Improvements in Sensorineural Hearing Loss After Cord Blood Transplant in Patients With Mucopolysaccharidosis

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Objective: To objectively determine changes in sensorineural hearing in children with mucopolysaccharidosis (MPS) by comparing audiological data before and after hematopoietic stem cell transplantation (HSCT).

Design: Retrospective medical chart analysis.

Setting: Tertiary referral hospital.

Patients: Thirty pediatric patients with the diagnosis of MPS who underwent HSCT and had audiological data before and after HSCT. Data were extracted from medical charts for patients seen at our institution from January 1, 1999, to December 1, 2009.

Main Outcomes Measures: Hearing was assessed using behavioral audiometry testing and auditory brainstem responses (ABR) before and after HSCT. Patient demographics, diagnosis, and age at HSCT were also evaluated.

Results: Thirty patients with MPS were included. Four (13%) had MPS type 3a, 2 (7%) had MPS type 2, and 24 (80%) had MPS type 1. The average age at HSCT was 19 months (range, 5-44 months). Hearing improvement was evaluated by audiogram (20 patients), ABR (8 patients), and qualitative measures (30 patients). On average, patients did not show improvement on audiogram ($P$ = .28; paired $t$ test). The ABR click threshold improved 19 dB on average ($P < .001$). Qualitatively, 3 patients had normal hearing before and after HSCT. Of the remaining 27 patients, 20 (67%) showed improvement in sensorineural hearing ($P < .001$). Five (17%) had hearing loss and did not improve. Two (7%) had worsening hearing. Hematopoietic stem cell transplantation at the age of 25 months or younger was significantly correlated with hearing improvement ($P = .03$).

Conclusions: Hematopoietic stem cell transplantation may provide improvement in MPS-associated sensorineural hearing loss. Hearing improvement is more likely to occur in patients who undergo transplantation at 25 months or younger.


THE MUCOPOLYSACCHARIDE S (MPS) ARE A GROUP OF lysosomal storage diseases in which there is a deficiency in the enzyme responsible for the breakdown of glycosaminoglycans (GAGs). Subtypes of MPS are designated according to the specific enzyme deficiency. The progressive buildup of GAGs in cells cause tissue and organ injury, resulting in a constellation of signs and symptoms. The type and severity of symptoms ultimately depend on the subtype of MPS, but many patients will exhibit hearing loss of some degree.$^1$

Most patients with MPS will present with a mixed hearing loss. It is well known that as MPS progresses, GAGs can accumulate in the nasopharynx affecting eustachian tube function and ultimately lead to chronic otitis media. MPS 1 type and MPS type 2 also commonly manifest with sensorineural hearing loss. The etiology of the sensorineural component is not completely understood, but hypotheses include congenital sensorineural hearing loss vs an acquired impairment as GAGs accumulate in the cochlea or the cochlear nerve.$^1$

Treatment of MPS has progressed immensely. Before enzyme replacement therapy (ERT), therapy goals were limited to symptom control only. Enzyme replacement therapy is effective in ameliorating symptoms of patients with MPS types 1, 2, and 6 with mild central nervous system manifestations. Recent work with hematopoietic stem cell transplan-
Many of these patients have been actively followed by our audiology department. We aim to demonstrate objective evidence of sensorineural hearing improvement in patients with MPS after HSCT.

Permission to perform this study was granted by the Duke University institutional review board. A retrospective review of medical records was completed to identify patients with the diagnosis (HSCT) for patients with MPS has been the only therapy to date that demonstrates long-term metabolic correction and neurocognitive improvement.

Most HSCT studies have been performed in patients with MPS type 1 (Hurler syndrome) and have demonstrated symptom improvement in multiple organ systems. A review of 27 patients with MPS type 1 treated with HSCT demonstrated improvement in facial features, cardiac function, joint mobility, skeletal growth and alignment, neuropsychological function, vision, and hearing. Hearing improvement has been demonstrated by other investigators as well. These studies, however, were not dedicated to assessing hearing improvement and have not looked at objective audiological studies before and after HSCT.

Over 500 patients with MPS have been treated with HSCT at our institution. Many of these patients have been actively followed by our audiology department. We aim to demonstrate objective evidence of sensorineural hearing improvement in patients with MPS after HSCT.

