The Treatment of Idiopathic Sudden Sensorineural Hearing Loss

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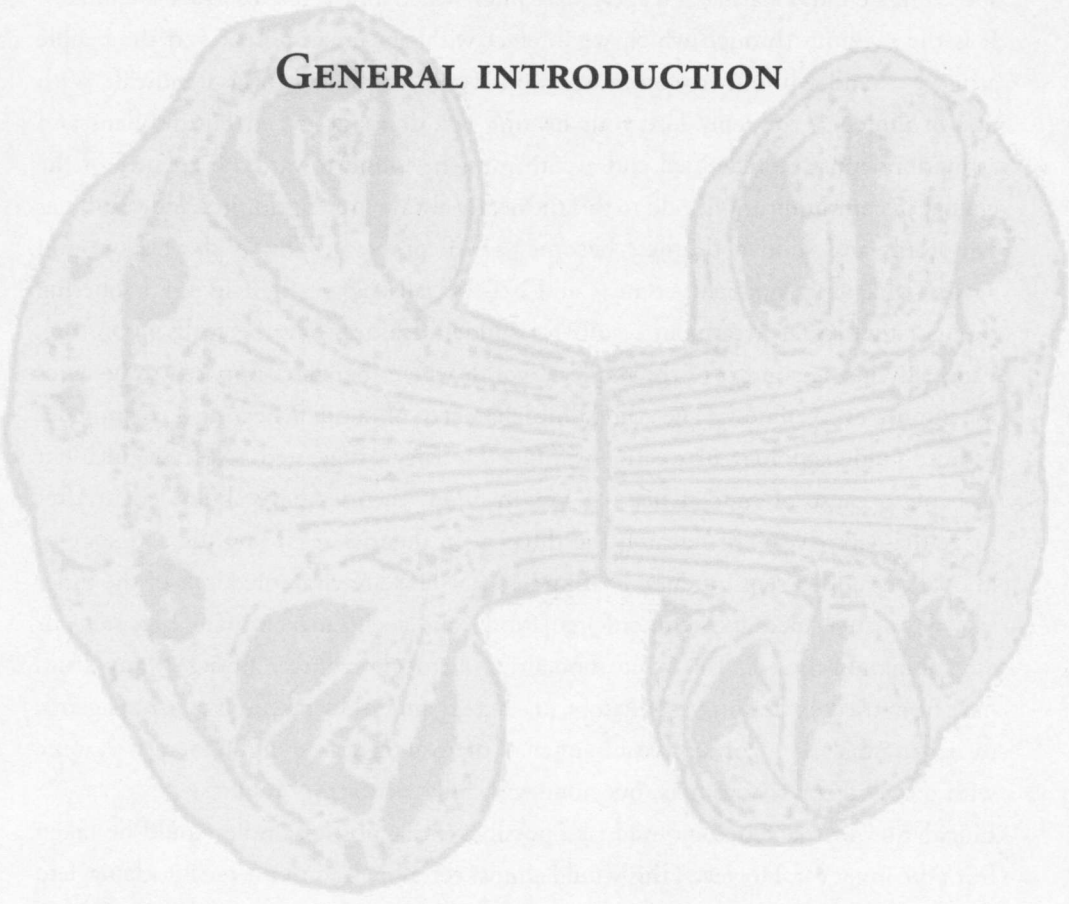
Chapter 1

General introduction



INTRODUCTION

Hearing is one of our most important senses. It is a prerequisite in the development of speech in a child. Hearing and speech are intertwined and define us as social animals. It is the medium through which we interact with our environment and the people around us and without it, communication would come to a near standstill. With this in mind, to suddenly lose your hearing is a dramatic event. Future plans and aspirations must be redefined and a path must be found towards acceptance of the change in communication. Add to this the nearly always present tinnitus and vestibular symptoms and sudden deafness becomes a real problem. This is the background against which many patients come to an ENT specialist asking for help. It is a sobering thought that so far, treatment results for sudden deafness have been disappointing. Especially in the context of the modern world, where there are supposed to be cures for almost every illness. The idiopathic character of sudden hearing loss provides little to guide aetiology or treatment. Since De Kleyn suggested a vascular incident as being a cause of sudden hearing loss in 1944, theories have abounded [1]. After more than sixty years of research the three main theories regarding the aetiology of idiopathic sudden sensorineural hearing loss (ISSHL) are viral infections of the inner ear [2, 2, 3], disturbances in the microcirculation [4] and cochlear membrane ruptures[5], or a combination thereof. Treatment modalities mirror these uncertainties. Many drugs have been tried, including vasodilators, plasma expanders, intravenous contrast agents, carbogen inhalation, corticosteroids, or all of them at once as 'shotgun therapy' [6], some with more success than others, but none with fully satisfactory results.

Elucidation of the aetiology might be possible if diagnostic samples could be taken from the inner ear. However, this would almost certainly lead to irreversible damage to the inner ear and permanent hearing loss for the patient. The natural history of ISSHL shows some spontaneous hearing recovery in 45-65% of patients, although few recover completely [2]. This makes diagnostic sampling ethically unfeasible. A second problem is that the low incidence of ISSHL impedes large clinical studies which eventually can lead us to optimal treatment results.

This thesis builds upon the results described in the thesis by R.J. Stokroos, entitled Idiopathic Sudden Sensorineural Hearing Loss (1997) [7]. In this thesis a literature survey of etiology and therapy of ISSHL provides the basis for the theory that a subclinical viral labyrinthitis plays an important part in the pathophysiology of ISSHL. Two animal models are presented in which the emphasis lies on a Herpes simplex virus

type 1 (HSV-1) labyrinthitis. In one study the histopathological effects are compared to the histopathological findings in ISSHL, in the other study the efficacy of aciclovir and prednisone are evaluated as a treatment in HSV-1 labyrinthitis. A Gadolinium enhanced MRI can be used to identify a (sub)clinical labyrinthitis, but only in the very first phase of the labyrinthitis. In the last chapter, a prospective, randomized, double-blind placebo-controlled clinical study is presented where 44 patients with ISSHL receive prednisone with double-blind aciclovir or placebo. No beneficial effect of aciclovir as adjuvant to prednisone on hearing recovery could be proven. The thesis still left a number of questions unanswered. Was the theory wrong or were there methodological shortcomings? Are there more ways to treat this hypothesized (sub)clinical labyrinthitis? We have tried to address some of these remaining issues.

OUTLINE OF THE THESIS

The aim of this thesis is to systematically evaluate two therapies for ISSHL. Our hypothesis is that an immune reaction, probably virally induced, in the inner ear is responsible for the sudden hearing loss. Based on the knowledge that steroids exert a small but clinically relevant effect on hearing recovery, we feel it is unethical to withhold this treatment from patients. In our studies we compared the trial medication with a tapered course of prednisone of 7 days. All patients with sudden hearing loss underwent a diagnostic protocol which included a complete history and physical examination, audiological and vestibular tests, magnetic resonance imaging of the temporal bone and cerebellopontine angle, and laboratory workup.

