

**Therapeutic options for sudden hearing
loss and the evaluation of treatment
influencing factors**

DOCTORAL (Ph.D.) THESIS

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I. Introduction

Types of hearing loss

According to World Health Organization (WHO) hearing loss affects more than 20% of the population worldwide and its prevalence is tending to increase. Hearing loss can be divided into conductive, sensorineural and mixed types. Whereas in conductive hearing loss, the structures like the external auditory canal and the middle ear, responsible for sound conduction and amplification are damaged. Sensorineural hearing loss occurs in case of failure of the signal reception and processing system.

Hearing loss with sudden onset can be triggered by a number of factors, even though the condition called sudden sensorineural hearing loss (SSNHL) is distinguished if the sensorineural hearing loss reaches minimum 30 decibels (dB) at least 3 consecutive frequencies within 72 hours.

The incidence of sudden hearing loss is estimated at 160-400 /1000000 individuals/year. It mostly occurs between the age of 50 and 60.

Diagnosis of sudden hearing loss

As a first step in the diagnostic process, in addition to an accurate history taking, a microscopic ear examination should be emphasised.

Hearing tests

The subjective hearing test, including pure-tone and speech audiometry test, requires an active participation of the patient. On the other side, objective hearing measurements, like

Auditory Brainstem Response (ABR) can determine the objective hearing threshold and the location of hearing loss without cooperation of the patients.

Testing the vestibular system

Since hearing system is in close connection with balance system, patients with sudden hearing loss often experience dizziness. In order to differentiate the peripheral and central causes, "HINTS" protocol (head impulse test, test for nystagmus, test of skew deviation) is cardinal which can be performed at bedside.

Differential diagnosis of sudden hearing loss

The pathomechanism of sudden hearing loss is remains unknown in 70%-90% of all cases (idiopathic sudden sensorineural hearing loss, ISSNHL). Although various theories like vascular, infectious or autoimmune origin. Rupture of the inner ear membranes is also suspected.

In addition to idiopathic cases, inner ear malformations, lesions affecting the endolymphatic spaces, inflammations, tumors may be responsible for the appearance of symptoms, as well as systemic disorders including cardiovascular, autoimmune and haematological diseases.

Prognostic factors effecting the hearing recovery in patients with sudden hearing loss

In the management of idiopathic sudden hearing loss, identification of the treatment influencing factors is crucial. The most important influencing factors have vascular origin. Associated cardiovascular disease, diabetes mellitus and older

age are all considered as negative prognostic factors. Tinnitus and vertigo may also impair hearing recovery.

Treatment of sudden hearing loss

Medical treatment

The most accepted and commonly used therapy for the treatment of sudden hearing loss is based on corticosteroids, because exact mechanism of action of which is unknown, there are no clear recommendations for their use. Steroid therapy can be administered orally, intravenously or topically (injected into the tympanic cavity, intratympanal [IT]), or a combination of these. Systemic steroid monotherapy has been used since the 1980s without strong evidence. Intratympanic treatment was initially used in cases of systemic treatment failure (salvage), although primary treatment is an option in order to avoid the systemic side effect. Combined treatment might achieve the highest drug concentration in the inner ear.

The efficacy of treatments based on various other assumed pathomechanisms (antiviral therapy, vasodilators) has not been scientifically proven.

Surgical treatment

In selected cases, surgical treatment of sudden hearing loss may also be considered. Explorative tympanotomy is performed to investigate the presence of perilymphatic leakage and to obliterate the potential "weak spots" (round, oval window, fissula ante fenestram [FAF]) with a soft tissue. Although no precise indications for the intervention exists, many authors recommend surgery in cases of severe hearing loss (60 dB<) after failure of medical treatment.

Rehabilitation of hearing loss

Depending on the degree of residual hearing, hearing can be rehabilitated with conventional hearing aid, CROS device, bone conduction implants (BAHA, Bonebridge) or cochlear implantation (CI). CI is the best option to restore binaural hearing in case of single sided deafness (SSD).

