UNILATERAL PROFOUND DEAFNESS – A POSSIBLE MECHANISM

Konstantin Georgiev¹, Yana Pacholova²,

1) LOR Department; MBAT Varna; Military Medical Academy, Bulgaria

2) Family Centre Pan, Psychological and Speech Therapy Practice, Varna, Bulgaria.

ABSTRACT:

Purpose: To explain the clinical findings of patients with profound unilateral deafness who have recovered the hearing function after a combined treatment of hyperbaric oxygenation and dehydrant therapy.

Material and method: 11 patients with profound sudden unilateral hearing loss above 90 dB SPL, intolerance to sounds similar to recruitment, at levels 10-20 dB above the hearing threshold (105-120 dB SPL), positive glycerol test and unexpected good recovery of hearing within 1-2 months are described.

Results: All patients have perfect outcome results without the use of glucocorticoids.

Conclusions: Based on articles about experiments with genetically modified animals and acquired deafness, we propose a possible mechanism of damage explaining the clinical findings and the favorable outcome of the disease – a disconnection between the tectorial membrane and stereocilia. Thus mechano-electrical transducer (MET) of hair cells cannot be activated. The combined use of hyperbaric oxygenation and dehydrant medications can lead to recovery of the hearing function.

Keywords: Unilateral Sensorineural Hearing Loss, Tectorial Membrane, Hair Cells

INTRODUCTION:

In our daily practice, we noticed a specific group of patients with the following characteristics: sudden unilateral sensorineural hearing loss (SNHL) above 90 dB Sound Pressure Level (SPL), intolerance to sounds similar to recruitment, at levels 10-20 dB above the hearing threshold (105-120 dB SPL), positive glycerol test and unexpected good recovery of hearing within 1-2 months. (Tab.1) The average hearing loss before treatment was 90.23 dB. On the 30-day follow up visit, the average hearing loss was only 24.77 dB. The clinical and instrumental findings differed from those in patients with unilateral deafness due to vascular accident, meningitis, cranial trauma. The last had no improvement. Some patients of the targeted group reported noticing the exact moment of hearing recovery, and the process lasted minutes. This led us to the following question: do we have damage to the nerve tissue, despite the poor bone audiometry, or do we observe a mechanical phe-

nomenon in the cochlea?

The external ear, the middle ear, the membranous labyrinth and the fluids of the inner ear conduct mechanically sound energy to hair cells. The change of position of the hair-cell stereocilia by the tectorial membrane (TM) opens mechanically gated ion channels, and then a cascade of reactions leads to tonic releasing of neurotransmitters to the synapses. Using a bone transducer, we transmit sound energy directly to the membranous labyrinth and suggest that any decrease of perception is due to injuries of nerve tissues.

The TM is a gel-like structure containing 97% water. Its dry weight is composed of collagen (50%), non-collagenous glycoproteins (25%) and proteoglycans (25%). Specific glycoproteins are expressed in the TM - α -tectorin, β -tectorin, otolin, ceacam-16 and otogelin. Of these proteins, α -tectorin and β -tectorin form the striated sheet matrix that regularly organises the collagen fibres. Radially the TM is divided into three zones, the limbal, middle and marginal zones. Of these, the limbal zone is the thinnest (transversally) and overlies the auditory teeth of Huschke with its inside edge attached to the spiral limbus. The marginal zone is the thickest (transversally) and is divided from the middle zone by Hensen's Stripe. (fig.1)

Fig. 1. Tectorial membrane by Henry Gray - Anatomy of the Human Body. 1918.

Fig. 2. MET By Rober Fettiplace [1]

Current theoretical conceptions state that sensorineural hearing loss is associated only with injuries of the hair cells and neurons of the auditory nerve. In the last years, there has been accumulating data that impaired extracellular proteins of TM like α -tectorin, otogelin, otolin, ceacam-16, or hair cells (plastin-1, polycystin-1, cochlin), cause disability of junction between TM and hair cell, without visible morphological or functional injuries of the hair cells. Consequently the intact mechano-electric transducer (MET) in the hair cells cannot be activated by a bone transducer. Thus the results of a number of tests, like threshold audiometry, distortion product otoacoustic emissions (DPOAE) and auditory brainstem response (ABR), can be interpreted like SNHL without real injuries of the nerve tissues.

Fig. 3. Luxation of TM (by courtesy of D. Stavrev)[2]

Fig. 4. OHC is detached from TM (R. Pujol)

A part of the syndromic and nonsyndromic hearing loss is inherited and caused by a disturbance of the binding of TM and cilia of the hair cells. There are families with hereditary neurosensory hearing loss with definitive genetic abnormalities. Thus laboratory tests were conducted with induced mutations in lab animals. It was proved that there is a relationship between the deficiencies in the synthesis of the structural proteins of TM and the stereocilia and the hearing loss [2].