Laboratory investigations were aimed at excluding the presence of an infectious, inflammatory autoimmune process or coagulopathy. An extensive serological evaluation for HSV, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, mumps, measles, influenza, parainfluenza, rubella, chlamydia and syphilis was performed on paired blood samples and a nasopharyngeal swab or aspirate. Consulting specialists for ophthalmology and internal medicine were asked to exclude Cogan's syndrome and systemic disease, respectively. After diagnostic samples were taken, a provisional diagnosis of ISSHL was made and treatment was started. In cases where a cause of the sudden hearing loss was identified later, patients were excluded from this study.

Chapter 2

Chapter 2 is a literature review of the aetiology and treatment of Idiopathic Sudden Sensorineural Hearing Loss (ISSHL).

Chapter 3

In chapter 3 we present a pilot study in which we investigated the inner ear and the cochlear nerve in fresh human tissue for the presence of herpes simplex virus, cytomegalovirus and varicella zoster virus using Polymerase Chain Reaction (PCR).

Chapter 4

Presents the results of a prospective, randomized, double-blind clinical trial comparing a combination of prednisone and acyclovir with the standard prednisone dose in the treatment of ISSHL.

Chapter 5

A pilot study is presented which assesses the bioavailability of a new 50 mg dexamethasone tablet for use in high-dose pulse therapy. This was done in co-operation with the departments of Dermatology and Otorhinolaryngology within the University Medical Centre Groningen. Pulse therapy is an established treatment in pemphigus vulgaris where its aim is to reduce the daily dose of glucocorticoids, thus limiting the hazards of continuous long-term steroid intake.

Chapter 6

Once the safety and bioavailability of the new 50 mg dexamethasone tablet had been established it was used in a new trial. A prospective, randomized, double-blind, multi-center clinical trial was set up to evaluate this new therapy in the treatment of patients with ISSHL. It compared pulse therapy with standard dose prednisone.

Chapter 7

The results and conclusion of this thesis are summarized in English.

Chapter 8

Nederlandse samenvatting.

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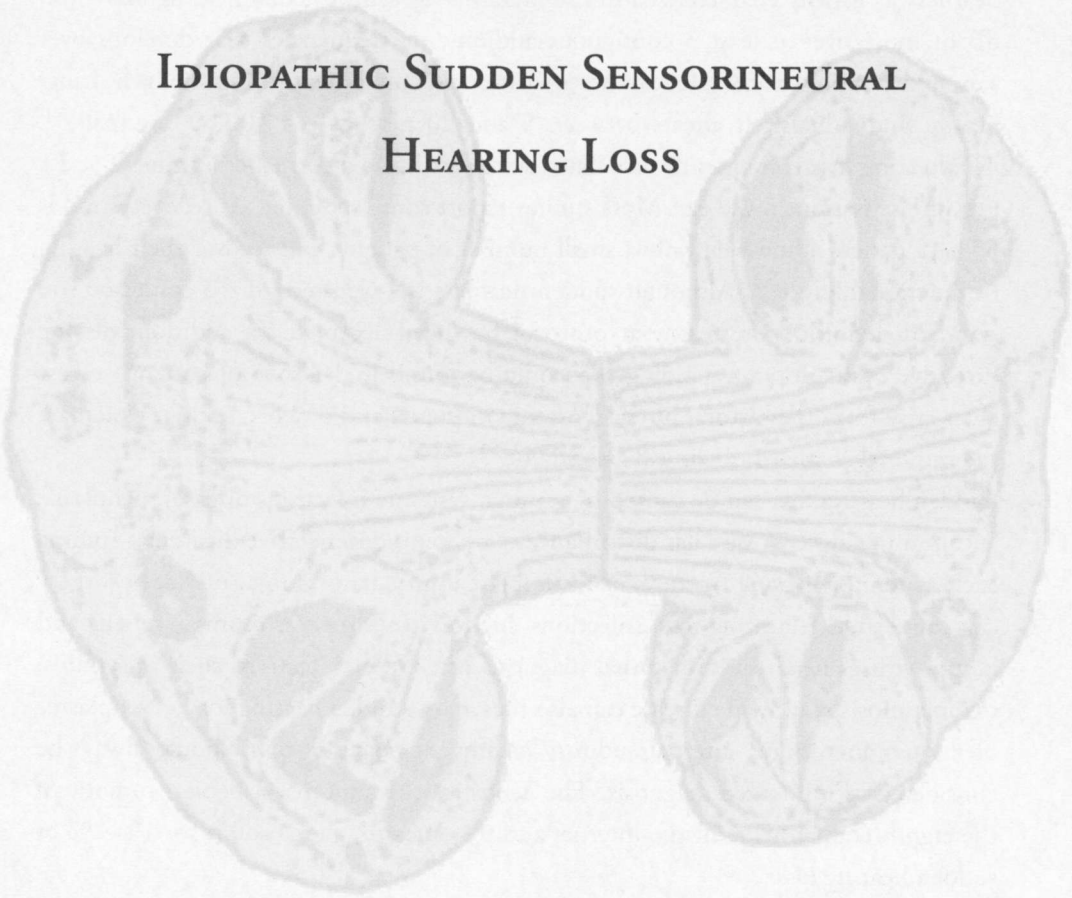
Chapter 2

Idiopathic Sudden Sensorineural Hearing Loss



INTRODUCTION

Idiopathic sudden sensorineural hearing loss (ISSHL), otherwise known as sudden deafness, is usually characterized in the literature by sensorineural hearing loss of 30 dB or more over at least 3 contiguous audiometric frequencies that develops over a period ranging from a few hours to three days in otherwise normally hearing, healthy individuals[1]. It affects between 5 and 20 persons per 100,000 annually [2]. The hearing loss is frequently associated with vestibular disturbances, tinnitus and a pressure sensation in the ear. Most studies report some spontaneous recovery in 45-65% of patients; however, only a small number of patients will recover their hearing to functional levels [3-6]. Although sudden deafness is a well-recognized condition, no standard definition or treatment protocol has been accepted. In addition, despite extensive evaluation, an aetiology can only be found in 10-15% of patients [7]. Few clues arise from the history, physical examination and audiometric testing, which are the minimal elements of clinical assessment.

Sudden hearing loss can be caused by trauma, systemic infectious diseases, neoplasia, autoimmune disease, vascular disturbances, and neurodegenerative disorders. Trauma such as temporal bone fracture, acoustic blast injury, barotrauma, or stapes surgery can cause sudden hearing loss. Infections due to viruses such as mumps, rubella and herpes viruses head the differential diagnosis list. Other infections such as syphilis, toxoplasmosis, and Lyme disease can also present as sudden hearing loss [8]. Neoplasms of the temporal bone, internal auditory meatus, or posterior fossa should always be considered as a possible diagnosis. The acoustic schwannoma, a benign tumour of the eighth cranial nerve in the internal auditory meatus, can account for 1%-2% of sudden hearing loss [9].

