We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,900
Open access books available

185,000
International authors and editors

200M
Downloads

Our authors are among the

154
Countries delivered to

TOP 1%
most cited scientists

12.2%
Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Chapter

Progenitor Cell Therapy for Sensorineural Hearing Loss in Infants

Linda Baumgartner, Michael Seidman, Deborah Lamontagne, Ernest Moore, David Shook, Steven Messina and James Baumgartner

Abstract

Typical language development requires typical hearing. With sensorineural hearing loss (SNHL), the damaged hair cells of the organ of Corti within the cochlea interfere with typical hearing and, as a result, cause impaired language development. Untreated SNHL causes significant neurocognitive differences in affected children. SNHL is a permanent sensory disorder affecting more than 270 million people worldwide. Congenital SNHL is found in 4 of 1000 newborns. Approximately half of congenital SNHL is hereditary and is the result of genetic mutations causing improper development of cochlear hair cells. Non-genetic congenital SNHL is thought to be the result of an injury to the cochlea typically from premature birth, infection, or exposure to ototoxic medications or noise. In mammals, the cochlea is postmitotic at birth, and no spontaneous repair occurs thereafter. Existing treatments for SNHL (hearing aids and cochlear implants) function by augmenting the damaged organ of Corti. No reparative treatments currently exist. In preclinical and clinical studies, progenitor cell therapy (cord blood and mesenchymal stem cells) has shown promise in reversing the underlying pathology of SNHL, the loss of cochlear sensory hair cells. Progenitor cell therapy may also allow functional reorganization of the auditory pathways including primary auditory cortex (Heschl's gyrus). We will present a summary of the effect of hearing loss on auditory development, existing preclinical and clinical data on progenitor cell therapy, and its potential role in the (re)habilitation of non-genetic SNHL.

Keywords: sensorineural hearing loss, human umbilical cord blood, stem cell, progenitor cell therapy, cochlea, auditory verbal therapy

1. Introduction

Affecting more than 270 million people worldwide, sensorineural hearing loss (SNHL) is a permanent sensory disorder which interferes with hearing. SNHL is found in 4/1000 in newborns, 8/1000 children aged 3–17 years, and 33% of adults aged 65–74 years [1–3]. Existing treatments (hearing aids and cochlear implants) improve the symptoms of SNHL by augmenting the damaged organ of Corti. These treatments do not reverse the underlying pathology of SNHL nor loss of sensory inner

hair cells within the organ of Corti. Inner and outer cochlear hair cells are necessary for hearing and transforming sound waves into electrical impulses transmitted to the brain. Loss of hair cells reduces auditory input to the brain, and with sufficient hair cell loss, hearing impairment develops. In mammals, the organ of Corti is postmitotic at birth, and no spontaneous hair cell regeneration occurs thereafter.

Among infants and children with SNHL, 23–50% is the result of a genetic mutation that adversely affects development of the organ of Corti (connexin 26, mutation, Waardenburg syndrome, Usher syndrome, Mitochondrial Disorders, etc.) [2–9]. The remaining infants and children have acquired SNHL, which is most commonly attributed to prematurity, infection (in utero or postdelivery), and exposure to noise or ototoxic drugs.

In preclinical and clinical studies, the intravascular delivery of mesenchymal progenitor cells following acute neuro-pathologic insults (stroke, traumatic brain injury, spinal cord injury, etc.) has shown significant promise [10–16]. Limited animal and human data suggest that repair of the mammalian cochlea is possible following progenitor cell therapy [3, 17–20]. If these early results can be translated to a reparative treatment for SNHL, it would be a transformative advance in auditory (re)habilitation.

1.1 Hearing loss and auditory development

Spoken language is learned and its development is dependent upon both the innate ability found within the human cortex as well as environmental stimulation. The time frame over which the cortex is capable of learning a fist spoken language is finite due to neuroplasticity [21]. Neuroplasticity refers to changes in neural connections, pathways, and networks as a result of maturation and development, sensory deprivation, injury, disease, dysfunction, and learning [22]. Although neuroplasticity exists to some degree throughout life, it is particularly robust during early life when neuronal groups are most capable of adjusting function based upon input. This window of heightened learning, known as the critical period, lasts roughly through 3 years 6 months of age. The critical period is a time when the brain effortlessly rewires in response to the environment, and at the end of which there is a decisive diminishing of neuroplasticity.