II. Objective

In our investigation on patients with idiopathic sudden sensorineural hearing loss, the different treatment options, aetiological and influencing factors were investigated. Our study is divided into 3 main parts:

1. The aim of our first survey was to retrospectively analyse the data of patients treated at our clinic for sudden hearing loss during the study period. We examined the efficacy of the therapy and the aetiological factors influencing the effectiveness of the treatment.

2. In the second part, we aim to present a case study to illustrate the options for staged surgical treatment in sudden hearing loss.

3. In the third part of our thesis, we compared the effectiveness of combination and systemic steroid treatment in a prospective randomised controlled trial and examined the factors influencing the hearing recovery.

III. Studies

1. A retrospective study of factors involved in the improvement of sudden hearing loss

Methods

Between 01/01/2015 and 31/12/2016, 149 patients were treated for sudden hearing loss at our clinic. We collected the ear history of the patients and their chronic diseases.

Audiograms measured before and 2 weeks and 6 months after treatment were analysed.

Based on pure-tone threshold measurement, the affected frequencies and the degree of hearing loss were investigated and the patients were grouped according to the degree of absolute (hearing loss in the affected ear) and relative hearing loss (compared to the opposite ear). We also assessed the effectiveness of the therapy based on the affected frequencies.

Furthermore, patients were divided based on the degree of hearing recovery.

Results

During the two-year period, 149 patients were treated, of whom 105 met the internationally accepted ISSNHL criteria. Our patients received a wide range of treatments. Intravenous steroid treatment was given to 145 (98%), vinpocetine to 111 (74.5%), thioctic acid to 138 (92.6%), vitamins B1 and B6 to 136 and 135 (91%), and beta-histine to 117 (78.5%) patients. More than one third of patients, who met the ISSNHL criteria (37/35.2%) presented with unservicable hearing.. Almost the same number of patients had severe hearing loss

(34/32.4%). Relative hearing loss more than 60 dB could be measured in one third of cases (35).

Looking at the results of hearing improvement, the group with significant improvement (>30 dB) included 35.2% of patients (n=37), while slight improvement (between 0-10 dB) occurred in 22.9% of the treated individuals (24 people). Hearing recovery was negatively influenced by hearing loss in high frequencies ($p = 0.012$), older age ($p = 0.005$), cardiovascular co-morbidity ($p = 0.009$), presence of diabetes ($p = 0.029$) and less initial hearing loss ($p < 0.001$). The time period between the onset of the symptoms and the start of treatment did not influence the improvement.

2. Stepwise surgical therapy

In November 2017, a 73 year-old patient was presented with a complete right-sided hearing loss started 4 days earlier. On examination, other causes of hearing loss were excluded. After an ineffective combined steroid treatment, an explorative tympanotomy was performed, and the inner ear windows and the fissula ante fenestram area were obliterated. Since no hearing improvement could be detected after the procedure, cochlear implantation was offered. The implantation was successfully performed through the round window, despite the previous exploration and obliteration. 18 months after implantation, free field hearing measurement showed an average hearing loss of 30.625 dB (on average at 500 Hz, 1,2,4 kHz) with a speech understanding of 90% at 50 dB.

3. Comparison of the efficacy of systemic and combination steroid treatment and prospective assessment of prognostic factors in sudden hearing loss

Methods

This part study was conducted between April 2017 and December 2021. The prospective analysis included patients with a sensorineural hearing loss on one ear, developed within 72 hours and affected at least 30 dB at 3 consecutive frequencies compared to the opposite ear. Patients aged 18 years or older presenting with complaints within 30 days were included. Patients with confirmed underlying cause of sudden hearing loss (non-idiopathic cases) were excluded, or lack of pre-treatment audiogram was available, or inability of hearing comparison due to hearing loss in the contralateral ear (and no previous audiogram available) was possible. We also excluded those in whom condition contraindicated corticosteroid treatment (e.g. uncontrolled diabetes, hypertension). In addition, we subsequently excluded patients who underwent explorative tympanotomy.

