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Advancements in Treatment for Sensorineural Hearing Loss: Implications for Rehabilitation Professionals

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Rehabilitation professionals work with a variety of people with disabilities who need a range of broadly defined services such as physical restoration, counseling, training, assistive technology, transportation, and job placement, to name a few. Some rehabilitation professionals have specialized caseloads that focus services on a specific homogeneous population, and are well-versed in the group's service needs. However, due to funding limitations, this may not always be feasible. In addition, there are many non-urban areas where services in every community, town or city are not possible (Watson, Jennings, Tomlinson, Boone & Anderson, 2008). The rehabilitation professional may provide services in a variety of locations on a regular or as-needed basis, preventing the consumer from having to secure transportation to other cities. In such situations, the rehabilitation professional needs to have a broader understanding of disabilities and treatments.

Hearing loss can result from a multitude of instances, such as an adverse effect from a medication. Some ototoxic drugs can lead to permanent hearing loss, like aminoglycosides, cisplatin and loop diuretics, and are still used in clinical practice due to continued efficacy in certain disease states (Saladin, Perez, Cruz & Tasnif, 2015). There are now more options available for people who choose to reduce hearing loss. Advanced therapies, such as cochlear implants, auditory brainstem implants, auditory midbrain implants and the regeneration of hair cells via stem cell therapy, have restored hearing to numerous patients once thought permanently deaf. This paper reviews hearing restoring therapies and their use in patients deafened by drug-induced ototoxicity.

Cochlear Implants

A cochlear implant (CI) is a small electronic device that can help provide sound stimulation through mechanicoelectric transduction to the auditory nerve (Ramsden, 2002). A CI consists of two basic parts: the external sound processor that acts like a microphone, and the implanted component that transmits the stimulus to the auditory nerves. Implants are typically utilized in severe deafness caused by progressive loss of hair cells in the organ of Corti. Hair cell loss caused by medications in the aminoglycoside class and cisplatin (a chemotherapeutic agent) may be restored with a cochlear implantation. The procedure to implant the internal components starts with a small postauricular incision followed by a mastoidectomy to access the middle ear (Ramsden, 2002). The round window niche is identified and drilled to enter the scala tympani of the cochlea (cochleostomy). The electrode is inserted via the cochleostomy into the cochlea. The operation is performed by an otologist and takes about 1.5 hours to complete (Ramsden, 2002).

Candidates for cochlear implantation fall into two main groups: prelingually (prior to speech acquisition) or congenitally deaf children and postlingually (after speech acquisition) deafened adults (Ramsden, 2002). Prolonged hearing loss between the critical periods of language development (between about 18 months and 13 years) typically renders the individual unable to acquire normal speech despite restored auditory function (Ramsden, 2002). Therefore, children with deafness caused by ototoxic drugs have better results the sooner the implantation is performed following the onset of hearing loss. Before considering cochlear implantation, an individual must show no benefit from hearing aids over several months. Subsequently, electrophysiology testing is used to confirm level of hearing loss and tomography or magnetic resonance imaging is used to determine cochlear anatomy (O'Donoghue, 1996). In general, an

individual with cochlear implants who previously had hearing abilities or had undergone years of intensive therapy can achieve high levels of speech understanding (over 90% in most cases) along with open set speech (without visual clues) understanding (Murugasu, 2005).

Based on its mechanism of action, cochlear implantation is a viable option for most cases of hearing loss caused by ototoxic agents. Cisplatin and aminoglycosides both cause apoptosis (programmed cell death) of hair cells leading to hearing loss. Cochlear implants bypass the damaged hair cells by stimulating the spiral ganglion of the auditory nerve directly. Although cochlear implantation will likely be beneficial in most of cases drug-induced hearing loss, severe cases that involve damage to the auditory nerve represent an absolute contraindication (Paludetti, Conti, Nardo, Corso, Rolesi, Picciotti, et al., 2012). The function of the auditory nerve is assessed before cochlear implantation; however, working CIs can lose benefit due to drug-induced ototoxicity affecting this nerve. In one case report, a patient with a functioning cochlear implant of 12 years lost the benefit of the device after the administration of cisplatin chemotherapy to treat osteosarcoma (Harris, Gilbert, Lormore, Musunuru & Fritsch, 2011). The patient had no functioning outer hair cells in the implanted ear; therefore, the change in hearing was likely due to direct injury to the spiral ganglion of the auditory nerve (Harris et al., 2011). Because damage to the auditory nerve cells renders cochlear implants useless, other modalities may be needed to preserve hearing.