Auditory development is particularly sensitive to the critical period. Auditory learning begins in utero [23] when synapses are formed and then strengthened at a remarkable rate [24]. At ~4 years of age, the abundant neurons within the auditory cortex undergo a rapid pruning phase, during which neurons and their synapses are eliminated when unused, and thus considered unnecessary [25, 26]. This pruning fundamentally alters the auditory cortex, which for the typically hearing child, equals improved language efficiency. Conversely, for the unamplified child with SNHL, pruning results in an inability to develop spoken language. It has been observed that if auditory stimulation is not delivered during the early optimal period of cortical plasticity, deficits are observed even after the child is amplified [27, 28]. A biomarker for auditory cortical maturation is the latency rates of the P1 component of the cortical auditory evoked potentials (CAEP). It has been demonstrated that the P1 component of the CAEP shows age-related decreases in latency, meaning faster transmission, in children without hearing loss. In a series of 245 children with congenital deafness, Sharma and Dorman found that the latency of the P1 CAEP decreases to within normal limits in children who receive a cochlear implant by 3.5 years of age. Children implanted after the age of 7 years demonstrate abnormal P1 CAEP responses which persisted even after years of experience with implant use. Children implanted between 3.5 and 7 years showed mixed auditory cortical development, with some children demonstrating normal P1

CAEP responses and others never reaching normal central auditory maturational status [28]. Supporting this finding are studies describing developmental outcomes of speech and language skills in children implanted at various ages, which indicate significantly improved outcomes with younger implantation age [29–31]. Improved outcomes are especially true in the development of oral spoken language [32].

In summary, when a child with SNHL is provided auditory access through hearing aids or a cochlear implant in a timely manner within the critical period, auditory development, and language acquisition may occur normally. Conversely, children who experience long periods of auditory deprivation are susceptible to large-scale reorganization of the auditory cortex areas responsible for the perception of speech and language [33]. When that reorganization happens, there is evidence that several areas of auditory cortex are recruited for visual and tactile input under the condition of auditory deprivation [34–37]. To date, the only task specific reorganization of the auditory cortex that has been proven is in deafened cats. Meredith and Lomber demonstrated that distinct auditory regions in cats with SNHL support peripheral visual localization and visual motion detection, and that the same regions support auditory localization in hearing cats [38].

1.2 Preclinical evidence for stem cell efficacy in the treatment of SNHL

Animal studies using mesenchymal progenitor cells have provided intriguing results in experimentally deafened animals. Using NOD-SCID mice experimentally deafened with kanamycin and noise, Revoltella et al. reported recovery of auditory function following intravenous treatment with CD-133+ cells derived from human umbilical cord blood. Some of the cord blood stem cells were shown to have reached the cochlea [17]. In a subsequent study from the same group, Bettini et al. treated NOD-SCID mice deafened with kanamycin with mesenchymal stem cells derived from either bone marrow or adipose tissue. Both cell types engrafted in the cochlea of damaged mice, inducing regeneration of the damaged sensory structures. Several hybrid human-mouse fusion cells were found within the cochlea but not in hair cells. The data suggest that human MSCs do not directly replace lost cells, but exert their regenerative potential mainly through paracrine effects [17, 18, 39].

Using an SNHL guinea pig model, Choi et al. demonstrated both physiological and anatomic improvement in the cochlea of animals treated with mesenchymal stem cells derived from human umbilical cord blood. Distortion-product otoacoustic emissions (DPOAEs) were decreased and auditory brainstem response (ABR) thresholds were improved by 40–50 decibels (dB) in treated guinea pigs. In addition, treated animals demonstrated an increase in both hair cells and spiral ganglion cells compared to control animals [19].

1.3 Clinical evidence for stem cell efficacy in the treatment of SNHL

DaCosta et al. reported the effect of cord blood transplantation on SNHL following myeloablation in patients with mucopolysaccharidosis [20]. The mucopolysaccharidoses (MPS) are a group of lysosomal storage diseases in which there is a deficiency in one of the enzymes responsible for the breakdown of glycosoaminoglycosides (GAGs). The progressive buildup of GAGs in cells causes tissue and organ injuries. Most patients with MPS present with a mixed hearing loss. As MPS progresses, GAGs accumulate in the tissues of the nasopharynx ultimately interfering with Eustachian tube function and causing chronic otitis media. MPS types 1 and 2 commonly also develop SNHL. The exact etiology of the MPS associated SNHL is not clear but may be a genetic congenital SNHL vs. an acquired injury secondary to the accumulation of GAGs in the cochlea or cochlear nerve [40].