MATERIAL AND METHODS:

In the current study, we use a sample of patients for whom we suppose to have a mechanical disconnection between the tectorial membrane and the stereocilia. Our group consists of 11 patients (4 males and 7 females). Patients' age varied between 9 and 74 years (mean age: 43,45 years; st. dev.: 18,88 years). The group is characterized by reduced air and bone perception of hearing over 90 dB SPL and intolerance of loud sound (>105dB SPL).

After a positive glycerol test, we applied dehydrating therapy, hyperbaric oxygenation (having an antihypoxic and dehydrating effect), Ginkgo biloba derivatives, Vinpocetine, salt-free diet. We did not use glucocorticoids since we believe that GC's only improve the results in cases of SNHL with autoimmune genesis. Descriptive statistics and T-test for the equality of means were performed by an IBM SPSS product.

RESULTS:

In the group of patients with sudden profound hearing loss, we observed general improvement of the hearing function after therapy. In every individual case, all frequencies displayed better results, and the patients reported greater hearing comfort.

Table 1. Individual patient hearing loss before and after therapy

				Hearing loss in dB before treatment				Hearing loss in dB follow up visit XXX day			
ID	Sex	Age	Ear	500 Hz	1000 Hz	2000 Hz	4000Hz	500 Hz	1000 Hz	2000 Hz	4000 Hz
495/17	M	40	r	90	90	90	90	20	20	60	40
2912/17	M	57	r	90	90	90	90	10	10	10	20
5338/16	F	19	l	90	90	90	90	20	30	40	40
1189/17	M	42	r	70	80	80	80	20	20	30	50
273/17	M	54	r	100	100	100	100	15	15	15	45
1123/16	M	38	l	90	90	90	90	20	20	30	40
977/16	M	37	l	100	100	100	100	30	40	50	50
2167/13	F	9	l	100	100	100	100	10	10	10	10
4612/15	M	65	l	90	90	90	90	20	20	30	50
7518/19	F	74	l	80	90	90	100	15	15	20	30
6751/19	F	43	r	60	70	80	90	10	10	10	10
Average hearing loss in all patients				87,3	90	90,9	92,73	17,3	19,1	27,7	35

Table 2. Paired Samples Statistics on four frequencies

Paired Samples Statistics					
		Mean	N	Std. Deviation	Std. Error Mean
Pair 1	Before therapy 500Hz	87,2727	11	12,72078	3,83546
	After therapy 500Hz	17,2727	11	6,0678	1,82951
Pair 2	Before therapy 1000Hz	90	11	8,94427	2,6968
	After therapy 1000Hz	19,0909	11	9,17011	2,76489
Pair 3	Before therapy 2000Hz	90,9091	11	7,00649	2,11254
	After therapy 2000Hz	27,7273	11	16,93571	5,10631
Pair 4	Before therapy 4000Hz	92,7273	11	6,4667	1,94978
	After therapy 4000Hz	35	11	15,32971	4,62208

As it shows on tables 1 and 2 the patients in the study were experiencing profound hearing loss (above 90dB) at initial examination.

A paired-samples t-test was conducted to compare the hearing loss at four frequencies before and after therapy. There were significant differences in the scores of all frequencies, as follows.

Table 3. Paired Samples Test on four frequencies

Paired Samples Test									
		Paired Differences					t	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	Before treatment 500Hz	70.000	12,4499	3,75379	61,63604	78,36396	18,648	10	.000
	After treatment 500Hz								
Pair 2	Before treatment 1000Hz	70,9090	10,6813	3,22054	63,73327	78,08491	22,018	10	.000
	After treatment 1000Hz	9	3						
Pair 3	Before treatment 2000Hz	63,1818	17,9266	5,40508	51,13855	75,22508	11,689	10	.000
	After treatment 2000Hz	2	2						
Pair 4	Before treatment 4000Hz	57,7272	17,7993	5,36672	45,76948	69,68506	10,757	10	.000
	After treatment 4000Hz	7	9						