Table 1 lists known causes of sudden sensorineural hearing loss at this moment. These account for 10-15% of cases of sudden hearing loss.

In the remaining 85%-90% the cause is never identified and thus the term idiopathic is used; Idiopathic sudden sensorineural hearing loss.

The different pathophysiological theories of ISSHL are described in the next section. As can be expected with many different theories about aetiology, the treatment options of ISSHL are numerous. The most important of these will be discussed in the section "treatment". In the conclusion, the aetiology and treatment will be put in perspective and our hypotheses, upon which our clinical trials are based, will be presented.

AETIOLOGY

The aetiology of ISSHL remains obscure. Disturbances in the microcirculation [10], viral infections [11, 12], cochlear membrane ruptures [13, 14] and immunopathological [15] processes or a combination of such mechanisms [3] have all been hypothesized as causes of ISSHL. The above mentioned causes will be discussed in more detail.

Disturbances in the microcirculation

The vascular theories of ISSHL describe a spectrum of supposed alterations at the capillary and microvascular level. They include embolism, bloodsludging, hypercoagulability, vasospasm, intracochlear hemorrhage, arteriosclerosis, systemic vascular disease and connective tissue disorders.

In many patients, the clinical picture of ISSHL is similar to that of other vascular diseases such as cerebral insult, myocardial infarction or retinal ischemia. The sudden incidence of the hearing loss strongly suggests a vascular insult.

Vascular disturbances can cause sudden hearing loss and it has been reported after open heart surgery [16] and unstable angina [17]. Hypercoagulability (an increased tendency of blood to clot) can also cause sudden hearing loss. Intracochlear hemorrhage can lead to sudden hearing loss and has been described for diseases such as Waldenstrom's macroglobulineamia, leukaemia, and carcinomatosis [18].

In animal experiments cochlear microcirculation is sensitive to changes and even limited impairment of perfusion leads to immediate loss of function of the organ of Corti [19]. The labyrinthic artery, a functional end artery, supplies the vestibulocochlear artery and the spiralis modiolic artery. These in turn supply the cochlea and the vestibular organ as an end organ. Shunting from the periphery cannot compensate for disturbances of regional blood flow in the inner ear.

Fisch et al. [20], using a polarographic method, measured the oxygen tension in the perilymph, first in cats and later in humans. They applied this technique to patients with ISSHL and discovered that the perilymphatic oxygen tension was decreased by 30% in patients with ISSHL versus normal subjects and who also responded to carbogen inhalation (a means of increasing perilymphatic oxygenation [21]. In patients with slowly progressive hearing loss normal values of perilymphatic oxygenation were found and a low response to carbogen inhalation. They conclude that there was a strong vascular component to ISSHL. In a prospective randomized study they found that carbogen inhalation yielded significantly better results that intravenous infusion

of papaverine and low molecular dextran. They recommend carbogen inhalation as an effective non-invasive treatment for ISSHL [21].When 16 cases of ISSHL were compared to 32 matched controls, Ciuffetti et al. [22] found disturbances in microcirculatory blood flow measured by whole blood filterability and felt that this was linked to ISSHL in humans. Whether vascular risk factors indeed play a role in ISSHL is still unclear [23, 24]. Ohinata et al. studied blood viscosity and plasma viscosity and found significant higher viscosity in patients with sudden deafness compared to a control group[25]. Chronic sensorineural hearing loss has been associated with whole-blood viscosity [26] and raised serum cholesterol has been associated with the development of noise-induced hearing loss [27, 28]. Therefore, rheologic factors can play a role in (sudden) hearing loss. Fibrinogen is a large glycoprotein (340 kDa) that defines rheological properties of whole blood by increasing plasma viscosity and inducing aggregation of erythrocytes, thrombocytes and leucocytes. Raised fibrinogen is also thought to be a possible cause of ISSHL [29].

In vascular disease such as cerebral stroke, infarction or myocardial infarction, fibrinogen is a well-established risk factor [30]. In a study by Marcucci et al. [31] independent thrombophilic risk factors for ISSHL were identified. Their preliminary data suggests that hypercholesterolemia, hyperhomocysteinemia, elevated plasminogin activator inhibitor-1 and anticardiolipin antibodies are associated with ISSHL, and indirectly support the hypothesis of a vascular component in the pathogenesis of ISSHL.
Running counter to this theory is that experimentally induced hearing losses of vascular origin are predominantly irreversible, which contrasts with the natural history of ISSHL. Fibrosis and ossification of the cochlea reported after experimentally produced impaired blood supply or by known infarction of the cochlea were not found in post-mortem temporal bone examination or by imaging techniques in patients with ISSHL [32-34]. In a recent histopathological study of temporal bones by Merchant et al [15] they found the hallmark of a vascular insult to the cochlea, deposition of connective tissue and bone, in one of their 17 studied ears, and in a literature search was reported twice in 27 ears. They conclude that vascular occlusion as an aetiologic event in sudden deafness is rare.

Viral aetiology

Viral infections such as measles, mumps, rubella, CMV, Epstein Barr virus and herpes can cause viral cochleitis with sudden hearing loss as a result. Moreover, the

histories of around 30% of sudden deafness cases include infections of the upper respiratory tract [11]. Serologic studies have shown a significantly increased rate of viral sero-conversion in patients with ISSHL [35, 36]. Post-mortem cochlear histopathological changes seen in patients with ISSHL, including atrophy of the organ of Corti and tectorial membrane, closely resemble changes seen after viral labyrinthitis [32]. A herpetic viral labyrinthitis, in particular, provided a histological pattern of cochlear damage that matched that of patients who had had ISSHL [37]. Magnetic resonance imaging studies of the inner ear have shown labyrinth enhancement in patients with sudden deafness [38]. Wilson [39] suggested that herpes virus may be implicated in the aetiology of ISSHL by one of several mechanisms, including labyrinthitis secondary to viraemia, labyrinthitis or neuritis secondary to meningitis, cranial neuropathy, reactivation of a latent ganglion cell infection, or alteration of the immune system. Herpes simplex virus (HSV-1) has been demonstrated as remaining latent in healthy human spiral ganglia [40]. Experimentally induced HSV-1 labyrinthitis resulted in sudden hearing loss in guinea pigs and the cochlear histopathological findings closely resembled those seen in ISSHL [41]. However, the evidence is circumstantial. Merchant et al [15] find that histopathological evidence is lacking. They conclude that evidence of direct viral invasion or infection, such as isolation of a virus from the labyrinth, demonstration of typical cytopathological abnormalities, demonstration of viral particles by electron microscopy, or identification of specific viral antigens, has yet to be found.