METHODS

89 Patients enrolled:
Patients diagnosed as having MPS (ICD-9 code 277.5)
Patients with procedure code for HSCT (ICD-9 code 41.06)

12 Excluded:
Wrong diagnosis (n = 9)
Did not survive HSCT (n = 12)

68 Medical charts reviewed for audiological data

38 Excluded:
Missing either before or after HSCT audiological data

30 Patients with before and after HSCT audiological data

22 Patients with before and after HSCT audiograms
8 Patients with before and after HSCT ABRs
3 Patients with before HSCT ABRs and after HSCT audiograms

20 Patients with sufficient data to calculate PTA
3 Patients with both audiograms and ABRs

Figure 1. Patient inclusion flowchart depicting inclusion and exclusion criteria as well as a breakdown of all available audiological data. Two patients with before and after hematopoietic stem cell transplantation (HSCT) audiograms did not have enough values to calculate a pure tone average (PTA) and were evaluated with auditory brainstem response (ABR) data. The second to the last row has 3 patient groups that add up to 33 because 3 patients had both before and after HSCT audiograms and auditory brainstem responses (ABRs). The third patient was evaluated with both ABR and audiogram data. ICD-9 indicates International Classification of Diseases, Ninth Revision; MPS, mucopolysaccharidosis.

Figure 1 provides a flowchart of the patient data included in the analysis.

Demographic information extracted for analysis included date of birth, MPS subtype, and date of HSCT. Audiological data, including pure tone audiograms and ABRs, were analyzed. When available on the medical chart, pure tone thresholds were collected for frequencies ranging from 500 to 4000 Hz via air or bone conduction using visual reinforcement audiometry (VRA), which serves as a reliable and objective assessment tool. The test capitalizes on a child’s natural, age-appropriate instinct to respond to auditory stimuli by turning in the direction of the sound. When the child turns, he or she is rewarded for that response with a brightly lit, animated toy. VRA is the developmentally appropriate hearing assessment procedure for patients functioning at 6 to 24 months of age.

The following describes the testing and methods used at our institution for the data elements extracted from medical charts for this analysis:

1. All testing was performed in a double-walled, sound-treated Industrial Acoustics Co booth. Testing was performed by 2 licensed pediatric audiologists (one of whom was G.O.), one controlling the equipment and the other in the room with the participant. Testers in the study are well trained and often use control trials to validate their data. Control trials occur when the participant is observed while no stimulus is presented. If the child turns in the absence of a stimulus at the same rate he or she turns when there is a stimulus presented, testing is not considered valid, and therefore results are not recorded. The room is quiet and toys are used to mildly distract the participant and keep him or her centered and facing forward. Test stimuli were generated by a Grason Stadler 61 audiometer (Grason Stadler) calibrated to American National Standards Institute standards.

2. Owing to the behavioral and medical issues associated with patients with MPS, testing was initiated in the soundfield with stimuli presented from speakers. Soundfield results give information regarding the “better hearing” ear. From this testing, it can be determined if hearing is adequate for communicative purposes. Testing in the soundfield was not performed below 20 dB hearing level (HL). If minimum response levels were obtained at 30 dB HL or worse via air conduction, bone conduction testing was attempted. Binaural data were obtained whenever possible.

3. Owing to the patients’ developmental delays, motor delays, lack of cooperation, poor head control, or inability to be
conditioned, some data were not obtained during examination. If behavioral testing could not be obtained, ABR was performed in conjunction with other sedated procedures. All ABR testing was performed with a Biologic Navigator Pro (Natus Medical Inc).

4. All patients had tympanostomy tubes placed before the ABR or already had them in place. Cerumen and debris were removed from the ear canal prior to ABR testing and effusion, if present, was evacuated prior to ABR testing when tympanostomy tubes were placed.

5. The ABR responses obtained were used to estimate hearing thresholds. For ABR measurements, air and bone conduction was measured using broadband clicks and tone burst stimuli at 500, 1000, 2000, and 4000 Hz monaurally. Not all frequencies were tested in every patient. Analysis was performed using the thresholds from the bone-conduction broadband click for the better-hearing ear.

Improvement in hearing was determined in 3 ways depending on the hearing studies available. For those patients who had audiograms before and after HSCT, 4-frequency PTAs were calculated by averaging the thresholds measured at 500, 1000, 2000, and 4000 Hz. If a patient did not have one of these thresholds measured, the average was calculated on the frequencies available. Bone conduction thresholds were used in the analysis unless only air thresholds were obtained. If a patient had more than 1 audiogram performed before or after HSCT, the calculated PTAs were averaged. Studies were included in the average if they had at least 2 frequencies measured.