The only treatment that demonstrates long-term metabolic correction and neurocognitive improvement in MPS is hematopoietic stem cell transplantation [41, 42]. In DaCosta's series, 26 of 30 patients had MPS 1 and 2. Following bone marrow transplantation, the ABR click threshold improved by 19 dB on average and 20 of 30 patients experienced an improvement in sensorineural hearing. The effect on SNHL was more prominent in children who underwent bone marrow transplantation at less than 25 months of age. The cord blood used for transplantation was allogenic and did not carry any of the MPS mutations [20].

1.4 Phase 1 trial: umbilical cord blood therapy for acquired SNHL in children

In a Phase 1 trial, 11 children less than 6 years of age, with severe to profound non-genetic SNHL were treated with their own umbilical cord blood mononuclear fraction intravenously. Subjects were recruited from a single private cord blood bank, cord blood registry, through the bank's patient email portal. Patients were evaluated before treatment and 1-, 6-, and 12-months posttreatment. Evaluations included physical and neurological examinations, speech language pathology testing, audiology evaluations, 3-Tesla MRI with diffusion tensor imaging (DTI), and laboratory testing.

No significant adverse events occurred during the study. Ten subjects experienced an expected improvement of speech language pathology test scores over the course of the trial. The only subject who failed to improve did not follow study mandated amplification and recommended auditory verbal speech language therapy, demonstrating the importance of speech language therapy in this vulnerable population. About 5 of the 11 treated subjects experienced an improvement in ABR thresholds which achieved statistical significance across the treatment population at three measured frequencies. The improvement in ABR threshold ranged from 15 to 20 dB (**Figure 1**). There was a trend toward improvement in the latency of signal transmission along cranial nerve VIII (Vestibulo-cochlear nerve). Improvements in both ABR thresholds and CN VIII latency were evident at 1-month follow-up testing and were durable throughout the 12-month study period. The rapid and durable change in latency was unexpected.

Using 3 T MRI data collected before and 12-months after cord blood treatment, subjects whose ABR thresholds had improved following were compared to subjects whose ABR thresholds had not changed following treatment (**Figure 2**). The DTI measure fractional anisotropy (FA), a marker of white matter tract integrity and myelination [43], trended toward improvement along the auditory pathways in responding subjects. The changes in FA were most prominent in the white matter of Heschl's gyrus, which is the primary auditory cortex (**Figure 3**).

All responding subjects received a cord blood cell dose of at least 15 million cells per kilogram [3].

This trial supports the concept that autologous intravenous cord blood therapy can facilitate repair of the cochlea. The data also suggest that improvement in the entire auditory pathway might occur following the progenitor cell therapy.

1.5 Possible mechanisms of action

While limited, the existing data suggest that progenitor cell therapy does not result in direct replacement of cochlear hair cells, but enables an intrinsic repair machinery to work. The immunomodulatory effect of MSCs acting systemically and the local effect of MSCs which reach and interact with the cochlear stroma and possibly cochlear stem cells may facilitate hair cell replacement. A similar process

