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

Julie A. Grieco, PsyD; Christopher J. Hartnick, MD; Brian G. Skotko, MD; Phoebe K. Yu, MD; Margaret B. Pulsifer, PhD

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.](image)

From the Department of Psychiatry (J.A.G., M.B.P.), Massachusetts General Hospital, Boston, Massachusetts, U.S.A.; Harvard Medical School (J.A.G., C.J.H., B.G.S., P.K.Y., M.B.P.), Boston, Massachusetts, U.S.A.; Department of Otolaryngology (C.J.H., P.K.Y., M.B.P.), Massachusetts Eye and Ear Infirmary, Boston, Massachusetts, U.S.A.; and the Down Syndrome Program, Division of Medical Genetics and Metabolism, Department of Pediatrics (B.G.S.), Massachusetts General Hospital, Boston, Massachusetts, U.S.A.

Editor’s Note: This Manuscript was accepted for publication on July 27, 2021.

This work was funded by LuMind IDSC Down Syndrome Foundation.

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. Within the past 2 years, he has received research funding from F. Hoffmann-La Roche, Inc. 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. Dr. Pulsifer serves in a nonpaid capacity on the Board of Directors for the Massachusetts Down Syndrome Congress.

Send correspondence to Julie A. Grieco, PsyD, MGH Psychology Assessment Center, One Bowdoin Square, 7th Floor, Boston, MA 02114.

E-mail: jagrieco@partners.org

DOI: 10.1002/lary.29808

Laryngoscope 00: 2021 Grieco et al.: Neurocognition Post Hypoglossal Stimulation
TABLE I.
Individual Participant Demographic, Anthropomorphic, Sleep, and Neurocognitive Data (N = 9).

<table>
<thead>
<tr>
<th>Participant</th>
<th>Age at Baseline</th>
<th>Gender</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
<th>Sleep Efficiency (%)</th>
<th>% Sleep Time with SpO2 &lt; 90%</th>
<th>Minimum SpO2 (%)</th>
<th>Apnea-Hypopnea Index</th>
<th>Intelligence*</th>
<th>Adaptive†</th>
<th>Expressive Vocabulary‡</th>
<th>Communication§</th>
<th>Working Memoryk</th>
<th>Attention Regulation¶</th>
<th>Processing Speed</th>
<th>Quality of Life**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>14.1</td>
<td>F</td>
<td>1.32</td>
<td>35.2</td>
<td>96.3</td>
<td>0.10</td>
<td>86</td>
<td>22</td>
<td>16.2</td>
<td>45</td>
<td>54</td>
<td>57</td>
<td>59</td>
<td>60</td>
<td>61</td>
<td>50</td>
</tr>
<tr>
<td>2</td>
<td>10.2</td>
<td>M</td>
<td>1.37</td>
<td>46.5</td>
<td>60.3</td>
<td>0.97</td>
<td>82</td>
<td>17.4</td>
<td>21.2</td>
<td>52</td>
<td>57</td>
<td>72</td>
<td>73</td>
<td>66</td>
<td>71</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>19.1</td>
<td>M</td>
<td>1.56</td>
<td>54.3</td>
<td>93.9</td>
<td>0.02</td>
<td>90</td>
<td>10</td>
<td>2.6</td>
<td>45</td>
<td>45</td>
<td>63</td>
<td>69</td>
<td>54</td>
<td>54</td>
<td>53</td>
</tr>
<tr>
<td>4</td>
<td>17.4</td>
<td>F</td>
<td>1.38</td>
<td>60.7</td>
<td>73.4</td>
<td>1.83</td>
<td>81</td>
<td>48.5</td>
<td>30.9</td>
<td>45</td>
<td>45</td>
<td>64</td>
<td>69</td>
<td>54</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>5</td>
<td>21.1</td>
<td>M</td>
<td>1.67</td>
<td>73.9</td>
<td>84.4</td>
<td>0.10</td>
<td>82</td>
<td>31</td>
<td>20.5</td>
<td>59</td>
<td>53</td>
<td>63</td>
<td>85</td>
<td>54</td>
<td>54</td>
<td>57</td>
</tr>
<tr>
<td>6</td>
<td>13.6</td>
<td>F</td>
<td>1.49</td>
<td>61.1</td>
<td>90.0</td>
<td>0.45</td>
<td>81</td>
<td>10.6</td>
<td>5.7</td>
<td>57</td>
<td>59</td>
<td>69</td>
<td>71</td>
<td>63</td>
<td>66</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>14.1</td>
<td>M</td>
<td>1.51</td>
<td>59.2</td>
<td>80.2</td>
<td>2.20</td>
<td>83</td>
<td>23.8</td>
<td>8.2</td>
<td>54</td>
<td>54</td>
<td>74</td>
<td>75</td>
<td>56</td>
<td>60</td>
<td>72</td>
</tr>
<tr>
<td>8</td>
<td>12.0</td>
<td>F</td>
<td>1.41</td>
<td>36.8</td>
<td>83.5</td>
<td>0.06</td>
<td>89</td>
<td>18.7</td>
<td>2.1</td>
<td>52</td>
<td>62</td>
<td>54</td>
<td>67</td>
<td>54</td>
<td>65</td>
<td>77</td>
</tr>
<tr>
<td>9</td>
<td>15.8</td>
<td>M</td>
<td>1.55</td>
<td>73.9</td>
<td>64.6</td>
<td>3.68</td>
<td>81</td>
<td>34.8</td>
<td>10.9</td>
<td>49</td>
<td>45</td>
<td>81</td>
<td>80</td>
<td>54</td>
<td>54</td>
<td>72</td>
</tr>
</tbody>
</table>

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.
kWide Range Assessment of Memory and Learning—2nd Edition, Sentence Memory.

*Peds Quality of Life, Total Score.
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 behavior5 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.

BIBLIOGRAPHY