7 (13.4) [−8.1 to −17.3]	−41.4 to 18.3			
Timepoint 1 to 3	−15.7 (13.1) [−11.2 to −20.2]	−44.9 to 27.6			
% Reduction in AHI					
Timepoint 1 to 2	−51.1 (53.5) [−32.8 to −69.3]	−97.5 to 161.0			
Timepoint 1 to 3	−59.6 (51.8) [−42.0 to −77.3]	−100.0 to 158.6			

Timepoint 1 = baseline, timepoint 2 = 1 year post-implantation, timepoint 3 = long-term follow-up.

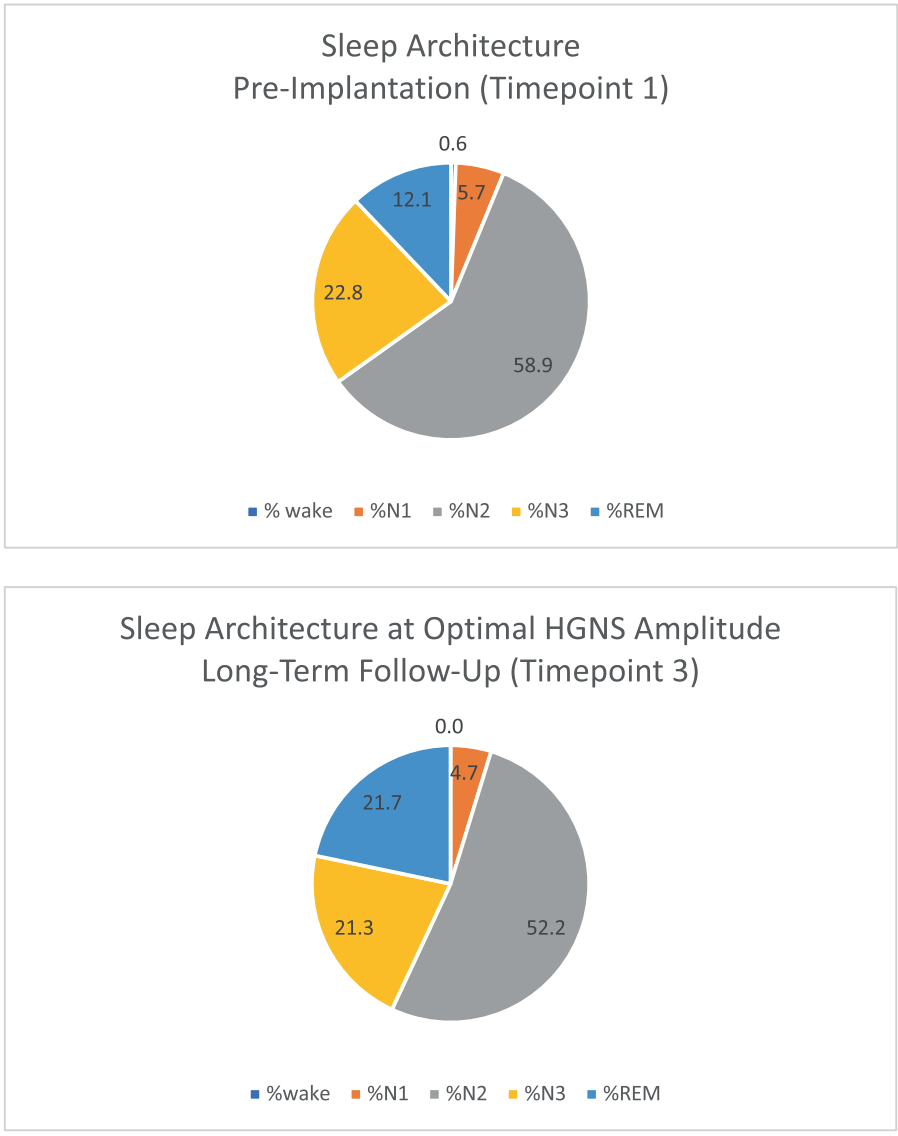

CHART 1. Sleep architecture of Massachusetts Eye and Ear subgroup. [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

reduction by 50%, reduction in AHI to under 10 (no longer severe), reduction in AHI to under 5 (mild), reduction to AHI under 2, or lack of positive airway pressure therapy requirement. Other measures looking at quality of life, neurocognition, and expressive language have also been proposed. In this study, over 50% of patients were over 18 and had therefore aged out of pediatric into adult OSA criteria, raising the question of how best to define success and characterize the severity of OSA in a population aging from adolescence to young adulthood. We chose to define therapy response as an AHI reduction by 50% or greater, a well-established definition used in many prior studies that allowed for consistent comparison across pediatric and young adult patients in whom severity of OSA would be classified differently. We have also reported the data by other criteria, as well.