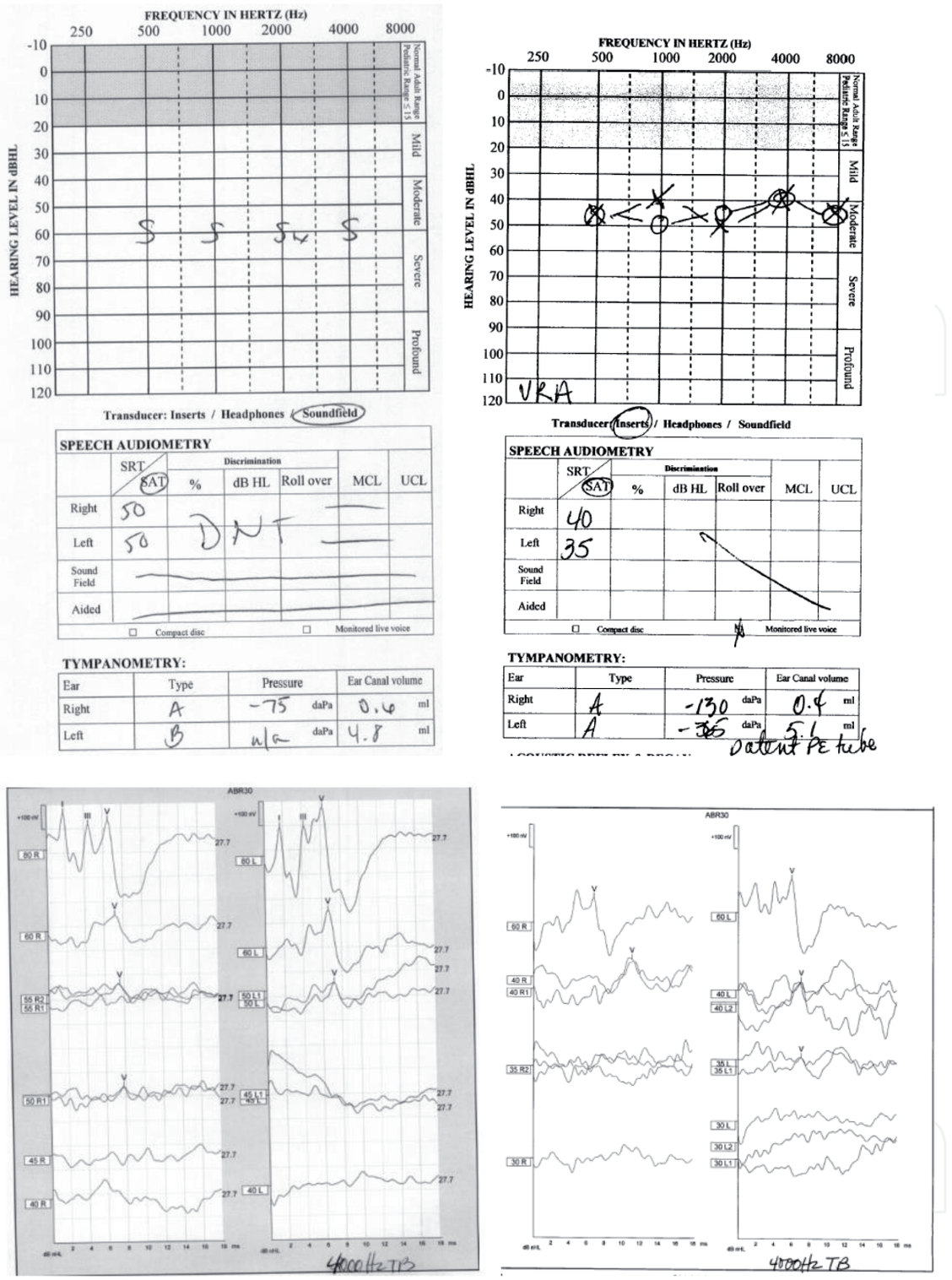


Figure 1.
Representative audiograms (top) and ABR recordings at 4000 Hz (below) of a responding subject before (left) and after (right) hUCB treatment for SNHL. The improvements on the behavioral testing (audiogram) match the changes found on the ABR recordings (physiologic).

involving MSCs which cross the blood brain and blood labrynthine barriers and interact directly with brain tissue may facilitate repair and reorganization of the white matter tracts of the auditory pathway.

While some infused mesenchymal progenitor cells do cross the blood brain barrier and reach the cochlea [17, 18], the majority fail to do so. Because mesenchymal stem cells have cell diameters larger than most terminal arterioles, most infused MSCs are found within the capillaries of the lungs within minutes of infusion

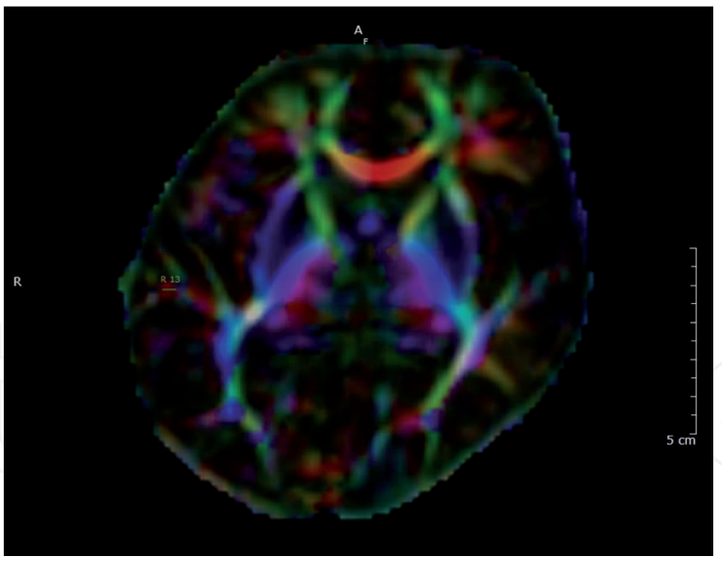


Figure 2.
Raw axial DTI image with the ROI of the right sided Heschl's gyrus used for FA analysis, outlined in red.