Cochlear membrane ruptures

A perilymph fistula is defined as an abnormal patency between the inner and middle ear that allows flow of perilymph. A well accepted mechanism for fistula production is blunt, penetrating or barometric trauma.

A sudden increase in pressure can rupture the inner ear membrane(s). In an implosive event, elevated cerebrospinal fluid pressure by valsalva is thought to be transmitted via subarachnoid connections to the inner ear [42].

The symptoms of a perilymph fistula include aural pressure, disequilibrium exacerbated by exertion, and both conductive and perceptive hearing loss. Once rupture has occurred, hearing loss is thought to result from either chemical or mechanical alterations in the different compartments in the cochlea where the sensory organs for hearing are located. Histopathological data is conflicting. Few cases of sudden hearing loss

show evidence of rupture, and congenital patencies are seen in normal patients [33, 43]. Valk et al. created an endolymphatic hydrops by repetitive microinjections of 0.5 µL of artificial endolymph at a rate of 50 nl/s in an experimental setting in guinea pigs while measuring cochlear function as measured by distortion product otoacoustic emissions [44].

A 'catastrophe' occurred in the inner ear when 2.5-3.5 µL of artificial endolymph was injected, corresponding to 53-74% of the original volume. A rupture of Reissner's membrane was then found, most often in the apical turn of the cochlea. This rupture had only minor effects on the endocochlear potential. The spontaneous occurrence of ISSHL without a history of (baro) trauma, even during sleep, makes a membrane rupture unlikely.

Immunopathological processes

Sudden deafness can be the first manifestation of systemic autoimmune diseases such as Cogan's syndrome, Polyarteritis nodosa or relapsing polychondritis. The hearing loss in autoimmune disease is usually bilateral and rapidly progressive, but it can also occur as a sudden hearing loss. McCabe [45] reported in 1979 that a group of patients with sudden deafness responded well to immunosuppressive treatment with steroids and cyclophosphamide and described autoimmune inner ear disease as a clinical entity. Harris [46] demonstrated the inner ear's capacity to respond to local antigenic challenge and produce systemic immunization. Since then (1983) there has been considerable investigation into the relationship between the immune system and sensorineural hearing loss. Ottaviani et al. [47] and Toubi et al. [48] have both found evidence of circulating antibodies in relation to sudden deafness, ranging from anti-epithelial auto antibodies, immune complexes, and production of auto antibodies to inner ear proteins, production of anticardiolipin antibodies and to cellular immune defects. Toubi et al.[48] found a lack of persistence of anticardiolipin antibodies in as many as half of their patients which strongly suggested a transient phenomenon (e.g. viral infection) that triggered anticardiolipin antibody activity. Liao et al. [49] also suggest a virally mediated immune response causing the cochlear damage, and thus the hearing loss, as a possible pathophysiology for ISSHL. The immune response can provoke the degeneration of the organ of Corti, stria vascularis and spiral ganglion [50].

The immune reaction in the inner ear as the cause of ISSHL is supported by a study by Wilson et al. [51] and Moskowitz et al. [52] in which corticosteroids had a limited but significantly better restorative effect on hearing than the placebo. It is possible that

immune-mediated inner ear disease accounts for at least some of the cases of steroid-responsive ISSHL [53, 54]. Because markers for autoimmune inner ear disease have been identified, further work is needed to evaluate whether autoimmune disease plays a role in ISSHL[55, 56].

TREATMENT

Since the aetiology of ISSHL is still unknown most studies have involved a multimodal treatment strategy based on the assumption that one or more medication or techniques will reverse the hearing loss.

This empiric strategy has the advantage that at least one effective treatment may be provided to the patient, but has drawbacks of obscuring the effect of any single treatment, as well as exposing the patient to side effects of a number of different treatments. Evaluation of treatments has further been hampered by the low incidence of ISSHL and the tendency for spontaneous hearing recovery.

The most widely used treatments for ISSHL are vasodilators, rheological/vasoactive substances, anti-inflammatory medication, antiviral medication, and hyperbaric oxygen. Other drugs such as intravenous contrast agents, Calcium channel blockers, and magnesium have all been assessed in clinical studies. These treatment strategies will be discussed in more detail below.

Vascular treatments

It has been frequently postulated that ISSHL has a vascular origin and "vascular" treatments have been widely used. Vasodilators increase the calibre of the blood vessels and thus improve blood flow whereas vasoactive/rheological substances increase flow through blood vessels by other mechanisms such as altering the viscosity of blood.

Numerous treatments have been proposed to improve cochlear blood flow (CBF) by either vasodilatation (histamine [5], papaverine [21], carbogen inhalation [57]) or by decreasing blood viscosity (defribinogenation therapy [58] dextran [59], pentoxifillin [60] and LDL apheresis [10, 61].

Intracranial blood flow possesses a strong auto-regulation that will, in most cases, override the effect of vasodilators [62]. Therefore, vasoactive treatments may in fact decrease CBF. Ohlsen et al. [63] studied the topical and systemic effects of hydralazine, sodium nitroprusside, papaverine, nicotinic acid, verapamil and histamine in an

animal model. Hydralazine, histamine and nitroprusside administered topically increased CBF. The effect systemically administered vasodilators had on CBF was highly variable and at times CBF was actually decreased. As a consequence, results with vasoactive therapies are mixed. Kronenberg et al. [59] could not prove the effectiveness of dextran in a double-blind randomized placebo-controlled clinical study. Dextran and pentoxifillin gave results no better than placebo or spontaneous recovery [60]. Rahko and Kotti [57] compared carbogen inhalation and intravenous heparin but could not prove one superior to the other. The patients in the latter study, however, were not selected and the study was not placebo controlled.

Other studies do report successes. In a large study by Suckfüll et al. [10] speech perception was significantly better after acute reduction of plasma fibrinogen and serum LDL using apheresis as compared to their standard treatment of prednisone, hydroxyethyl starch and pentoxifylline. The overall pure tone thresholds, however, were slightly but not significantly better in the apheresis group.

In an uncontrolled pilot study by Ullrich et al. [61], 80% of sudden-onset hearing loss patients showed complete recovery in a four-week period. They were treated with specific fibrinogen apheresis. Their definition of ISSHL was not very strict. What both studies did prove was that apheresis significantly reduces fibrinogen.

Anti-inflammatory treatment

Steroids are anti-inflammatory drugs which are used to suppress inflammatory changes such as cellular infiltration and tissue oedema, limitations of which increase tissue perfusion. The specific action of steroids is unknown but they may be beneficial in infectious, inflammatory and immune-mediated conditions. Corticosteroids are widely used in the treatment of ISSHL. In spite of their wide clinical use, few randomized, double-blinded clinical trials are available in the treatment of ISSHL.

Nevertheless, steroid therapy is among the few treatment methods in ISSHL to have been subjected to single modality, randomized prospective studies demonstrating effectiveness.

