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Preliminary Neurocognitive Results Post Hypoglossal Nerve Stimulation in Patients With Down Syndrome

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INTRODUCTION

Hypoglossal nerve stimulation (HGS) is a safe and effective intervention to treat obstructive sleep apnea (OSA) among typically developing individuals.[1,2] Effective management of OSA has demonstrated improvements in neurocognitive and behavioral functioning in neurotypical children.[3–6]

Children with Down syndrome (DS) have a high incidence of OSA, with approximately 80% diagnosed compared to <5% in the general pediatric population.[7] Residual OSA after adenotonsillectomy is common and minimally invasive therapy (continuous positive airway pressure [cPAP]) can have limited effectiveness in this population due to reduced tolerability.[8] When untreated, residual OSA in children with DS can affect their neurocognitive abilities, with one study documenting a lower verbal IQ by approximately nine points.[9]

HGS is currently being investigated at Massachusetts Eye and Ear Infirmary (NCT0234418) to assess safety, OSA severity reduction, and sleep quality among children and adolescents with DS. Preliminary results indicate that it is a safe and effective intervention.[10,11] Prior anecdotal reports by parents of participants in this clinical trial have described neurocognitive and behavioral improvements and have raised inquiry about the potential of HGS to improve these aspects of functioning.

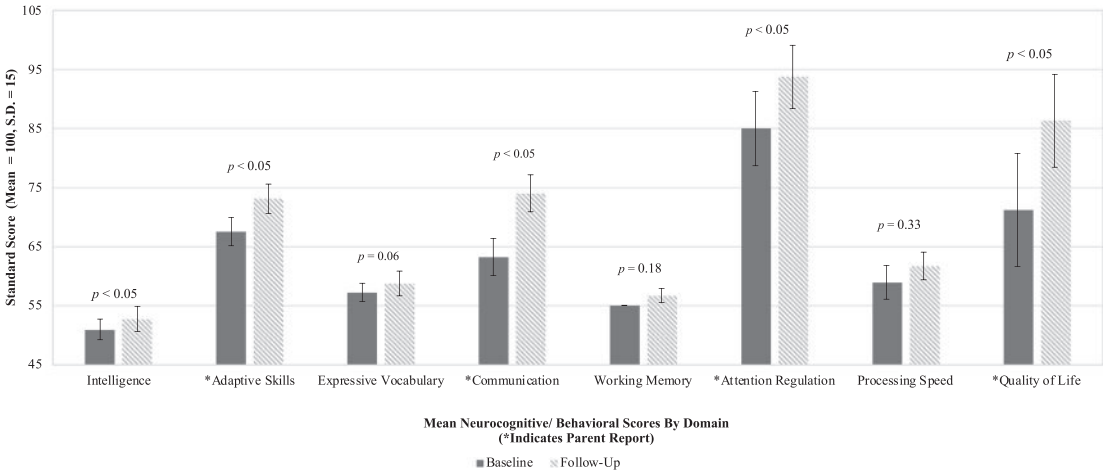

Fig. 1. Results from mean neurocognitive and behavior measures (N = 9), where higher standard scores indicate or reflect better performance.

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TABLE I.
Individual Participant Demographic, Anthropomorphic, Sleep, and Neurocognitive Data (N = 9).

	Demographic, Anthropomorphic, and Sleep Data									Neurocognitive Data															
Participant	Age at Baseline	Gender	Height (m)	Weight (kg)	Sleep Efficiency (%)	% Sleep Time with SpO2 < 90%	Minimum SpO2 (%)	Apnea-Hypopnea Index		Intelligence*		Adaptive†		Expressive Vocabulary‡		Communication§		Working Memory‖		Attention Regulation¶		Processing Speed#		Quality of Life**	
			BL	BL	BL	BL	BL	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU	BL	FU
1	14.1	F	1.32	35.2	96.3	0.10	86	22	16.2	45	54	57	59	60	61	50	55	55	55	80	127	55	65	33	38
2	10.2	M	1.37	46.5	60.3	0.97	82	17.4	21.2	52	57	72	73	66	71	74	74	55	55	98	84	55	55	104	112
3	19.1	M	1.56	54.3	93.9	0.02	90	10	2.6	45	45	63	69	54	54	53	70	55	55	107	85	55	70	105	108
4	17.4	F	1.38	60.7	73.4	1.83	81	48.5	30.9	45	45	64	69	54	54	55	70	55	55	82	112	55	70	57	83
5	21.1	M	1.67	73.9	84.4	0.10	82	31	20.5	59	53	63	85	54	54	57	89	55	55	91	102	55	60	82	100
6	13.6	F	1.49	61.1	90.0	0.45	81	10.6	5.7	57	59	69	71	63	66	71	71	55	55	55	126	80	70	30	66
7	14.1	M	1.51	59.2	80.2	2.20	83	23.8	8.2	54	54	74	75	56	60	72	79	55	65	104	100	65	55	91	79
8	12.0	F	1.41	36.8	83.5	0.06	89	18.7	2.1	52	62	65	77	54	54	65	77	55	60	56	120	55	55	53	86
9	15.8	M	1.55	73.9	64.6	3.68	81	34.8	10.9	49	45	81	80	54	54	72	81	55	55	92	100	55	55	86	105

AHI = apnea-hypopnea index; BL = baseline; F = female; FU = follow-up; kg = kilograms; m = meters; M = male; SpO2 = oxygen saturation.
For all neurocognitive measures, scores are reported as standard scores (mean = 100, standard deviation = 15).
*_Wechsler Abbreviated Scale of Intelligence_—2nd Edition—Intelligence Quotient.
†_Vineland Adaptive Behavior Scale_—3rd Edition, Adaptive Behavior Composite.
‡_Expressive One Word Picture Vocabulary Test_—4th Edition.
§_Vineland Adaptive Behavior Scale_—3rd Edition, Communication Domain.
‖_Wide Range Assessment of Memory and Learning_—2nd Edition, Sentence Memory.
¶_Behavior Assessment Scale for Children_—3rd Edition—Attention Problems.
#_Wechsler Intelligence Scale for Children_—5th Edition/Wechsler Adult Intelligence Scale—4th Edition, Cancellation.
**Peds Quality of Life, Total Score.