We assessed our patients' complaints and co-morbidities using a questionnaire. All patients underwent an ear, nose and throat examination and an audio-vestibular examination. Pure tone audiometry, speech audiometry, electronystagmography, multifrequency tympanometry and auditory brainstem response (ABR) were performed in all patients. If the ABR examination assumed retrocochlear lesion or no recordable waves were present, an inner ear MR scan was requested.

Our patients were randomly divided into two groups. Patients receiving systemic monotherapy (SS) received 250 mg intravenous methylprednisolone for the first 3 days, followed

by 125 mg for two days, which was reduced to 8 mg per os in half doses every two days. For patients receiving combination steroid treatment (CT), systemic treatment was supplemented with daily intratympanic dexamethasone (40mg/5 ml).

Pure-tone threshold measurements were used to assess the effectiveness of the therapy and to investigate the impact of prognostic factors. Regarding the effectiveness of hearing loss, we used the Siegel's, Kanzaki's and modified Siegel's grading to eliminate the potential bias of grading differences. In addition, we also compared the mean of the hearing thresholds measured at 4 different frequencies (5000; 1000; 2000; 4000 kHz) (PTA4 improvement).

Results

During the study period, 214 patients were hospitalised at our clinic due to sudden onset hearing loss. 99 patients were randomised and 21 patients were excluded from our study due to subsequent exploratory tympanotomy. Data from 78 patients were analysed. Combination therapy was used in 35 cases and systemic monotherapy in 43 cases. No differences in demographic data between the two groups were found, so their bias could be excluded.

In our study, we used the audiogram results after the longest follow-up time for each patient. The mean follow-up time was 104.62 (\pm 85.1) days in the CT group and 81.83 (\pm 64.2) days in the SS group ($p=0.248$).

The primary objective of our study was to compare the effectiveness of systemic steroid monotherapy (SS) and combination therapy (CT). According to Siegel's classification, the majority of our patients were in the no improvement group (IV), whereas complete improvement group (group I) included

20% and 14% of patients of the CT and SS group retrospectively. No difference was found according to Siegel classification ($p=0.604$). According to the modified Siegel classification, the majority of our patients were in the "no hearing improvement" group, but no difference was found between the two treatment groups ($p=0.524$). According to Kanzaki's classification, no difference was found between the two treatment groups ($p=0.720$). We examined the degree of improvement in both treatment groups based on PTA4, but no significant difference was seen between the two treatment groups ($p=0.251$). Hearing improvement of at least 10 dB was achieved in 58.1% of patients in the SS group, compared to 60% in the CT group. A minimum improvement of 15 dB was achieved with 57.1% in both the SS and CT groups.

Factors affecting hearing loss

For patients with cardiovascular risk factors (16 in the CT group and 22 in the SS group), we found a significant difference in the distribution of hearing improvement between the groups. Associated vertigo (10 in CT group, 9 in SS group) also negatively affected hearing improvement. The degree of hearing loss at the start of treatment also significantly affected hearing improvement. Those with an initial hearing loss greater than 70 dB were placed in the better modified Siegel groups, meaning that a greater degree of initial hearing loss was present, the greater rate of hearing improvement was achieved. No significant differences were found for the other tested risk factors.