Wilson et al. [51] designed a prospective, randomized, double-blind study evaluating steroids in the treatment of ISSHL. Sixty-seven patients were enrolled in the study: 33 received steroids and 34 received a placebo. Fifty-two patients refused treatment and functioned as an untreated control group. After matching for age and vertigo, the steroid group achieved significantly better hearing ($p = 0.017$). Subsequently, Wilson reported a 78% recovery rate for patients with moderate (35-90 dB) hearing loss

versus 38% for the placebo [64]. The authors conclude that given the nature of the hearing loss and it's susceptibility to improvement with steroid therapy lend support to the hypothesis that viral cochleitis is the primary cause of ISSHL.

Moskowitz et al. [52] conducted a prospective randomized trial , fashioned after the Wilson study, on 36 patients with ISSHL. It confirms the findings in the Wilson study. Twenty-seven patients received dexamethasone, whereas nine patients received a placebo. The steroid group recovered to 89% functional hearing levels compared with the placebo recovery rate of 44%. This difference was statistically significant ($0.005 < p < 0.01$). Unfortunately the study was not double-blinded, which decreased it's internal validity.

Fetterman et al. [5] retrospectively reviewed the charts of 837 patients with sudden sensorineural hearing loss to evaluate the prognostic value of specific clinical parameters and the effectiveness of steroid and vasodilator treatments. Treatment response was defined by the patient's subjective response and audiological criteria. Patients who were treated with steroids, vasodilators or both were more likely to improve. However, the best rate of recovery was 62.9% in the steroid/vasodilator group. Patients who improved had worse initial pure tone averages than did those who did not improve. In addition, younger patients, those with poorer initial speech discrimination scores, worse initial thresholds at 4000 Hz and a greater number of treatments were more likely to improve.

The mechanism of steroid action in the inner ear remains open to speculation; they increase the microvascular blood flow in the cochlea, reduce the inflammation and the onset of endolymfatic hydrops [65]. Rarey and Curtis [66] reported the presence of glucocorticoid receptors in the spiral ligament and in other parts of the inner ear.

Hearing improvement following administration of glucocorticoids might be due to (1) their anti-inflammatory effect; (2) increasing stria vascularis synthesis of Na+-K+ adenosine triphosphatase, which decreases vascular permeability (particularly to circulating immune mediators); and (3) increasing cochlear expression of aquaporin 1 and 3 [67].

In 2006 the Cochrane collaboration published it's review for "Steroids for idiopathic sudden sensorineural hearing loss" [68]. They found only two randomized controlled trials addressing the effectiveness and safety profile of ISSHL which met their minimum criteria. The included studies were of poor quality and contained relatively low number of patients. Of the 516 abstracts retrieved from the search, 486 articles were excluded

as they did not focus on ISSHL; the treatment effect was not targeted primarily on steroids or the steroids were used as control for the comparison of other treatments. Of the remaining 30 studies only two were included in the review. The rest were excluded as they were non-randomised and non-controlled studies. The two studies were by Cinamon et al.[6] and Wilson et al. [51]. In the Cinamon study no difference in treatment was found between placebo and steroids whereas in the Wilson study a positive effect of steroids was found. The Cochrane collaboration concludes that there is no good evidence to suggest the effectiveness or the lack of effectiveness of steroids in the treatment of ISSHL. The incidence of side effects and the cost of steroid treatment in ISSHL still remain to be determined. They acknowledge however, that the low incidence and high spontaneous recovery significantly impedes methodological sound studies with large enough patients groups to accurately determine the effectiveness of steroids.

Antiviral treatment

Hughes et al. [69] have suggested the use of aciclovir in the treatment regimen for ISSHL but Stokroos et al [70]. and Tucci et al. [71] could not prove the effectiveness of aciclovir or valaciclovir as adjuvant therapy to prednisone in the treatment of ISSHL. Interferon (IFN) has been reported as being beneficial in the treatment of ISSHL. Kanemaru et al. [72] administered IFN-alpha, low-molecular-weight dextran and steroids to 42 patients with ISSHL. Complete recovery was found in 27 patients (64.3%). This is comparable to the spontaneous recovery rates of 45-65% as reported by Mattox and Simmons [11]. However, IFN has recently been reported as potentially ototoxic and had serious side effects [73]. Therefore the efficacy of IFN in the treatment of ISSHL is still unproven.

Intratympanic steroid treatment

Intratympanic therapy can be defined as delivering a medication to the round window membrane with uptake into the inner ear. Advantages of this technique are (1) the diseased ear is treated directly without affecting the entire body, (2) a higher concentration of medication can be obtained, (3) systemic side effects of the drug are prevented [74]. It is based on the findings from animal studies that demonstrate steroid uptake through the round window membrane into the cochlea when the drug is instilled into the middle ear [75]. There are several means of delivering steroids to the round window membrane: single intratympanic (IT) injections, repeated IT injections

or insertion of sustained release vehicles through the tympanic membrane.

IT offers the ability to achieve higher inner ear drug concentrations, freedom from adverse systemic effects (of steroids) and can be used in patients for whom systemic steroids are contraindicated.

The procedure, however, is not risk free. Known adverse effects include tympanic membrane perforation, increased dizziness and possible compromise of residual hearing [76].

Intratympanic pharmacotherapy was first used by Schuknecht in 1956 [77] when aminoglycosides were installed for the treatment of vertigo in Menière's Disease. Since that time, intratympanic applications of other agents have been used for various other inner ear disorders. These agents include corticosteroids, local anaesthetics, otoprotective drugs and other antibiotics [78].

There is now a large body of work demonstrating intratympanic steroid uptake through the round window membrane in animal models [79-81]. Nakashima et al. [82] recently visualized and followed intratympanically administered drugs into the inner ear with the use of intratympanic injections with diluted Gadolinium and a MRI-scan. Although much of the literature is focused on the application of intratympanic steroid therapy for the treatment of Menière's disease with intractable vertigo [83, 84], this treatment option is receiving broader indications. In particular, treatment of autoimmune inner ear disease, sudden hearing loss and tinnitus has been reviewed.

Slattery et al. [85] conducted an open-label clinical trial of intratympanic steroid injection for ISSHL in subjects who failed oral steroid therapy. Twenty subjects received 4 injections within a two-week period. Hearing, dizziness and tinnitus were evaluated. A total of 11 subjects (55%) clinically improved in either pure tone audiogram (PTA) or speech discrimination scores (SDS) at one month after treatment. One patient improved 26 dB, exceeding 50% of baseline by 9 dB, 5 subjects experienced a 10 dB improvement and a total of 7 subjects had a clinically significant improvement in SDS greater than 12%.