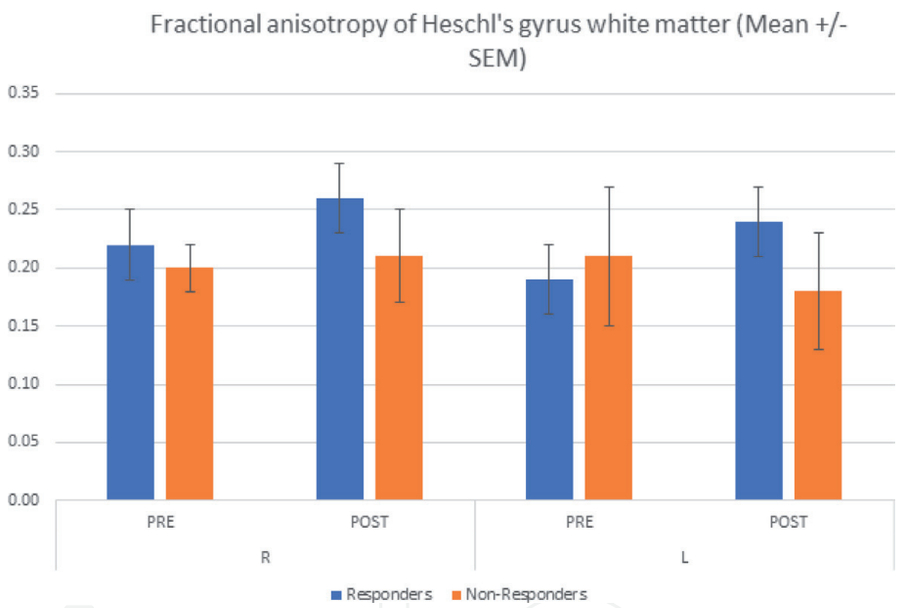


Figure 3.
Graphical representation of mean fractional anisotropy between responding (blue) and non-responding (orange) subjects at region of interest sites in Heschl's gyrus following cord blood mononuclear treatment for SHNL in children. The data suggest an increase in fractional anisotropy in responding subjects, but not in non-responders. An increase in the fractional anisotropy suggests improved white matter tract integrity and possibly the repair of primary auditory cortex.

[44–46]. In both humans and animals, this rapid pulmonary entrapment is followed by clearance from the lungs and accumulation in the liver and spleen over subsequent hours to days [43–45]. The MSCs, while entrapped, cause a marked change in circulating cytokines and immune system phenotype [47]. Notably, human MSCs have been shown to be capable of migrating to an area of injury and recruiting tissue specific progenitor cells and regulating the immune response through the secretion of immunomodulatory cytokines and microvesicles (exosomes) containing a variety of bioactive molecules including enzymes, coding and non-coding RNAs, and growth factors [48]. MSCs are also known to secrete molecules that modulate both innate and adaptive immune responses [49]. These secreted molecules act to inhibit the maturation of monocytes into antigen presenting dendritic cells [50], promote a shift in macrophage phenotype from M1 to M2 [51], inhibit the

proliferation and activation of B and T lymphocytes [52], and promote the clonal expansion of regulatory T lymphocytes [53]. This extensive systemic alteration of the immune system may facilitate repair through a systemic paracrine effect.

Likewise, the previously identified fusion of MSCs with cochlear support cells may also allow cochlear support or cochlear stem cells to differentiate into hair cells [18]. Epigenetic regulation of regeneration has recently emerged as a possible pathway to hair cell replacement [54]. The improved FA found at Heschl's gyrus may represent a rescue of the auditory cortex from sound deprived visual fate back to its original hearing function. That recovery appears to depend upon repair of the cochlea, the spiral ganglion, the eighth cranial nerve, and the white matter tracts of the auditory pathways. All of these repairs may be facilitated by intravenous mesenchymal stem cell treatment [55].

2. Conclusion(s)

SNHL is a permanent sensory disorder and a significant worldwide public health problem. Untreated sound deprivation causes permanent reorganization of the auditory pathways that first interferes with and then prevents the development of spoken language. Current treatments augment the function of a damaged cochlea and no reparative treatments currently exist. Both preclinical and clinical data suggest that treatment with progenitor cells may result in cochlear repair in mammals. In addition, very limited data suggest that the repair process may extend beyond the cochlea to the auditory pathways and auditory cortex. This evolving area of research may allow the development of a reparative treatment for non-genetic SNHL.

Acknowledgements

The cord blood phase one trial [3] was supported by a research grant from cord blood registry (CBR®).

Conflict of interest

The authors have no relevant conflicts of interest to report related to this chapter.