IV. Discussion

Even though several papers are published about sudden hearing loss, many questions remain unanswered regarding the therapy, pathophysiology and factors influencing hearing improvement in ISSNHL, partly due to poorly designed studies. The most accepted and widely used treatment is based on corticosteroids. They are used because of their proven effect in other inner ear diseases (Ménière's, acoustic trauma, ototoxicity). Its use in ISSNHL dates back to by Wilson's study in 1980. However, subsequent studies have not been able to confirm their effectiveness, but they are considered as a "gold standard" without strong evidence. The route of administration can be systemic or topical, with the frequency, dose or type of steroid varying from centre to centre. In Hungary, high-dose intravenous treatment according to the German recommendation has become common and was used in our own studies. Systemic steroid treatment is also associated with possible short-term side effects (peptic ulcer, hyperglycaemia, mood changes). These side effects can be avoided by intratympanic (IT) drug administration and higher drug concentration can be achieved in the inner ear, in which case the choice of the highest available concentration is recommended. Combining the two routes of drug delivery (combination therapy) drug dose may achieve higher levels. Several meta-analyses have investigated the difference between steroid treatments, although no significant difference could be detected or minimal efficacy of combined treatment was reported. Our prospective study was the first RCT to investigate the efficacy of high-dose systemic steroid monotherapy compared with combination treatment. Based on our analysis, we found no differences between the two groups according to any of the grading systems examined.

However, these empirical treatments are widely used in national and international practice. Further drug treatments (vasodilator, antiviral, antioxidant) based on various suspected aetiologies are not recommended. Our retrospective study showed that our therapeutic plan was not consistently applied in our clinic in the past.

When of sudden hearing loss thought to be idiopathic, an unrecognised perilymphatic fistula may be present in some cases. The diagnosis of PLF is difficult due to the absence of specific symptoms and diagnostic signs. However, there is no specific localisation of fistula formation, with rupture of the membrane of the oval and round window and the fissula ante fenestram being the most common predilection sites. In the event of failure of conservative treatment, surgical exploration of the middle ear (exploratory tympanotomy) and covering of the inner ear windows, regardless of the surgical findings, may be offered. The residual deafness after unsuccessful treatment can lead to a reduction in quality of life. In such cases, the best hearing rehabilitation is achieved by cochlear implantation. In our case presentation, we were among the first to show that cochlear implantation through a round window can be successfully performed even after window obliteration.

In sudden hearing loss, not only the choice of therapeutic protocol, but also the identification of the factors influencing hearing improvement is of paramount importance. Previous studies have mainly investigated the impact of cardiovascular disease.

People with cardiovascular disease are more likely to develop ISSNHL and have a worse prognosis for the course of the disease. In Hungary, the impact of cardiovascular

comorbidities is even more important, because of their high prevalence and high mortality rates. In our retrospective study 59.1% of patients and in our prospective study 48.7% of patients had some cardiovascular comorbidities and in both analyses we found a negative impact on hearing recovery. Diabetes mellitus may also influence hearing improvement on a vascular basis, but its role as a risk factor is poorly understood. In our retrospective study, we found it to be a negatively influencing factor, and in our prospective study, we could not detect a diabetes-related association. The role of other factors, presumably also on a vascular basis, such as older age, associated dizziness and tinnitus, is obvious in the literature. We found older age to be a negative influencing factor in our retrospective study and dizziness to be a negative influencing factor in our prospective study. Because of the reversibility of sudden hearing loss, most clinicians recommend early treatment. However, a clear correlation between the time of initiation of treatment and hearing improvement has not been demonstrated in previous studies or in our own studies.

V. Summary

1. In our retrospective study, we reviewed the effectiveness of empirical therapy in our clinic and influencing factors on a large number of patients. Our results highlight the negative predictive role of older age, hypertension and diabetes.

2. In patients with ISSNHL, oval and round windows and obliteration of the FAF may be effective treatment options in the event of unsuccessful conservative treatment. In cases of single sided deafness, only cochlear implantation can achieve

true binaural hearing. We have not encountered any difficulties in inserting the cochlear implant electrode after obliteration, thus we can conclude that cochlear implantation can be performed successfully in cases of single sided deafness after obliteration of the round window.

3. As far as of our knowledge, our prospective, randomised trial is the first to compare the efficacy of high-dose systemic to combination steroid therapy. Our results suggest that associated symptoms and disorders such as cardiovascular comorbidity, dizziness and pre-treatment hearing loss above 70 dB have a greater impact on hearing improvement than the use of added intratympanic steroid.