For patients who had ABRs performed before and after HSCT, the broadband click threshold in the better-hearing ear was used for analysis and compared with the same ear in post-HSCT studies. In patients with more than 1 posttransplant ABR, the broadband click thresholds of the same ear were averaged. Studies were included in the average if they had at least 2 frequencies measured.

For all patients, including those not included in the 2 groups in which audiograms were compared with ABRs and vice versa, the study was translated to a written description according to their degree of hearing loss. Patients with thresholds ranging from 26 to 40 dB were considered to have a mild hearing loss, patients with thresholds ranging from 41 to 55 dB were considered to have a moderate hearing loss, patients with thresholds ranging from 56 to 70 dB were considered to have a moderately severe hearing loss, patients with thresholds ranging from 71 to 90 dB were considered to have a severe hearing loss, and patients with thresholds higher than 91 dB were considered to have a profound hearing loss. These written descriptions were converted into numerical representations for easier analysis: normal hearing, 7; mild loss, 6; mild-to-moderate, 5; moderate, 4; moderate-to-severe, 3; severe, 2; and profound, 1.

Data were tabulated and analyzed with Microsoft Excel software. One-tailed paired \( t \) test was used to compare the PTAs, broadband click threshold averages, and the numerical conversions of descriptive analyses. \( \chi^2 \) Test was used to compare HSCT with sex and age of HSCT.

RESULTS

Four patients (13%) had MPS type 3a, 2 (6%) had MPS type 2, and the remainder had MPS type 1 (81%). Sixteen patients (53%) were male, and 14 (47%) were female. The average age at HSCT was 19 months (range, 3-44 months). Patients typically received 1 audiogram (range, 1-2 examinations) and/or 1 ABR prior to HSCT. The average age at first audiogram was 1.8 years (range, 0.5-11.3 years.) The average time between the first audiogram and HSCT was 79 days (range, 25-373 days).

After HSCT, patients had a median of 3 audiograms (range, 1-16 examinations) and/or a median of 2 ABRs (range, 1-4 examinations). The average age at the post-HSCT examination was 4.8 years (range, 1.2-18.0 years). The average time between HSCT and posttransplant audiograms was 2.4 years (range, 0.23-8.0 years). Typically, patients were scheduled for testing once they left the transplant unit and then were tested annually in their routine follow-up visits to Duke. However, owing to the quaternary nature of our institution, many of our patients had routine care outside of the state, and it was not always possible to have yearly examinations.

Twenty patients had complete before and after HSCT transplant audiogram data. All pretransplant audiograms were performed as soundfield testing with unmasked bone testing. Before HSCT, 8 patients were able to participate in conventional audiometry, but the rest still required soundfield/unmasked bone testing. The Table shows the calculated 4-frequency PTA data for these 20 patients. Figure 2 is a scatterplot of the PTA data in the Table that includes before and after audiogram data and interim recordings (indicated with Xs).

The “before” study is the study just before his or her transplant. The “after” study is the most recent study available. “Interim” represents every study in between. When comparing a patient’s before study to their “after” study, the aggregate hearing improvement among all patients was 1 dB, which was not statistically significant (\( P = .28; \) paired \( t \) test). Among these 20 patients, 8 patients had a decline in their hearing. Among those who did have improvement (12 patients), the improvement was measured as only 5 dB. Eight patients had ABR threshold information before and after HSCT. The average broadband click threshold for the pre-HSCT group was 51.9 ± 7.0 dB. The post-HSCT average was 33.2 ± 9.5 dB. Hearing threshold improvement was 19 dB, which was statistically significant (\( P < .001; \) paired \( t \) test). This is detailed in the Table and depicted in Figure 3.

All 30 patients were evaluated qualitatively by comparing results from hearing tests just before HSCT with those from the most recent hearing test. Three patients (10%) had normal hearing before and after HSCT. Twenty patients (67%) showed some degree of improvement (\( P < .001; \) paired \( t \) test). Eleven of these 20 patients showed improvement to normal levels. Five patients (17%) had hearing loss and did not improve. Two patients (7%) had worsening hearing. Sex was not found to have a significant correlation to hearing improvement (\( P = .60; \chi^2 \) test). Age at HSCT, however, had a significant correlation with improvement of sensorineural hearing if the patient underwent a transplant at 25 months or younger (\( P = .03; \chi^2 \) test).