IntechOpen

Author details

Linda Baumgartner[1], Michael Seidman[2], Deborah Lamontagne[3], Ernest Moore[4], David Shook[5], Steven Messina[6] and James Baumgartner[7]*

1 Clarke School for Hearing and Speech, and Little HEARoes, Orlando, Florida, USA

2 Department of Otorhinolaryngology, College of Medicine, Advent Health Celebration and University of Central Florida, Orlando, Florida, USA

3 University of Tennessee, Memphis Tennessee, USA

4 University of North Texas, Denton, Texas, USA

5 Advent Health Orlando, Orlando, Florida, USA

6 Department of Radiology (Neuroradiology), Mayo Clinic College of Medicine, Rochester, MN, USA

7 Department of Neurological Surgery, College of Medicine, Advent Health Orlando and University of Central Florida, Orlando, Florida, USA

*Address all correspondence to: lbaumgartenr@clarkeschools.org

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. CC BY

References

[1] Lin FR, Niparko JK, Ferrucci L. Hearing loss prevalence in the United States. Archives of Internal Medicine. 2011;**171**:1851-1852

[2] Mehra S, Eavey RD, Keamy DG Jr. The epidemiology of hearing impairment in the United States: Newborns, infants and adolescents. Otolaryngology and Head and Neck Surgery. 2009;**140**:461-472

[3] Baumgartner LS, Moore E, Shook D, Messina S, Day MD, Green J, et al. Safety of autologous umbilical cord blood therapy for acquired sensorineural hearing loss in children. Journal of Audiology and Otology. 2018;**22**(4):209-222

[4] Shibata SB, Shearer AE, Smith RJH. Genetic sensorineural hearing loss. In: Flint PW, Haughey BH, Lund VJ, Niparko JK, Robbins DT, Thomas JR, editors. Cummings Otolaryngology-Head and Neck Surgery. 6th ed. Philadelphia, PA: An Imprint of Elsevier; 2014. pp. 2285-2300

[5] Canalis RF, Lambert PR. The Ear: Comprehensive Otology. 1st ed. Philadelphia, PA: Lippincott, Williams and Wilkins; 2000

[6] Smith RJ, Bale FJ Jr, White KR. Sensorineural hearing loss in children. Lancet. 2005;**365**:879-890

[7] Seidman MD, Bai U, Khan MJ, Murphy MP, Quirk WS, Castora FJ, et al. Association of mitochondrial DNA deletions and cochlear pathology: A molecular biologic tool. The Laryngoscope. 1996;**106**(6):777-783

[8] Bai U, Seidman MD. A specific mitochondrial DNA deletion ($mtDNA^{4977}$) is identified in a pedigree of a family with hearing loss. Hearing Research. 2001;**154**:73-80

[9] Seidman MD, Khan MJ, Tang WX, Quirk WS. Influence of lecithin on mitochondrial DNA and age-related hearing loss. Otolaryngology – Head and Neck Surgery Journal. 2002;**127**(3):138-144

[10] Prockop DJ. Marrow stromal cells as stem cells for nonhematopoietic tissues. Science. 1997;**276**:7-14

[11] Cox CS Jr, Baumgartner JE, Harting MT, Worth LL, Walker PA, Shah SK, et al. Autologous bone marrow mononuclear cell therapy for severe traumatic brain injury in children. Neurosurgery. 2011;**65**:588-600

[12] Vahidy FS, Rahbar MH, Shu H, Rowan PJ, Bambhroliya AB, Savitz SI. Systematic review and metanalysis of bone marrow-derived mononuclear cells in animal models of ischemic stroke. Stroke. 2016;**47**:1632-1639

[13] Savitz SI, Mistra V, Kasam M, Junija H, Cox CS Jr, Alderman S. Intravenous autologous bone marrow mononuclear cells for ischemic stroke. Annals of Neurology. 2011;**70**:59-69

[14] White SV, Czisch CE, Han MH, Plant CE, Harvey AT, Plant GW. Intravenous transplantation of mesenchymal progenitors distributes solely to the lungs and improve outcomes in cervical spinal cord injury. Stem Cells. 2016;**34**:1812-1825

[15] van Velthoven CT, Dzietko M, Wenddland MR, Derugin N, Faustino J, Heijnen CG, et al. Mesenchymal stem cells attenuate MRI-identified injury, protect white matter and long-term functional outcome after neonatal focal stroke in rats. Journal of Neuroscience Research. 2017;**95**:1225-1236