Auditory Brainstem Implants

The auditory brainstem implant (ABI) is a device technologically similar to a cochlear implant. However, the electrode is placed on the surface of the cochlear nucleus of the brainstem (Paludetti et al., 2012). Candidates for ABI have hearing loss due to non-functional or non-existent auditory nerves, thus cochlear implants are contraindicated in these individuals (Sennaroglu & Ziyal, 2012). The Food and Drug Administration (FDA) has only approved ABIs for use in neurofibromatosis type 2 (NF2) patients 12 years old or older who have lost hearing due to resection of acoustic neuromas (Schwartz, Otto, Shannon, Hitselberger & Brackmann, 2008). ABIs indications in western European countries include temporal bone fractures, VIII nerve aplasia, and severe ossification of the cochlea (Paludetti et al., 2012). Acquired disorders that compromise the auditory nerve similar to severe drug-induced ototoxicity are potentially suitable for treatment with ABIs. Another study demonstrated use of ABIs as a salvage treatment by reporting favorable outcomes with ABIs in 5 patients who had poor results with CIs (Colletti, Fiorino, Carner, Miorelli, Guida, & Colletti, 2004). Three adults with no word/sentence discrimination with cochlear implants exhibited 85-100% two- or three-syllable word discrimination with ABIs. Two children with no hearing ability with CIs were able to detect sound and words as early as two months after ABI activation (Colletti et al., 2004).

Because the surgical landmarks used in ABIs are not always obvious, this treatment option is much more complex than cochlear implantation. Auditory brainstem implantation starts with an incision in the retromastoid region followed by a craniotomy to expose sigmoid sinus. The dura is opened, and the cerebellum retracted to identify the VII and VIII nerve complex. The straight vein (found on the IV ventricle floor) leads to the site of implantation at the cochlear nucleus (Raghunandhan & Kameswaran, 2010). An electrically evoked auditory brain stem response is used to verify the position of the ABI and to decrease the risk of non-auditory stimulation of

adjacent cranial nerves (glossopharyngeal, accessory, trigeminal, and facial) (Ramsden, 2002). Despite the complexity of the procedure, Colletti et al. (2010) demonstrated the rate of major complications associated in 114 surgeries over 11 years was minimal (14%). Major complications were lower in nontumor patients (5) versus NF2 patients (11). Minor complications (including transient facial palsy, balance problems, and cerebrospinal fluid leakage) were generally managed easily and resolved completely (Colletti et al., 2010).

Six to eight weeks after implantation, the ABI is stimulated for the first time and the device is programmed. At the initial stimulation, emergency medical assistance should be available due to the possibility of changes in vital signs occurring (Schwartz et al., 2008). During the initial stimulation, the device is programmed, and pitch scaling, nonauditory stimulation, and comfort levels are evaluated. Because the various electrodes elicit highly variable pitch perceptions, the programming process is complex. Follow-up is conducted to optimize ABI performance every three months for the first year, then yearly thereafter (Schwartz et al., 2008).

In most cases, ABIs generally do not perform as well as cochlear implants and often require speechreading to facilitate oral communication (Murugasu, 2005). This may stem from the fact that most ABI users are NF2 patients. One study compared the performance of ABIs in 10 tumor and 10 non-tumor patients (Colletti & Shannon, 2005). Non-tumor patients showed a significantly greater auditory benefit with results comparable to cochlear implantation (Colletti & Shannon, 2005). Though only indicated for NF2 in the United States, auditory brainstem implants may be beneficial in patients with drug-induced destruction of the auditory nerve.

