EDITORIAL

New research in hearing loss treatment

Raluca Enache, MD, PhD
ENT Sarafoleanu Medical Clinic, Bucharest, Romania

According to the World Health Organization, almost 466 million people worldwide, representing over 5% of the world's population, suffer of a degree of hearing loss[1]. Of these, 34 million are children. Researchers also estimate that by 2050 one in every ten people (over 900 million people) will have disabling hearing loss[1].

Many causes which can lead to the decrease in the hearing level are described: genetic causes, infectious diseases, chronic ear infections, certain complications during birth, drugs (ototoxicity), exposure to excessive noise, aging, etc. WHO statistics show that 1.1 billion young people, 12-35 years of age, present a risk of hearing loss due to exposure to recreational noise, and 60% of childhood hypoacusis is due to preventable causes[1].

Hearing impairment has functional, social, emotional and economic impact upon the affected individual, society and state. WHO estimates that 750 billion US dollars represent the annual global cost for unaddressed hearing loss[1].

Analysing these entire data one can realize that any intervention to prevent, identify and treat hearing loss is cost-effective and also has a great positive impact upon individuals. This is why all medical and researchers communities try to find methods which can help treating hearing impairment, especially the sensorineural one.

During the last year two new possible treatment methods have been brought to our attention. It is very well known that the sensorineural hearing loss (SNHL) appears when either the sensory hair cells in the cochlea or the auditory nerve cells are destroyed, since these cells could not be replaced after their death. The new therapies test two mechanisms by which the cochlear support cells can be regenerated.

Considering the positive results of intravenous delivery of mesenchymal progenitor cells in an acute neurologic pathology (e.g. stroke, spinal cord injury)[2-4], myeloablation and human umbilical cord blood transplantation in patients with mucopolysaccharidosis[5] or cord blood mononuclear cells transplantation in experimentally deafened mice and guinea pigs[6,7], researchers from Florida, USA, tried to examine ***SNHL treatment using umbilical cord blood***. James E. Baumgartner, Linda S. Baumgartner and their colleagues evaluated the safety of autologous umbilical cord blood (hUCB) therapy in children with acquired sensorineural hearing loss[8]. This phase 1 clinical trial was conducted under de Federal Investigational New Drug, approved by the Florida Hospital Committee for the Protection of Human Subjects and Florida Hospital Office of Research Administration, and it was conducted in the Florida Hospital for Children. The results were first published online in August 2018, in the Journal of Audiology and Otology.

11 children with moderate to severe acquired SNHL were included in this study. All patients were evaluated before the hUCB intravenous administration, 1 month, 6 months and 12 months after. Each evaluation included physical and neurological evaluation, OAE and ABR testing, and a brain MRI with DTI sequences. The infusion-related toxicity was monitored by evaluating the pulmonary, renal, neurological, hematologic and hepatic functions.

During the follow-up visits, changes greater than 5dB ABR threshold, or 0.5 milliseconds in peak 5 of CN VIII conduction latency, were considered significant and were found in almost 45% of the children included in the study. Also, there were no

Corresponding author: Raluca Enache, MD, PhD, ENT Sarafoleanu Medical Clinic, Bucharest, Romania
e-mail: enache.raluca@yahoo.com

changes in the haematological profile and no neurological, renal, pulmonary, hematologic or hepatic complications.

The results of this phase 1 study suggest that the hUCB treatment is safe, feasible, well tolerated, and can produce repair at the cochlear level, spiral ganglion and the entire auditory pathway. Even if the exact mechanism of action is not really known, it seems that human umbilical cord blood spurs the regeneration of the ciliary hair cells and the support cells within the cochlea ("stem-like" progenitor cells).

Due to its low number of patients, the results of the study cannot be applied to a larger population, but considering it is the first clinical evidence on humans it can warrant the implementation of a larger phase 2/3 trials.

A team of scientists from the University of Rochester Medical Center and Harvard Medical School's Massachusetts Ear and Eye Infirmary tested the ***implication of the epidermal growth factor (EGF) in cochlear support cells regeneration*** in mice with hearing loss. It is already known that EGF has this effect on the auditory organs of birds. To verify this theory, the researchers focused on one member of the epidermal growth factor receptor family, ERBB2, which can be found in the cochlear support cells[9]. The results of the study were first published in September 2018, in the European Journal of Neuroscience.

The researchers investigated, on mice, three methods to activate the EGF signalling pathway by targeting ERBB2. They used a virus to target ERBB2 receptors, mice genetically modified to overexpress an activated ERBB2 and two drugs first developed to stimulate the stem cells activity in the eyes and pancreas.

In all cases, a series of cochlear events were generated, which led to a proliferation of cochlear support cells and activated other neighbouring stem cells to become new sensory hair cells. It seems that the process not only influences the regeneration of the sensory hair cells, but also supports their relation with the nerve cells.

The authors conclude that: "Our data suggest that signalling from the receptor tyrosine kinase ERBB2 can drive the activation of secondary signalling pathways to regulate regeneration, suggesting a new model where an interplay of cell signalling regulates regeneration by endogenous stem-like cells."[9].

Even if these studies are in preliminary phases and need more research on humans, one can say that they represent an important step in developing new safe, feasible and well-tolerated treatment methods for hearing loss.

REFERENCES

1. World Health Organization. Deafness and hearing loss [Internet]. Available from: https://www.who.int/news-room/fact-sheets/detail/deafness-and-hearing-loss.
2. Savitz SI, Misra V, Kasam M, Juneja H, Cox CS Jr, Alderman S, et al. Intravenous autologous bone marrow mononuclear cells for ischemic stroke. Ann Neurol. 2011;70:59-69.
3. White SV, Czisch CE, Han MH, Plant CD, Harvey AR, Plant GW. Intravenous transplantation of mesenchymal progenitors distribute solely to the lungs and improve outcomes in cervical spinal cord injury. Stem Cells. 2016;34:1812-25.
4. van Velthoven CT, Dzietko M, Wendland MF, Derugin N, Faustino J, Heijnen CJ, et al. Mesenchymal stem cells attenuate MRI-identifiable injury, protect white matter, and improve long-term functional outcomes after neonatal focal stroke in rats. J Neurosci Res. 2017;95:1225-36.
5. Da Costa V, O'Grady G, Jackson L, Kaylie D, Raynor E. Improvements in sensorineural hearing loss after cord blood transplant in patients with mucopolysaccharidosis. Arch Otolaryngol Head Neck Surg. 2012;138:1071-6.
6. Revoltella RP, Papini S, Rosellini A, Michelini M, Franceschini V, Ciorba A, et al. Cochlear repair by transplantation of human cord blood CD133+ cells to nod-scid mice made deaf with kanamycin and noise. Cell Transplant. 2008;17:665-78.
7. 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. Biochem Biophys Res Commun. 2012;427:629-36.
8. Baumgartner LS, Moore E, Shook D, Messina S, Day MC, Green J, et al. Safety of Autologous Umbilical Cord Blood Therapy for Acquired Sensorineural Hearing Loss in Children. J Audiol Otol. 2018;22(4):209-222. Published online August 22, 2018. DOI: https://doi.org/10.7874/jao.2018.00115.
9. Zhang J, Wang Q, Abdul-Aziz D, Mattiacio J, Edge ASB, White PM. ERBB2 signalling drives supporting cell proliferation in vitro and apparent supernumerary hair cell formation in vivo in the neonatal mouse cochlea. Eur J Neurosci. 2018;48(10):3299-316. DOI: 10.1111/ejn.14183. Epub 2018 Oct 24.