[16] van Velthoven CT, Sheldon RA, Kavelaars A, Derugin N, Vexler ZS, Willement HO, et al. Mesenchymal stem

cell transplantation attenuates brain injury after neonatal stroke. Stroke. 2018;**44**:1426-1432

[17] Revoltella RP, Papini S, Rosellini A, Michleini M, Franscechini V, Ciroba A, et al. Cochlear repair by transplantation of human cord blood CD-133+ to nod-scid mice deafened with kanamycin and noise. Cell Transplantation. 2008;**17**:665-678

[18] Bettini S, Franceschini V, Astolfi L, Simoni E, Massanti B, Martini A, et al. Human mesenchymal stromal cell therapy for damaged cochlea repair in nod-scid mice deafened with kanamycin. Cytotherapy. 2018;**20**:189-203

[19] Choi MY, Yeo SW, Park KH. Hearing restoration in a deaf animal model with intravenous transplantation of mesenchymal stem cells derived from human umbilical cord blood. Biochemical and Biophysical Research Communications. 2014;**427**:629-636

[20] DaCosta V, O'Grady G, Jackson L, Kaylie D, Raynor E. Improvement in sensorineural hearing loss after cord blood transplant in patients with mucopolysaccharidosis. Archives of Otolaryngology – Head & Neck Surgery. 2012;**138**:1071-1076

[21] Sharma A, Nash AA, Dorman M. Cortical development plasticity and reorganization in children with cochlear implants. Journal of Communication Disorders. 2009;**42**(4):272-279

[22] Sharma A, Glick H. Cortical neuroplasticity in hearing loss: Why it matters in clinical decision-making for children and adults. Hearing Review. 2018;**25**(7):20-24

[23] Lieu JEC, Tye-Murray N, Karzon RK, Piccirillo JF. Unilateral hearing loss is associated with worse speech-language scores in children. Pediatrics. 2010;**125**(6):1346-1355

[24] Holtmaat A, Wilbrecht L, Knott GW, Welker E, Svoboda K. Experience-dependent and cell-type-specific spine growth in the neocortex. Nature. 2006;**441**(7096):979-983

[25] Huttenlocher PR, de Courten C. The development of synapses in the striate cortex of man. Human Neurobiology. 1987;**6**(1):1-9

[26] Huttenlocher PR, Dabholkar AS. Regional differences in synaptogenesis in the human cortex. The Journal of Comparative Neurology. 1997;**387**(2):167-178

[27] Ponton CW, Eggermont JJ. Of kittens and kids: Altered cortical maturation following profound deafness and cochlear implant use. Audiology & Neuro-Otology. 2001;**6**(6):363-380

[28] Sharma A, Dorman MF. Central auditory development in children with cochlear implants: Clinical implications. Advances in Oto-Rhino-Laryngology. 2006;**64**:66-88

[29] Oh SH, Kim CS, Kang EJ, Lee DS, Lee HJ, Chang SO, et al. Speech perception after cochlear implantation over a 4-year time period. Acta Oto-Laryngologica. 2003;**123**(2):148-153

[30] Geers AE. Factors influencing spoken language outcomes in children following early cochlear implantation. Advances in Oto-Rhino-Laryngology. 2006;**64**:50-65

[31] Geers AE, Moog JS, Biedenstein J, Brenner C, Hayes H. Spoken language scores of children using cochlear implants compared to hearing age-mates at school entry. Journal of Deaf Studies and Deaf Education. 2009;**14**(3):371-385

[32] Holt RF, Svirsky MA. An exploratory look at pediatric cochlear implantation: Is earliest always best? Ear and Hearing. 2008;**29**(4):492-511

[33] Gilley PM, Sharma A, Mitchell TV, Dorman MF. The influence of a sensitive period for auditory-visual integration in children with cochlear implants. Restorative Neurology and Neuroscience. 2010;**28**(2):201-218

[34] Meredith MA, Krylywy J, McMillan AH, Malhotra S, Lum-Tai R, Lomber SG. Crossmodal reorganization in the early deaf switches sensory, but not behavioral roles of auditory cortex. Proceedings of the National Academy of Sciences of the United States of America. 2011;**108**(21):8856-8861

[35] Bola L, Zimmerman M, Mostkowski P, Jednorog K, Marchewka A, Rutkowski P, et al. Task-specific reorganization of the auditory cortex in deaf humans. Proceedings of the National Academy of Sciences of the United States of America. 2017;**114**(4):E600-E609

[36] Zhang JS, Guan AL, Zhang XG, Beydoun H, Seidman M, Elisevich K, et al. Cortical electrical suppression of tinnitus and modulation of its related neural activity. The New Zealand Medical Journal. 2010;**123**(1311):77-167