Auditory Midbrain Implant

The most recent technology in auditory prostheses has started to target higher levels of the auditory pathway through implantation in the inferior colliculus of the auditory midbrain. Auditory midbrain implants bypass the cochlear nucleus and implant in the inferior colliculus (IC), the major ascending auditory convergence center (Lim, Lenarz & Lenarz, 2009). Using the lateral supracerebellar-infratentorial approach, the surgeon performs a craniotomy and separates the dura to expose the brain. The cerebellum is retracted to expose the inferior colliculus, and the electrode array is placed on the dorsal surface of the IC. Though surgery is safe overall, accurate placement is difficult, leading to dramatically different results between patients (Lim et al., 2009). Even the best performer cannot achieve open set speech perception; however, AMIs still provides recipients with improvement in sound awareness and speech understanding in face-to-face conversation (Shannon, 2012). Ototoxic drugs have not displayed damage to the brainstem, so AMI is not a viable option with patients deafened by medication use. NF2 patients with limited success from an ABI appear to have the greatest benefit with auditory midbrain implantation (Colletti, Shannon, Carner, Sacchetto, Turazzi, Masotto, et al., 2007).

Gene and Cell-based Therapy

The ability to hear depends on functioning hair cells. As stated earlier, these cells are often the first targets of ototoxic drugs. Unlike other epithelia in the gut or skin, the inner ear epithelia cells contain no stem cells, thus damage to these cells is permanent (Murugasu, 2005). Recent advances have shown cochlear gene therapy as a possible treatment for hearing loss. Atoh1

(Math1 in mice) encodes a transcription factor that induces development of sensory hair cells from cochlear supporting cells. In another study, young adult guinea pigs (n=30) were deafened with kanamycin and ethacrynic acid and infused Atoh1 transgene via adenoviral vector into the left cochlea four days after the ototoxic treatment (Izumikawa, Minoda, Kawamoto, Abrashkin, Swiderski, Dolan, et al., 2005). After incising the area between the mandible and clavicle and drilling a small hole into the exposed cochlea, 5 µl of the replication-deficient adenovirus was injected in the scala media (Ishimoto, Kawamoto, Kanzaki, & Raphael, 2002). Eight weeks after Atohl incolution, scanning electronic microscopy showed large number of inner and outer hair cells and auditory brain-stem responses showed a substantial improvement in hearing thresholds (Izumikawa et al. 2005). Gene therapy may also regenerate vestibular hair cells destroyed by ototoxic drugs. Staecker, Praetorius, Baker and Brough (2007) showed a 60% recovery of vestibular hair cells in vivo and in vitro after destruction with neomycin. Both Izumikawa and Staecker used adenovirus to deliver Atoh1 to the mammalian inner ear. Kesser, Hashisaki, Fletcher, Eppard, and Holt (2007) generated an in vitro model from 26 human sensory epithelia, excised at the time of labyrinthectomy that demonstrated adenoviral transfection in hair and supporting cells. These breakthroughs in Atoh1 and adenovirus research suggest a viable future option for restoring damage caused by ototoxic drugs with inner ear gene therapy.

As the severity of hearing loss increases, the need to maintain or regenerate auditory nerves is of utmost importance. Preservation of auditory nerves is particularly important to users of cochlear implants. Neurotrophins (a family of molecules crucial for neural maintenance and development) are used in cell-based therapy aimed at the preservation of spiral ganglion neurons. After guinea pig hair cells were eliminated using kanamycin and ethacrynic acid, significantly more spiral ganglion cells survived after 43 days when inoculated with adenovirus containing human neutrophic factor ($p < 0.05$) (Kanzaki, Stover, Kawamoto, Prieskorn, Altschuler, Miller, et al., 2002). This increased survival has been shown with cochlear implants in cats, therefore, neurotrophins could potentially extend the duration and benefit of the implant (Wise, Fallon, Neil, Pettingill, Geaney, Skinner, et al., 2011). In addition to preservation, there was also a robust regrowth of nerve fibers in deafened guinea pigs with neurotrophins (Shibata et al., 2010). Most animal studies use two methods of chronic neurotrophin administration: inoculation with adenoviral vectors (similar to Atoh1), and mini- osmotic pump via surgical implant (Budenz, Pfingst & Raphael, 2012). Unfortunately, the mini- osmotic pump requires periodic replenishment of a neurotrophin reservoir, limiting its clinical utility. Further clinical research is needed; however, neurotrophin therapies could provide a means of treating hearing loss and increase the benefit of cochlear implants.