Herr et al. [86] also studied intratympanic steroid therapy in patients with sudden hearing loss as a salvage treatment. These patients were refractory to ten days of intravenous steroid, pentoxifylline and hydroxyethyl starch (HES) treatment. Forty consecutive patients participated in this prospective study. The patients were divided into three groups of hearing loss: (1) twenty-one patients with flat audiograms with a hearing loss of more than 30 dB but less than 80 dB, (2) ten patients with profound hearing loss of more than 100 dB and (3) nine patients with high frequency hearing loss.

In group 1, 33% patients recovered to within 10 dB of the hearing threshold of the unaffected ear, with no complete recoveries seen in groups 2 and 3. No improvement of more than 10 dB was found in 29% patients in group 1, 40% patients in group 2 and 56% patients in group 3.
They conclude that intratympanic treatment of dexamethasone/hyaluronic acid significantly improved hearing in a subgroup of patients. However, there were no control groups (placebo), blinding or comparison between groups. Furthermore, the dividing of an already small patient population into three subgroups may not have been wise.
In a review by Doyle et al. in 2004 [76] of the period 1996 to 2003, they found 5 studies that were all retrospective case series or uncontrolled prospective cohort studies in which intratympanic steroids had been administered for sudden deafness. In 2 studies even patients with various other inner ear maladies were included. The intratympanic treatment was found to be most promising as salvage therapy after a failed course of steroids. However, the quality of the studies was insufficient to answer the question of the efficacy of the treatment.

It would seem that intratympanic steroid therapy as a salvage treatment in patients with ISSHL infractory to systemic steroid treatment is an option. It is not advised as a primary treatment option. The lack of quality of the available studies make it all the more urgent to start prospective randomized blind clinical trials before any definitive conclusions can be drawn.

Hyperbaric oxygen therapy

In 2005 the Cochrane collaboration published its review regarding hyperbaric oxygen therapy (HBOT) for idiopathic sudden sensorineural hearing loss and tinnitus [87]. It concluded that on the basis of the five selected studies there is limited evidence from methodologically poor studies that hyperbaric oxygen therapy improves hearing in patients with ISSHL who are treated within two weeks of their hearing loss. There is no evidence that any improvement is functionally important. They conclude that routine use of HBOT in ISSHL could not be justified.

Shotgun (combination) and miscellaneous therapy

The idea behind shotgun therapy is that treatments are given for several etiologies, hoping that one or more will work. Usually a combination of vasoactive treatments and steroids are given. Wilkins et al. [88] treated 109 patients with idiopathic sudden hearing loss with a regimen that included dextran, histamine, Hypaque (Winthrop Pharm), diuretics, steroids, vasodilators and carbogen inhalation. Thirty-three patients received the entire protocol and 76 patients received most, but not all, of the protocol drugs. There was no statistically significant difference in outcome between patients treated with the complete protocol and those who received only part of the protocol. Furthermore there was no difference between those patients receiving and not receiving treatment. These results suggest that this "shotgun" approach for treatment of sudden hearing loss offers no better outcome than is reported in the literature for spontaneous recovery.

Redleaf et al. [89] performed a retrospective chart analysis on 39 patients treated with a combination of diatrozide and dextran. Diatrozide (Hypaque), a triodobenzoic acid derivative, is thought to interact with the epithelium of stria vascularis and preserve generation of endocochlear potentials. All of the patients were treated for five to seven days with daily injections of diatrozide and dextran. Of these patients, 64% improved their pure tone averages, speech reception thresholds and speech discrimination levels while receiving treatment. They found no difference in recovery between patients treated within seven days and those treated more than seven days after onset of the sudden hearing loss. Because of the lack of control group no conclusions can be drawn, but there seemed to be some effect in a subpopulation for which intravenous contrast is efficacious. They suggest further trials with diatrozide and dextran. Emmett and Shea [90] also used a combination of carbogen, intravenous histamine, steroids, diuretics, low-salt diet and Hypaque to treat ISSHL. Again there was no control group of untreated patients. The results in this highly selective group treated within one month of onset, with no vertigo and incomplete hearing loss showed an 80% rate of recovery. No statistical conclusions could be drawn from this study.

Diatrizoate meglumine (Hypaque; Winthrop Pharm, New York, NY, U.S.A.[89, 90] and xanthinolnictone (Compalamine) [91] have also been used to treat ISSHL. Morimitzu[92] first reported the use of diatrizoate in ISSHL and subsequently compared the results of 60 treated patients with the results in the Japanese registry. He found statistically significant improvement (37% complete recovery) but the treated group did not have vertigo and no untreated control was used.

Calcium channel blockers have vasodilatory and spasmolytic action on cerebral vessels. Calcium channel blockers also lower intracellular calcium and can reduce the adenosine triphosphate use in the damaged cells, thus protecting hypoxic sensory cells. Studies in European literature show no significant benefit from the use of calcium channel blockers in the management of ISSHL [93].

In a prospective, randomized, double-blind placebo-controlled clinical trial, Nageris et al. [93] found that in 28 patients with ISSHL, magnesium as adjuvant to prednisone therapy improved the proportion of patients with hearing recovery as well as a significant mean improvement of hearing recovery. Magnesium is a critical cation in intracellular metabolism and energy production and consumption. It also serves as a cofactor in enzymatic processes involved in protein construction and aerobic phosphorylation. There is a close functional relationship between magnesium concentration and calcium metabolism.

Vitamins are believed to reduce free radicals that are toxic to sensory end-organs, such as the inner ear. Several vitamins in combination with vasodilator therapy have been used in the past. Studies of ginkgo biloba extract have shown no significant efficacy in the management of ISSHL [94].

Conclusion

ISSHL remains a baffling and controversial phenomenon. A universal definition would be an important step in creating a clear picture of this disease. The Cochrane collaboration uses a definition that should become the universal definition: sudden sensorineural hearing loss is an abrupt or rapidly progressive hearing loss of at least 30 dB in at least three contiguous frequencies over a period of no more than three days. Idiopathic sudden sensorineural hearing loss (ISSHL) is sudden hearing loss where clinical assessment fails to reveal a cause.

The different theories discussed in this chapter are disturbances in the microcirculation, viral infections, cochlear membrane ruptures, immunopathological processes or a combination of these mechanisms. Maybe ISSHL is a symptom rather than a distinct disease with different causes. The clinical picture of ISSHL however, gives no clue that allows us to differentiate between different underlying pathophysiological mechanisms.. The inner ear is well protected and diagnostic samples are contraindicated because of

the high percentage of spontaneous recovery. However, in 10-15% of cases, sudden hearing loss is caused by a known pathological mechanism. Therefore, a complete history and medical evaluation remain necessary, complete with audiological and vestibular tests, laboratory evaluation and MRI of the cerebellopontine angle. Most studies report a spontaneous recovery of 45-65%. Until now nobody has been able to predict who will recover and how large that recovery will be. Furthermore, recovery is reportedly influenced by factors such as time of presentation, hearing loss levels, and accompanying factors as vertigo and tinnitus. All these factors must be taken into account when comparing treatment results between different studies.