VI. Publications

4.1. Publications on the subject of the thesis

Analysis of prognostic factors influencing the effectiveness of treatment insudden sensorineural hearing loss

Márton Kovács, János Uzsaly, Gréta Bodzai, Kinga Harmat, Adrienn Németh, Imre Gerlinger, Péter Bakó. Orv Hetil. 2019 May;160(18):687-693. IF:0,497; Q3

Staged surgical management of idiopathic sudden sensorineural hearing loss refractory to medical treatment

Márton Kovács, János Uzsaly, Gréta Bodzai, Imre Gerlinger, István Szanyi, Péter Bakó Orv Hetil. 2021; 162(51): 2055–2060. IF: 0,707; Q3

Efficacy of high dose systemic versus combined (systemic and intratympanic) corticosteroid therapy in idiopathic sudden sensorineural hearing loss: A prospective randomized trial and risk factor analysis

Márton Kovács, János Uzsaly, Gréta Bodzai, István Pap, Bálint Lippai, Tímea Dergez, Adrienne Németh, Imre Gerlinger, István Szanyi, Péter Bakó *Am J Otolaryngol*, 2024 Jan-Feb;45(1):104099. IF: 2,5; Q1

4.2. Other publications

First experiences with Cochlear Implant Function Index (CIFI) in Hungary

Gréta Bodzai, Márton Kovács, János Uzsaly, Kinga Harmat, Adrienn Németh, Alexandros Koukkoullis, Imre Gerlinger, Péter Bakó. *Orv Hetil.* 2019 Aug;160(33):1296-1303. doi: 10.1556/650.2019.31453. IF: 0,497; Q3

Is the bispectral index monitoring protective against postoperative cognitive decline? A systematic review with meta-analysis

Tímea Bocskai, Márton Kovács, Zsolt Szakács, Noémi Gede, Péter Hegyi, Gábor Varga, István Pap, István Tóth, Péter Révész, István Szanyi, Adrienne Németh, Imre Gerlinger, Kázmér Karádi,

László Lujber. PLOS ONE 2020 febr; doi: 10.1371/journal.pone.0229018. IF:3,2; Q1

The first direct acoustic middle-ear implantation in Hungary
János Uzsaly, Imre Gerlinger, Gréta Bodzai, Márton Kovács,
Péter Bakó. Orv Hetil. 2020 Jun;161(24):1015-1019.doi:
10.1556/650.2020.31735. IF:0,497; Q3

Third window syndrome – classification, diagnosis, therapy
Péter Kalinics, Imre Gerlinger, Péter Révész, Péter Bakó, Ildikó
Végh, Márton Kovács, Attila Fehér Orv Hetil. 2020 Nov
15;161(46):1944-1952. doi: 10.1556/650.2020.31842.
IF:0,497; Q3

Subtotal Petrossectomy and Cochlear Implantation in
Children With Chronic Suppurative Otitis Media: A Single
Institutional Experience
Péter Bakó, Márton Kovács, János Uzsaly, András Burián, Gréta
Bodzai, Adrienne Németh, Arnold Tóth, István Szanyi, Imre
Gerlinger. J Audiol Otol. 2022 Oct;26(4):214-222 IF:1,1; Q3

Tág aquaeductus vestibuli okozta harmadikablak- szindróma
komplex sebészeti ellátása

Szabó Éva, Kovács Márton, Németh Adrienne, Gerlinger
Imre, Szanyi István, Bakó Péter, Molnár Krisztián, Beke Zsolt
Fül-Orr-Gégegyógyászat, 2022, 68. évfolyam, 4. szám

Quality-of-life outcomes with endoscopic and microscopic type I tympanoplasty-a prospective cohort study

István Pap, Márton Kovács, Barbara Bölcsföldi, Zsolt Szakács, Imre Gerlinger, Bence Imreh, Alexandra Csongor, Vilmos Warta, István Szanyi. Eur Arch Otorhinolaryngol, 2023 Oct;280(10):4401-4408. IF: 2,6; Q1