Stem Cells

Developments in stem cell technology provide another potential treatment of sensorineural hearing loss via the replacement of damaged hair cells and spiral ganglion neurons. Stem cell-based replacement could help patients deafened by drug-induced ototoxicity, even in severe cases involving the auditory nerve. Two strategies have achieved stem cell-based replacement: induction of the cell cycle of inner ear progenitors and transplantation of stem cell-derived cells or exogenous stem cell into the inner ear (Hu & Ulfendahl, 2013).

Li, Liu and Heller (2003) first reported that adult mouse utricles contain sphere-forming stem cells that give rise to new hair-like cells. Another study subsequently found sphere-forming cells in the organ of Corti, stria vascularis, vestibular sensory epithelia, and spiral ganglion of early postnatal mice (Oshima, Grimm, Corrales, Senn, Monedero, Géléoc, et al., 2007). These cells also differentiated to hair cell-like cells with function similar to nascent hair cells. Hu, Luo, Zhang, Lu, Dong, Monsell, et al. (2012) studied human sensory epithelial cells from two utricles removed via translabyrinthine for acoustic neuroma treatment. Using PCR and immunofluorescence in vitro, it was discovered that these cells expressed proteins and genes present in prosensory and stem cells revealing that the inner ear can re-enter the cell cycle. They also used epithelial-to-mesenchymal (EMT) as the mechanism to activate proliferation of cloned human utricular cells (Hu, Luo, Zhang, Lu, Dong, Monsell, et al., 2012). EMT has previously demonstrated the ability to generate cells with stem cells properties and could, therefore, be used to induce human utricular cells into new hair cells (Mani, Yang, Ayyanan, Eaton, Liao, Guo, et al., 2008).

Numerous types of cells have been transplanted into the inner ears of mammals. These include inner ear stem cells, stem cell-derived neurons, mesenchymal stem cells, induced pluripotent stem (iPS) cells, neural stem cells, and embryonic stem cells (Hu & Ulfendahl, 2013). Because the microenvironment of the organ of Corti of host mammals is significantly different from the culture conditions in vitro, the transplantation of new hair cells has rarely been reported (Hu & Ulfendahl, 2013). However, recent advances have focused on the replacement of spiral ganglion neurons (SGN) by stem cell transplantation. It is necessary to gain access via surgery to the transplantation site in the SGN area while minimizing trauma as much as possible. Surgical procedures include: translabyrinthine approach for direct access to the auditory nerve (TL); localized of fracture of the osseous spiral lamina for direct access to Rosenthal's canal (RC); and cochleostomy into the scala tympani (ST). Backhouse, Coleman and Shepard (2008) performed the three procedures on normal adult guinea pigs and compared the survival of SGNs (ST>RC>>TL) and inflammation (TL>>RC≥ST) at four weeks. Needham, Minter, Shepherd and Nayagam (2013) reviewed over 30 studies that investigated various methods of exogenous stem cells delivery. In vivo, neural proteins expression was found in 27 of 39 experiments; however, glial proteins expression was found in only 11 experiments. Overall, survival rates varied between a few days to several weeks with small to no localized tissue response reported (Needham, Minter, Shepherd & Nayagam, 2013). To date, stem cell-derived growth neurons from the cochlear nucleus to synapse on brainstem neurons has not been reported. Challenges with growth and survival still need to be addressed, but current studies provide another possible means to overcome hearing loss.