COMMENT

In patients with MPS, HSCT has allowed the halting of progressive tissue damage from accumulated GAGs, resulting in alleviation of symptoms. This has been demonstrated across multiple organ systems and in hearing improvement as well. Souillet et al looked at 27 patients with MPS type 1 after HSCT and found hearing im-
### Table. Change in Pure Tone Average Before and After Hematopoietic Stem Cell Transplantation (HSCT) by Patient*

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<th>Patient No.</th>
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Abbreviation: HSCT, hematopoietic stem cell transplantation.

^a From calculated 4-frequency data.

^b Across all tests.

^c Paired 1-tailed t test; \( P = .28 \) (before HSCT vs after HSCT).

**Figure 2.** Average auditory brainstem response (ABR) data before and after hematopoietic stem cell transplantation (HSCT). The bar graph shows average broadband air click thresholds from ABR data of 8 patients before and after HSCT. These were the only 8 patients who had before and after HSCT ABRs. The pre-HSCT average threshold was 51.9 ± 7.0 dB, and the post-HSCT average was 33.2 ± 9.5 dB. The hearing threshold improvement was 19 dB \( (P < .001 \text{ paired } t \text{ test}) \). The error bars indicate ±1 SD.

**Figure 3.** Patient-level pure tone averages (PTA) before and after hematopoietic stem cell transplantation (HSCT). A scatterplot depicts audiometry data in 20 patients with studies available before and after HSCT (Table). Four-tone PTAs were calculated and are visually represented herein. Each patient is represented by a vertical line. The straight bar represents the “pre-HSCT” study, which is the study just before transplantation. The solid square represents the most recent study available, and each “x” represents a study in the interim. The average improvement for all 20 patients was 1 dB, which was not statistically significant \( (P = .28; \text{ paired } t \text{ test}) \). HL indicates hearing level.
We did not have the luxury of having a control group of patients with MPS who did not undergo transplantation. All patients with MPS who come to our institution undergo HSCT. In the retrospective study by Papasin et al, they were able to identify a control population of untreated patients with MPS. None of these patients had normal audiogram results, and they found particularly worse hearing in patients with MPS types 1, 2, and 6. On average, there is a mild to moderate sensorineural hearing loss in the untreated population, which is comparable with the hearing loss we see in our pretransplant patients.9

HSCT is not without its complications. The required immunosuppressants significantly increase a patient’s risk for infection. Patients require isolation in a transplant ward; they often receive rigorous screenings for infection with prophylactic antimicrobials and typically receive prophylactic pressure equalizing (PE) tubes, tonsillectomy, and adenoidectomy. There is also the risk of human leukocyte antigen mismatch, graft rejection, and graft vs host disease. Overall HSCT survival rates can range from 50% to 85%. Prasad and Kurtzberg9 published a series of 45 patients with Hurler syndrome who were treated with HSCT with a 60% to 75% overall event-free survival. The 1- and 5-year survival rates were 77.3% and 74.5%, respectively. However, forgoing treatment of any kind will ultimately lead to clinically significant morbidity and mortality in these patients.

Enzyme replacement therapy for MPS has had limited success. Improvement in liver size and function, improved growth, and improvement in obstructive sleep apnea symptoms have been demonstrated with ERT.11 However, ERT as a single modality has also shown progression of hearing loss and heart disease.10 It is also not effective against treating mental retardation, coarse facial features, and skeletal abnormalities, among other symptoms.11 There are mixed results in the literature regarding changes in hearing loss status with ERT in patients with MPS. O’Connor et al12 indicated that there were behavioral and auditory improvements in rats with MPS type VII. Furujo et al13 noted improvement in hearing in a female patient with MPS type VI who started enzyme treatment at 6 weeks of age, while her brother, who started treatment at 5 years, did not improve. However, Mercimek-Mahmutoglu et al14 reported progression of hearing loss in a patient with MPS type I treated with ERT; this would avoid the risks of HSCT, but therapeutic outcomes would not be ideal.