The sudden loss of hearing strongly resembles other vascular diseases such as cerebral insult, myocardial infarction or retinal ischemia. When Fisch et al [20] discovered lowered perilymphatic oxygen tension in patients with ISSHL as compared to control subjects the vascular theory was born. Since then a whole spectrum of changes in the blood supply to the cochlea have been proposed as aetiology for ISSHL. It is extremely unlikely that an occlusion of the labyrinthic artery, by any mechanism, is the cause of ISSHL. The irreversibility of the hearing loss as a result and the absence of cochlear ossification do not fit the clinical picture in ISSHL. This does not imply that disturbances in the microcirculation do not play a role in ISSHL.

With the exception of carbogen, systemic vasodilator therapy does not appear to actually increase cochlear blood flow and may, in fact, decrease the blood flow to the inner ear [21, 63]. Changing the rheologic properties of blood by fibrinogen/LDL apheresis can reduce the blood viscosity by about 20% Although some studies have shown promising results, no randomized, large, controlled, single-modality blinded studies have reported improved hearing levels when using vasoactive therapy. The theory of disturbances in the microcirculation continues to have many followers.

Viral infections can cause sudden hearing loss and post mortem histolopathologic studies have shown remarkable resemblances between ISSHL and virally induced hearing loss. A labyrinthitis is thought to be the cause of the hearing loss. The viral theory has undergone a modification since the inner ear was shown to be capable of a response to local antigenic challenge and produce systemic immunisation [13].

There seems to be a relationship between the immune system and sensorineural hearing loss. In an assimilation of the viral theory and the immunologic theory it is thought that a (virally) induced labyrinthitis starts an immune challenge to the inner ear which in turn leads to hearing loss. It is the immune reaction that does the damage to the inner ear. Absent virus particles or infection in the inner ear as seen by Merchant et al [15] can now be explained.

Membrane ruptures are extremely unlikely as a cause of ISSHL, therefore this theory is of academic interest.

Several single-modality, prospective studies of steroids have demonstrated statistically significant improvement in recovery for ISSHL[35, 51, 52].

However, other studies have questioned the effectiveness of steroids [3, 6, 68]. Although treatment with steroids appears to have the greatest degree of scientific support, further study is required. This is confirmed by a review done by the Cochrane collaboration in 2006 [68]. They conclude, on the basis of just two trials that satisfied their inclusion criteria, that 'the value of steroids in the treatment of idiopathic sudden sensorineural hearing loss remains unclear since the evidence obtained from randomised controlled trials are contradictory in outcome, in part because the studies are based upon too small a number of patients'. Unfortunately, other than these two studies, there is an almost universal lack of proper studies with adequate control groups in the literature on the treatment of ISSHL.

A meta-analysis by the Cochrane group is underway to study the effects of vascular therapies.

No universally accepted treatment for ISSHL exists. The treatment chosen for ISSHL is dependent on the theory of choice which probably is more culturally defined than evidence based. We feel that a (virally) induced immune reaction in the inner ear is the main cause of ISSHL and we treat it accordingly. In the following chapters two trials are presented in which the treatment of ISSHL is systematically evaluated. The first trial concentrates on treating a possible virus infection; the second trial concentrates on the immune reaction, as a cause of the hearing loss.

After 60 years of research, the aetiology and treatment of ISSHL is still open to debate. It even remains uncertain whether ISSHL is a symptom with a multifactorial aetiology or a disease entity in itself. Perhaps it would be best to return to basics and methodically test the different hypotheses, while always testing treatment options against a placebo. Unfortunately, however, the low incidence of ISSHL hampers the inclusion of adequate numbers of patients, having a placebo in a control arm it will be that much more difficult to enrol enough patients into the study.

The treatment of ISSHL is best studied in large, controlled, multicenter treatment protocols. We would also strongly urge the reporting of actual hearing levels in results and the abandonment of multi-drug therapy protocols.

Table 1. Differential Diagnoses in Sudden Deafness

1.	Inflammatory		
1.1	Viral	1.1	- Mumps - Rubella - Measles - Parvovirus B19 - Cytomegalovirus - Infectious mononucleosis - Herpes simplex - Varicella-zoster - HIV
1.2	Bacterial	1.2	- Acute otitis media - Typhoid fever - Mycoplasma pneumoniae - Chlamydia trachomatis - Chlamydia pneumoniae - Chlamydophila psittaci - Ehrlichiosis - Lyme disease - Toxoplasmosis - Syphilis - Congenital - Acquired
2.	Vascular	2.1	Stroke
		2.2	Recent heart surgery
		2.3	Buerger's disease
		2.4	Sickle cell disease
3.	Hematological	3.1	Leukaemia
		3.2	- Increased viscosity - Polycytaemia vera - Waldenstrom's - macroglobulineamia - Cryoglobulineamia
		3.3	Coagulation disorder

4.	Connective tissue disorders	4.1 SLE 4.2 Polyarteritis Nodosa 4.3 Cogan's syndrome 4.4 Wegener's granulomatosis 4.5 Relapsing polychondritis 4.6 Rheumatoid arthritis
5.	Metabolic disorder	5.1 IDDM 5.2 Renal failure 5.3 Renal tubular acidosis
7.	Ototoxic drugs	
8.	Traumatic	8.1 Head Trauma 8.2 Barotrauma 8.3 Acoustic Trauma 8.4 Otological Surgery
9.	Menière's disease	
10.	Meningitis	
11.	Multiple sclerosis	
12.	Sarcoidosis	
13.	Friedrich's ataxia	
14.	Amyotrophic lateral sclerosis	
15.	Vogt-Kayanagi-Harada syndrome	uveitis/alopecia/vitiligo/dysacusia
16.	Tumours	16.1 Acoustic neuroma 16.2 Carcinomatous neuropathy 16.3 Metastasis
17.	Central deafness	
18.	Feigned hearing loss	

See relevant chapters for literature references.

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Chapter 3

Herpes simplex virus, cytomegalovirus virus and varicella zoster virus DNA detection in the inner ear and cochlear nerve in fresh human tissue using the Polymerase Chain Reaction (PCR) analysis.

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INTRODUCTION

Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) annually occurs between 5 -20 per 100.000 persons annually in the Netherlands and Flanders, but its aetiology and therapy remain subject to contradiction [1]. A viral cause was hypothesized because clinical observations reported a viral upper respiratory infection often preceding ISSHL in about 30% of cases [2]. This led to the supposition of viral cochlear labyrinthitis to cause ISSHL [3]. Infections by several viruses such as mumps, measles, rubella, varicella zoster virus, cytomegalovirus virus, Lassa virus and herpes simplex are known causes of acute sensorineural hearing loss [4-7]. Cochlear changes in post mortem temporal bone histology found in ISSHL resemble those found after hearing loss associated with rubella and mumps [8] Such changes are also found in experimentally induced labyrinthitis.