Further Considerations

Research about the mechanism and etiology of ototoxic drugs illuminate how recent advancement in treatment and prevention can be viable therapies for drug-induced hearing loss. Before administration, clinicians should be aware of factors that can increase the risk including: younger age (García, Martínez, Agustí, Mencía & Asenjo, 2001; Li, Womer, & Silber, 2004), coadministration of ototoxic agents (García et al., 2001), genetics (A1555G mutations), and higher cumulative doses (Bokemeyer, Berger, Hartmann, Kollmannsberger, Schmoll, Kuczyk, et al., 1998; Cooperman & Rubin, 1973). Mechanisms of ototoxic drugs provide the basis for the

creation of protective agents. Protective agents are the only non-prosthetic therapy to show benefit in humans with support from randomized controlled trials (Chen, Huang, Zha, Qiu, Wang, Sha, et al., 2007; Feldman, Efrati, Eviatar, Abramsohn, Yarovoy, Gersch, et al., 2007).

The pahophysiology of ototoxicity helps determine which therapies can be used based on the degree of hearing loss. In less severe ototoxicity, hair cells are the primary site of dysfunction. In this scenario, cochlear implants have shown to be the most proven and effective means of hearing restoration. Though still in animal testing phase, Atoh1-based gene therapy could provide a viable therapy in time. Auditory nerve damage is the greatest concern in the most severe cases of ototoxicity. Because it bypasses the auditory nerve, auditory brainstem implants could be a useful option in this situation (currently, it is only FDA-approved for NF2). Generally, ABIs have shown to be not as effective as CIs in restoring functioning. Of note, a small study showed nontumor patients displaying greater auditory performance comparable to cochlear implants (Colletti & Shannon, 2005); however, more studies are needed before suggesting ABIs a legitimate option for drug-induced hearing loss. Auditory midbrain implants do not appear to possess any benefit apart from NF2 patients with limited success from ABIs.

Neurotrophins have shown in animal models to preserve (Kanzaki et al., 2002; Wise et al., 2011) and regrow hair cells (Shibata, Cortez, Beyer, Wiler, Polo, Pfingst, et al., 2010), which could preserve and continue CI use. Although animal models show the possibility of stem cells to grow hair cells and auditory neurons, the challenges with survival and growth must be overcome before clinical use in humans. Drug-induced hearing loss is life-altering; however, it is not life-threatening. As a result, treatment-associated risks must be minimal, and the clinical application these therapies must carefully be considered.

Implications for Rehabilitation Professionals

The rehabilitation professional needs to know and understand the root cause and extent of an individual's hearing loss. This understanding will help the consumer and the rehabilitation professional when consulting with physicians and pharmacists to determine which, if any, treatment modality is appropriate. In addition, the rehabilitation professional needs to consider the noise level of the environments where the consumers live and work, and other genetic issues that may potentially compound the hearing loss (Fischel-Ghodsian, Prezant, Chaltraw, Wendt, Nelson, Arnos et al., 1997; Xing, Chen, & Cao, 2007; Zimmerman & Lahav, 2012). When an individual's hearing loss is caused by ototoxic medications, current treatment options vary between cochlear implants or ABIs. In the near future, other treatment modalities such as AMIs and gene- and cell-based therapies may be viable, or even preferred, options The rehabilitation professional needs to understand which treatment has the best outcomes based on the needs of the individual and be mindful of the emerging research in hearing loss and protective agents (Chen, Huang, Zha, Qiu, Wang, Sha, et al., 2007; Ciarimboli, Jürgens, Knief, Deuster, Schlatter, Koepsell, et al., 2010; Feldman, Efrati, Eviatar, Abramsohn, Yarovoy, Gersch, et al., 2007; Rybak, 2007).

In addition to the provision of counseling, other services may be needed in a more comprehensive plan. For example, psychological services may be needed for those who do not recover their hearing and/or have a prolonged recovery time. These individuals may need to

adapt to and learn coping strategies to assist them in daily living activities and in communicating within their environments. Both the individual and the rehabilitation professional need to understand the selected technology that may be part of the treatment. Additionally, depending on the individual's employment history, there may need to be additional training within their career field or, possibly, another career altogether. The rehabilitation professional needs to ensure the individual is able to communicate in visual formats to move forward with the agreed-upon plan.

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