At 500 Hz, the mean hearing loss was 87,2727 dB (SD=12,72dB) at initial examination and was reduced to 17,2727 dB (SD=6,07dB) at the 30th-day follow-up visit. The difference is significant; $t(10)=18,648$, $p<0.001$ (Tabl. 3). The patients were able to distinguish speech and most low frequency surrounding sounds. At 1000 Hz, the mean hearing loss before therapy was 90,00 dB (SD=8,94dB) and was reduced to 19,0909 dB (SD=9,17dB) at the 30th-day follow-up visit. The reduction is also significant; $t(10)=22,018$, $p<0.001$ (Tabl.3). There was a significant difference between the values of hearing loss at 2000Hz at initial examination ($M=90,90$ dB; $SD=7,01$ dB) and after treatment at the 30th day follow up visit ($M=27,73$ dB; $SD=16,94$ dB); $t(10)=11,689$, $p<0.001$ (Tabl. 3). We also observed a significant improvement of hearing function at 4000Hz. The mean hearing loss before therapy was 92,7273 dB (SD=6,47dB) and was reduced to 35,00 dB (SD=15,33dB) after therapy. The reduction is again significant; $t(10)=10,757$, $p<0.001$ (Tabl.3). The values of T-test scores are higher and the standard deviation values are lower for the lower frequencies (500 Hz and 1000 Hz). This can be interpreted as greater and more definitive improvement for the lower frequencies (500Hz and 1000Hz) as compared to the higher (2000Hz and 4000Hz). The greater part of intelligible speech lies between 80 and 300 Hz with the highest frequency of human voice at singing being 1400Hz. This explains why most patients report improvement of hearing comfort on an everyday basis, witnessing of full recovery of hearing function. We did not observe any relapses after even 6-12 months after treatment. These findings persuaded us that there is a specific pathogenetic mechanism, which has been interrupted by the applied treatment. Further impairments were also prevented. The possible mechanism of injury will be discussed below.

DISCUSSION:

Tectociliar junction can be disrupted by genetic or acquired factors.

There are several proteins and glycoproteins with structural function in this junction. At least 12 mutations in the TECTA zone are found in people (locus 11q23.3). These are typically in the sound transducing part of the hearing analyzer but are classified as a neurosensory hearing loss: 3 of the mutations lead to recessive NSHL DFNB 21; the remaining 9 lead to dominant NSHL type DFNA12. Otogelin is an N-glycosylated protein that is present in the acellular membranes. 3 mutations were discovered in locus 11p15. Affected individuals had moderate hearing impairment DFNB18B that was sometimes associated with vestibular dysfunction. CEACAM-16 is a secreted glycoprotein with no transmembrane domain or glycosylphosphatidylinositol anchor stated to chromosome 19q13.31-q13.32. They proposed that CEACAM16 may have a role in connecting stereocilia with the tectorial membrane. There are 2 mutations of the gene, and affected persons suffer from deafness type DFNA4B. (<https://omim.org/>)

Induced mutation Y1870C, same TECTA, leads to hearing loss of 50-80 dB in mice, as the studying mice with targetly destroyed entactin G1-like domain in TECTA [4], establishes a luxation and deformation of m. tectoria, as well as thinning of the membranes of utriculus and sacculus – these are other places in the labyrinth where α -tectorin is

produced. The adhesive area with the cilia is reduced, and the matrix of the membrane is destroyed [3]. In m. tectoria, the other 2 glycoproteins - β -tectorin and otogelin, are not expressed. Morphologically the stereocilia and the cupula in the labyrinth are not changed, and the endocochlear potentials resemble those of the controls. No DPOAE is established, even at acoustic stimuli of 60 dB.

In PLS KickOut mice, without Plastin1, Taylor et al. [5] observed analogical to Legan profound hearing loss with morphological change only in cilia, without any other structural and electrophysiological impairments.

What will happen in cases of protein impairment with a preserved connection between cilia and m. tectoria? A study of Jones et al. [6] on mice with mutations *Tecta*^{Y1870C/+}, *Tectb*^{+/+}, and *Otoa*^{EGFP/EGFP} reports that impairments of proteins lead to changes in the amplitude-frequency characteristic of m. tectoria. In this case, there is disruption of the process of TRANSMISSION of sound energy to cilia. However, the test result from the bone transducer examination will show a decrease of PERCEPTION.

Fig. 5. Intact cilia in the mutants control group (Legan)

Fig. 6. Morphological changes in m. tectoria (Legan)

The other side of tecto-ciliar junction – cilia of hair cells bounded with many extracellular proteins like a sailing boat tackle. A number of them take part in transmembrane ion transport, but others have only support function, and if they are impaired or missing, this should not worsen the electrophysiological function of hair cells. Steigelman et al. [7] published a study on Polycystin-1, reported to function as a fluid flow-sensor in the kidney. Mutations on this protein cause polycystic kidney disease and SNHL in involved people. Based on 3 type mice – mutants, they first proved binding of Polycystin-1 with F-actin in the hair cell. Then using mutants, they observed significant differences in ABR and DPOAE thresholds between mutants and wild-type (WT) controls. In other cochlear structures and MET channels of mutants, they did not find any anatomical and functional abnormalities.