Our data show that patients with a diagnosis of MPS type I had more hearing improvement after HSCT, which correlates with findings from other studies.3,4,9 However, our very small population of patients with MPS type 2 and type 3a makes it difficult to draw any meaningful conclusions regarding subtype on hearing improvement. Future studies with larger patient cohorts of other MPS subtypes may help elucidate any differences. HSCT at an earlier age (<25 months) does have a significant correlation to hearing improvement. The pathogenesis of the MPS is progressive in nature, and this correlation is likely due to treatment of symptoms with HSCT before irreversible damage is done by accumulated GAGs. This has been shown to be true for multiple other symptoms, including neural function, corneal clouding, and both conductive and sensorineural hearing improvement.2

Accumulation of GAG in the nasopharynx, the eustachian tube, and middle ear mucosa has been previously described and is a known cause for middle ear disease and a source of conductive hearing loss (CHL).1 Placement of PE tubes will largely alleviate any conductive component of hearing loss due to chronic otitis media or Eustachian tube dysfunction. This is a common practice in patients with MPS, and all of our patients had at least 1 set of PE tubes placed. At least 8 patients required multiple tubes. Six patients had evidence of conductive hearing loss before HSCT, and 4 different patients had evidence of conductive loss after HSCT. The original 6 patients had resolution of CHL. Many of these patients were younger and/or unable to comply with tympanometry. Tympanometry could yield inaccurate results, and middle ear status could be missed. Also, PE tubes can dysfunction owing to cerumen impaction or extrusion.

There were various other limitations to our study. We performed a medical chart review of a relatively small number of patients (n = 30). Many of our patients were young and had been treated at outside facilities in the past. Multiple patients were excluded from the study because they did not have available audiological test results before their transplantation. Many of these patients had hearing studies performed at an outside hospital that we did not have access to. This made us unable to assess for durability of hearing improvement over time, and therefore this measure was not included in the scope of our study. We were able to compare audiograms with audiograms and/or ABRs to ABRs for most of our patients; however, there were multiple patients who did not have pre-HSCT audiograms or post-HSCT ABRs. As a result, hearing could be assessed only by qualitatively comparing descriptions of a pre-HSCT ABR to post-HSCT audiograms, which may not have direct comparisons.

Our quantitative audiogram data did not show a statistically significant improvement in hearing compared with our quantitative ABR data. When performing ABR testing, hearing was evaluated at ideal conditions. The patient was intubated and sedated, which eliminated potential confounding factors related to noisy breathing and noncompliant behavior. This also allowed us to get reliable bone conduction thresholds, which are not always possible in the awake pediatric patient. Also, the audiogram data analysis was performed by comparing a pre-HSCT study to the most recent study available. Often, the patient had other post-HSCT studies that showed improved thresholds. Variations in post-HSCT test results can be due to conductive hearing loss from eustachian tube dysfunction with nonfunctioning PE tubes, behavioral noncompliance, or simply test-to-test variance.

Our patients typically had multiple medical problems and may have had other medical ailments or medications that may have caused hearing loss and confounded our data. Occasionally, poor behavior precludes most conventional audiometry, necessitating soundfield studies that measure only the better hearing ear and are unable to measure HLLs higher than 4000 Hz. These patients would be best evaluated with ABR testing, but they may not be stable enough to undergo sedation which...
is required in young children for accurate results. Maturation may have played a role in better hearing during audiogram testing, but ABR thresholds do not change with maturity. 15

Future studies would focus on prospective analysis of hearing improvement along with an improved effort to keep medical records in a centralized location. Many patients had multiple post-HSCT audiograms regardless of if they had a pre-HSCT study. Another future study could look at the duration of hearing improvement by assessing progressive hearing improvement over time after transplantation.

In conclusion, HSCT may provide improvement in MPS-associated sensorineural hearing loss. Hearing improvement is more likely to occur when transplantation occurs before the age of 26 months.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Da Costa and Raynor. Acquisition of data: Da Costa and O’Grady. Analysis and interpretation of data: Da Costa, O’Grady, Jackson, Kaylie, and Raynor. Drafting of the manuscript: Da Costa. Critical revision of the manuscript for important intellectual content: Da Costa, O’Grady, Jackson, Kaylie, and Raynor. Statistical analysis: Da Costa and Kaylie. Administrative, technical, and material support: Da Costa, O’Grady, and Jackson. Study supervision: Kaylie and Raynor.

Conflict of Interest Disclosures: None reported.

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REFERENCES