[37] Zhang JS, Guan ZL, Ramachandran V, Dunford J, Seidman M, Bowyer SM, et al. Electrical modulation of tinnitus related activity. Seminars in Hearing. 2008;**29**(4):313-326

[38] Meredith MA, Lomber SG. Somatosensory and visual crossmodal plasticity in the anterior auditory fields of early deaf cats. Hearing Research. 2011;**280**(1-2):38-47

[39] Seidman MD, Van de Water T. Pharmacologic manipulation of the labyrinth with novel and traditional agents delivered to the inner ear. Ear, Nose, and Throat Journal. 2003;**82**(4):276-304

[40] Zanetti D. Characterization of hearing loss in children with mucopolysaccharidosis. In: Hatzopuolos S, editor. An Excursus into Hearing Loss. Rijeka, Croatia: Intech Open; 2018. DOI: 10.5772/intechopen.74196

[41] Simmons MA, Bruce IA, Penney S, Wraith E, Rothera MP. Otorhinolaryngological manifestations of the mucopolysaccharidoses. International Journal of Pediatric Otorhinolaryngology. 2005;**69**(5):589-595

[42] Taylor M, Khan S, Stapleton M, Wang J, Chen J, Wynn R, et al. Hematopoietic stem cell transplantation for mucopolysaccharidoses: Past, present and future. Biology of Blood and Marrow Transplantation. 2019. DOI: 10.1016/j.bbmt2019.02.012

[43] Mukherjee P, Miller JH, Shimony JS, Philip JV, Nehra D, Snyder AZ, et al. Diffusion-tensor MR imaging of gray and white matter development during normal human brain maturation. AJNR - American Journal of Neuroradiology. 2002;**23**:1445-1456

[44] Devine SM, Cobbs C, Jennings M, et al. Mesenchymal stem cells distribute to a wide range of tissues following systemic infusion into nonhuman primates. Blood. 2003;**101**:2999-3001

[45] Gholamrezanezhad A, Mirpour S, Bagheri M, et al. In vivo tracking of 11in-oxine labeled mesenchymal stem cells following infusion in patients with advanced cirrhosis. Nuclear Medicine and Biology. 2011;**38**:961-967

[46] Krueger TEG, THorek DLJ, Denmeade SR, Isaacs JT, Brenned WN. Concise review: Mesenchymal stem cell-based drug delivery: The good, the bad, the ugly and the promise. Stem Cells Translational Medicine. 2018;7:651-663

[47] Leyendecker A Jr, Gomez Pinheiro CC, Amano MT, Bueno DF. The use of human mesenchymal stem

cells as therapeutic agents for the in vivo treatment of immune-related diseases: A systemic review. Frontiers in Immunology. 2018;**9**:2056. DOI: 10.3389/fimmu.2018.02056

[48] Fierabracci A, Del Fattore A, Luciano R, Muraca M, Teti A, Muraca M. Recent advances in mesenchymal stem cell immunomodulation: The role of microvesicles. Cell Transplantation. 2015;**24**:133-149

[49] Gebler A, Zabel O, Seliger B. The immunomodulator capacity of mesenchymal stem cells. Trends in Molecular Medicine. 2012;**18**:128-134

[50] Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. Nature Reviews. Immunology. 2008;**8**:726-736

[51] Zhang QZ, Su WR, Shi SH, Wilder-Smith P, Xiang AP, Wong A, et al. Human gingiva derived mesenchymal stem cells elicit polarization of m2 macrophages and enhance wound healing. Stem Cells. 2010;**28**:1856-1868

[52] Le Blanc K, Tammik L, Sundberg B, Haynesworth SE, Ringden O. Mesenchymal stem cells inhibit and stimulate mixed lymphocyte cultures and mitogenic responses independently of the major histocompatibility complex. Scandinavian Journal of Immunology. 2003;**57**:11-20

[53] Singer NG, Caplan AI. Mesenchymal stem cells: Mechanisms of inflammation. Annual Review of Pathology. 2011;**6**:457-478

[54] VandenBosch LS, Reh TA. Epigenetics in neuronal regeneration. Seminars in Cell & Developmental Biology. 2019. DOI: 10.1016/j.semcdb.2019.04.001

[55] Liang X, Ding Y, Zhang Y, Tse HF, Lian Q. Paracrine mechanisms of mesenchymal stem cell-based therapy: Current status and perspectives. Cell Transplantation. 2014;**23**(9):1045-1059