In this study, using the treatment response definition of >50% postoperative decrease in AHI, 69.7% of patients achieved a therapy response 1 year after surgery, and 87.9% of patients achieved a therapy response in long-term follow-up. These results suggest that many patients were further titrated after the original study period to achieve improved results. Over the past several years, significant progress has been made pertaining to device optimization and titration. In Yu et al.'s article, device titration was performed slowly, including not titrating above 1.0 V for the first month and not increasing voltages outside of titration studies.[17] Since the original study, we have started increasing the voltage earlier on in the first months and using a range of voltages to allow for titration between sleep studies. Advanced titration, which includes titrating the electrodes on the stimulator and sensing leads to different configurations, has also allowed for further optimization of results.

The IPG used in these devices has an expected battery life of 8–12 years. IPG replacement in adults has been studied; however, the frequency of pediatric IPG

replacement has not been previously established.[18,19] Here, our data preliminarily suggest that in an average 4-year follow-up period, five patients, or 15.2%, required IPG replacement. Longer term follow-up studies will need to confirm these findings.

Several weaknesses are inherent in this study. First, the current study focuses only on sleep study results and AHI as the primary outcomes and does not assess long-term effects on quality of life, neurocognition, or expressive language, measures that could more significantly enhance understanding of the therapy's long-term impact. Second, there is no defined protocol as to when or how often children should undergo PSG beyond 1-year post-implantation, limiting standardization of the timing of follow-up PSGs. Third, this study highlights the challenge of conducting long-term follow-up studies in vulnerable populations, such as patients with DS, and the possibility of selection bias affecting long-term results. Development of naturally occurring comorbid cardiopulmonary and neurologic conditions, such as pulmonary hypertension and seizures, can render follow-up sleep studies difficult or impossible to obtain, contribute to patient loss to follow-up, and limit the overall number of children that can be followed over time.

In this study, long-term follow-up data were available for only 33 of the 42 patients originally enrolled in the study. If we assume the nine patients (21%) lost to follow-up would have had unfavorable sleep study outcomes (i.e., would not have met the treatment response definition of >50% decrease in AHI), the therapy response rate in long-term follow-up would drop from 87.9% (29/33) to 69% (29/42). This would suggest stability of therapy response rate as opposed to improvement in therapy response rate over the study period. Therefore, patient loss to follow-up is a major weakness in this study, prohibiting us from drawing definitive conclusions about improved long-term outcomes in this patient population.

Despite its limitations, the current study provides the longest-term results to date of pediatric HGNS therapy for severe OSA in patients with DS. These preliminary results provide compelling evidence that adolescents with DS and severe persistent OSA may experience improved efficacy of their device beyond 1-year post-implantation. Currently, no standardized, best-practice approach for treatment monitoring and therapy modification exists for this patient population. The creation of a best-practice post-implantation algorithm may allow patients to optimize use of their device more quickly after implantation. Given the well-documented cardiovascular and neurocognitive consequences of untreated OSA, an algorithm to expedite time to optimal treatment response would be beneficial for this population. Further studies are needed to look at the long-term effects of HGNS therapy on expressive language and neurocognition in this patient population.

CONCLUSION

Here, we present the first long-term follow-up study on the effect of HGNS in adolescent patients with DS and severe persistent OSA. In this study, the data suggest that 69.7% of patients achieved a therapy response 1 year after surgery, and 87.9% of patients achieved a therapy response in an average 4-year follow-up period. The increase in device optimization and improvement in outcomes after the first year likely reflects the stringency of the early post-implant optimization protocols and suggests that our current, updated optimization strategies can produce superior results. Further studies are needed to determine best practices for post-implantation algorithms to minimize delay to device optimization post-implantation.

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