Given the high prevalence rates of residual OSA in DS[7,12] and limited effective treatment interventions, exploration of alternative interventions to improve health status, cognition, and behavior is needed. This preliminary work describes neurocognitive and behavioral data collected prior to and following HGS in a sample of pediatric patients with DS and severe OSA to determine whether improvements in cognition and behavior are objectively supported.

Patients were eligible to undergo HGS if they were aged between 10 and 21 years, diagnosed with DS, had severe residual OSA despite intervention (e.g., adenotonsillectomy, cPAP), and were able to communicate via spoken language. A total of nine participants met criteria and received neurocognitive and behavioral testing at baseline (immediately prior to HGS) and at a mean of 6.5 months (SD = 3.1) post-surgery to assess change. This study was approved by the Partners Human Research Committee.

The apnea-hypopnea index (AHI), a marker of OSA severity, was measured on overnight polysomnography at baseline and a follow-up titration. Neurocognitive and behavioral testing was conducted using standardized measures appropriate for individuals with DS.[13,14] Age-appropriate direct assessment of the participant included measures of intelligence,[15] processing speed,[16] expressive vocabulary,[17] working memory,[18] and parent-reports assessing behavior,[19] adaptive skills,[20] and quality of life.[21] Participant task demands included manipulating blocks to match designs, completing patterns, naming and pointing to pictures, matching shapes under timed conditions, and repeating sentences. Caregiver rating scales assessed participants' attention regulation, communication, functional independence, and quality of life.

Descriptive statistics were performed to characterize the sample at baseline and follow-up. Because of the small sample size, Wilcoxon's signed-rank tests were used to assess the change in pre- and post-implantation neurocognition, behavior, and AHI. Raw scores from neurocognitive and behavioral measures were transformed to age-based standard scores (mean = 100; standard deviation [SD] = 15) to compare performances across all age groups using the same metric for comparison. Results are reported as standard scores where higher scores reflect better performance. The test-retest reliability of the measures administered are considered adequate or higher (Pearson r coefficients, 0.76–0.97)[22] reflecting confidence that the changes in scores are secondary to actual changes in the trait measured and not due to instability of the test itself. Analyses were performed using SPSS version 24 (SPSS, Chicago, Illinois).

Clinically meaningful change in neurocognitive and behavioral functioning among individuals with DS and associated developmental delay and intellectual disability requires special considerations, as the developmental trajectory of these individuals differs due to developmental gains occurring at approximately half the pace of the typical population and plateauing at a mean mental age of approximately 6 years old.[23,24] Although a change of 1 SD (15 points) would be considered clinically and statistically meaningful among a typically developing individual, a change of 0.5 SD (7.5 points) would be more than notable among individuals with DS given their unique developmental trajectory.

For the nine participants, mean age at baseline was 15.2 years (SD = 3.4). All patients had severe OSA at baseline (mean AHI of 24.1, SD = 12.3, range = 10.0–48.5); there was a significant mean decrease by 11.0 post-HGS at follow-up ($P < .01$) (mean AHI follow-up = 13.1, SD = 9.8, range = 2.1–20.5). Neurocognitive scores improved in all domains assessed (Fig. 1). Improvement in expressive vocabulary approached significance ($P = .06$). Parent-reported adaptive and behavioral measures revealed significant improvements in all domains ($P < .05$) (Fig. 1). Individual participant's demographic, anthropomorphic, and sleep data and neurocognitive scores are reported in Table I.

DISCUSSION

This pilot study examined neurocognitive and behavioral outcomes in a small cohort of pediatric patients with DS and severe OSA following HGS. Benefits were demonstrated not only in a reduction in AHI but also in improvements in several neurocognitive and behavioral outcomes. Clinically significant improvements in participants' communication, attention regulation, and quality of life were demonstrated; improvement in adaptive behavior did not quite meet the threshold for clinically meaningful change, however showed change in a positive direction. The neurocognitive and behavioral findings obtained from objective measures with this small cohort of pediatric patients with DS are consistent with prior anecdotal reports from parents and similar to the domains of improvements seen in the neurotypical population.[3–6]

The underlying mechanisms of neurocognitive and behavioral improvements are not yet clearly understood. Effective management of disrupted sleep patterns can facilitate improved sleep quality and oxygen perfusion leading to greater sleep-dependent learning/consolidation of explicit knowledge,[25,26] processing efficiency,[27] and improved behavior[5] in neurotypical populations, which may be applicable to those with DS. As such, HGS is a promising intervention to promote treatment efficacy as measured by not only better sleep quality but also improved neurocognitive and behavioral functioning in this population. Although preliminary results are favorable, a limitation of this study includes the very small sample size, which reduces overall generalizability and statistical power. Our ongoing research will assess neurocognitive and behavioral functioning in a larger, multisite cohort.

CONCLUSION

Treatment of severe OSA using HGS in nine pediatric patients with DS resulted in clinically meaningful improvements in neurocognitive and behavioral functioning. These preliminary results are novel and encouraging and warrant further investigation to determine whether the findings are confirmed in a larger sample. The use of HGS to treat severe OSA in this population may have more associated benefits beyond health than originally anticipated, including benefits in

neurocognitive, behavioral, adaptive functioning, and quality of life.

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