What about acquired impairments of tectociliar junction? In 1986 Uziel [8] published a paper about the relation between hypothyroidism and malformations of TM. Forest [9] reported that injuries of receptors of the thyroid hormone (TH) or iodine deficit cause deafness both in people and mice. Encoding gene $TR\alpha$ and $TR\beta$ expression continue pre- and postnatal. In mice $THRb$ mutation, $THRb(PV)$ leads to the loss of binding of thyroid hormone (T_3) to the TRb protein. Orthologous human $THRB(PV)$ mutation and other similar mutations in human $THRB$ cause resistance to thyroid hormone (RTH), which is occasionally associated with sensorineural hearing impairment and malformations of m. basillaris, stria vascularis and m. tectoria. [10] Having in mind that in Pendred syndrome (mutation of PDS gene 7q31), except deafness and hypothyroidism, there is a hydrops of aqueductus vestibule and saccus endolymphaticus. Forest, as others did not find cochlear malformations, but in 2009 Winter et al. [11] described increased autoimmune reaction against alpha- and beta-tectorin and abnormal m. tectoria in $TR\beta^{-/-}$ mice, as in the apical region of the cochlea, changes are stronger. Winter stated that “abnormal structure of the tectorial membrane and enhanced tectorin levels suggest that disturbed mechanical performance is the primary cause of deafness resulting from $TR\beta$ deficiency”.

Autoimmune deafness constitutes about 1% of all cases and is often associated with antibodies against HSP-70, tectorin and cochlin proteins. Cochlin is large widespread in the cochlea, and in case of mutation, patients suffer SNHL type DFNA9 and vestibular dysfunctions, and up until now, 9 mutations are described (<https://omim.org/>).

Solares et al. [12] investigated murine with induced autoimmune reaction against cochlin and β -tectorin and reported a significant increase of CD4+ T-cells and increased ABR threshold. This paper shows the possibility to acquire autoimmune hearing loss and good treatment results with glucocorticoids.

Physical factors can also harm the junction between m. tectoria and stereocilia. Using sound source 105 dB

SPL for 72 hours, Canlon [13] induces in vitro alteration, both in tectorial membrane and stereocilia. Typically those injuries correspond to frequencies with hearing loss. This can be explained part of cases of acquired hearing loss. Flock et al. [14] investigated cochleae, which have been acoustically traumatized by pure tone 140 Hz with 112 dB SPL. They found temporary and convertible displacement of Deiters and Hensen's cells, with adequate decreasing of microphonic potentials of the cochlea. Restitution of cells and microphonic potentials lasted about an hour, and hearing function was restored. Similar were the results of Cotanche [15] in mature avian, but he described in addition cells regeneration.

There are many examples of concomitant injury of hair cells and cochlear membranes. Song et al. [16] investigated the regulation of the protein prestin, which is important for hearing. Using mice mutants $TECTA C 1509G$, with malformative m. tectoria do not contact with all OHC, Song demonstrates local autofeedback, as in isolated from m. tectoria hair cells level of prestin decrease, but secondary.

CONCLUSIONS:

Using the results of aforesaid papers, of observation of impaired tectorial membrane and some cell-junction proteins, we can expect the following results on examination:

- Profound hearing loss measured by a bone transducer, low amplitude of ABR;
- Increase of DPOAE threshold. SOAE should be normal (not enough evidence);
- All resting cochlear potentials are normal;
- Absent ipsilateral and normal contralateral stapedius reflex at a unilateral hearing loss;
- Probable intolerance of extremely loud sounds.

Audiologists interpret and treat these results at present as sensorineural hearing loss. Interestingly similar are the results in cases with auditory neuropathy, where impairments are retrocochlear, but in those cases, DPOAE is normal, and contralateral stapedius reflex and speech perception are worse. Investigations of Legan and Solares show us that injuries of tectorin and cochlin can do harm to both auditory and vestibular function.

The assertion of Mattox [17] that 65% of cases of SNHL recovered completely spontaneously and independent of treatment in the first 14 days of accident sounds so extreme. But in these cases, we can ask a question – is there a general injury of the nervous tissue, so that we could diagnose SNHL? Is it possible that in some cases of longstanding deafness, the primary impairments in the structural proteins of the cochlea end in secondary degeneration of hair cells and the auditory nerve?

If we concentrate our clinical thinking on the fact that real conductive hearing impairment may be interpreted like SNHL, we can be more effective with our treatment.

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Please cite this article as: Georgiev K, Pacholova Y. Unilateral profound deafness – a possible mechanism. *J of IMAB.* 2021 Jul-Sep;27(3):3829-3834. DOI: <https://doi.org/10.5272/jimab.2021273.3829>

Received: 17/10/2020; Published online: 01/07/2021

Address for correspondence:

Konstantin Georgiev,
LOR Department, Multiprofile Base for Active Treatment - Varna, Military Medical Academy,
3, Hristo Smirnenski Str., 9000 Varna, Bulgaria.
E-mail: drkgeorgiev@abv.bg