Reports of seroconversion of herpes antibody titers in ISSHL and the presence of latent neurotropic herpes viruses in the spiral ganglia of asymptomatic individuals, have drawn attention to the possible role of this virus family in causing ISSHL [9-11]. This brings up another possible mechanism: latent virus infection of the ear and its reactivation. According to current concepts of virology it is apparent that the group of herpes viruses such as herpes simplex virus type-1 (HSV-1), HSV-2, varicella zoster virus (VZV) and cytomegalovirus (CMV), all have a strong neurotropism [12]. The HSV-1 DNA and the HSV-2 DNA have been detected in post mortem human spiral ganglia, as well in geniculate, trigeminal and vestibular ganglia [11, 13-16]. Both viruses initially infect and replicate in mucoepithelial cells and then travel retrogradely along sensory nerves to the sensory ganglia where latency is established. A recurrence can be activated through various stimuli (e.g. stress, trauma, fever or sunlight). In this event the virus travels back down the nerve causing lesions to develop at the site innervated by this nerve [17]. VZV has similar characteristics and latent VZV has been demonstrated in the human trigeminal, thoracic and geniculate ganglia [18]. Finally, it has been speculated that CMV-labyrinthitis may not solely be associated with congenital infections but also with the reactivation of a latent virus later in life [19].

So far, HSV-1 and HSV-2 have been detected post mortem in spiral ganglia and in animal models. In this pilot study, specimens from fresh nervous tissue of the inner ear were taken during operations in which access had to be gained to the cerebellopontine

angle. Samples of the inner ear were then analyzed to detect HSV-1, HSV-2, VZV and CMV using the polymerase chain reaction analysis (PCR). Under the hypothesis that ISSHL is the result of a reactivation of a herpes family virus, latent virus should be present and detectable in a proportion of the "normal" population.

MATERIALS AND METHODS

Patients and specimens

This study is based on 21 patients with need for neuro-otologic surgery in which the inner ear was sacrificed. No history of ISSHL or recent herpes infection was present. All patients signed an informed consent before inclusion in the study. During surgery, samples from different parts of the inner ear and neural tissue were collected. Before the modiolus was resected, 0.2 ml of perilymphatic fluid was collected. The nervus cochlearis (N VII) was located and a clinical specimen of endoneurial fluid was collected by absorbing it with a small sterilized surgical sponge immediately after the epineural sheath was incised. A small sample of the nerve itself was then collected. All specimens including the modiolus were immediately stored at -80°C and remained stored at that temperature until PCR analysis was done. Peri-operatively 10 ml of blood was collected. The serum was analyzed for HSV-IgG, CMV-IgG and VZV-IgG.

During all procedures care was taken not to contaminate the samples.

Laboratory Methods

The serum was analyzed for HSV-IgG, CMV-IgG and VZV-IgG.

The PCR analysis was done at the Laboratory for Infectious diseases, Groningen, using a well established DNA-extraction method and using routine "in-house" PCR tests.

RESULTS

In the period 1999-2001 21 patients were enlisted in the study. All patients underwent surgery to the temporal bone in which the inner ear was sacrificed. There were 15 males and the average age was 57 years (range 30-74). Fourteen patients were operated

because of a vestibularis schwannoma, two patients underwent a petrosectomy, one patient had a N. Facialis schwannoma, one patient had cholesteatoma, one patient with a glomus jugulare type c2, one patient with an adenocarcinoma of the parotid gland, and one patient with an osteoma.

Sample collection

It proved more difficult than anticipated to collect all required samples. Especially endoneurial fluid and ganglion spirale were particularly difficult to obtain. Only 11 endoneurial fluid samples and 14 ganglion spirale samples could be collected and tested. perilymph (21 samples), ganglion vestibulare (21 samples) and n. cochlearis (19 samples) were more easily collected.

Serum samples

Of the 21 patients, 18 were positive for HSV-IgG and VZV-IgG, one was negative for both and two were not tested. CMV serology was different. Seven patients had a positive CMV-IgG, eleven were negative and three were not tested. In short almost all patients were positive for HSV and VZV, but only 40% were positive for CMV.

PCR-analysis

Two patients had a positive CMV-PCR and one patient had a dubious positive CMV-PCR. The CMV-PCR was positive in the spiral ganglion and perilymph respectively. The dubious positive was located in the perilymph. The two patients with a positive CMV-PCR had a dubious positive VZV-PCR in the n. cochlearis. All other samples were negative.

An inverse relationship was noted for serology and PCR tests concerning CMV. All patients with a positive IgG for CMV were negative in their PCR tests. Of the 11 negative CMV-IgG samples three had a positive (or dubious) CMV-PCR.

Discussion

In our patient group we detected only two positive PCR-reactions for CMV and three dubious positives for VZV (n=2) and CMV (n=1). Furthermore, it proved impossible to collect all required samples. This is in contrast with results from the literature where Fukuda et al. [11] Murakami et al. [20] Furuta et al. [14 21] and Schulz et al. [22] could collect

and detect herpes family viruses with PCR in spiral ganglia, endoneurial fluid and vestibular ganglia with relative ease.

Worldwide, more than 90 percent of people are seropositive for HSV-1 by their fourth decade of life, especially those of lower socioeconomic groups [23]. This is corroborated by our own findings that 18 out of 21 patients had a positive IgG for HSV.

Not one of our PCR samples was positive for HSV. Although the failure to detect a herpes simplex virus in our series and the very low incidence of VZV and CMV was unexpected, some methodological limitations are apparent which might explain our results in part.

We collected samples from live patients and not from cadaver dissection as is the case in the literature. This is probably the major factor which influenced all aspects of our sampling. Radical excision of the ganglion spirale and vestibulare is not the same during surgery when compared to cadaver dissection. This influenced the volume of the samples, which was very small. The small volume influenced the sensitivity of the tests and it is possible that not enough virus particles were present in the samples for detection.

The study was set up as a pilot study to see if it was possible to collect samples intraoperatively and to detect virus particles in these samples. No negative controles were collected during sampling. This might have influenced the internal validity of the study. All PCR tests were performed with positive and negative controls.

The analysis by PCR was done after all samples had been collected. This had a logistical and financial reason. It is much easier and cheaper to perform a "batch" analysis than to analyse each sample separately.

The combination of sample collection from live patients and collective PCR analysis meant that after the results came in, there was no possibility of changing our methods to improve our success rate.

The positive CMV-PCR combined with negative CMV-IgG in three patients is noteworthy. These results can be explained by a possible reactivation of a latent CMV-infection before the formation (or reappearance) of antibodies against CMV. Two of the three patients were fighting an infection (cholesteatoma and osteoma) and this could have lowered the cellulair immunity, making them more susceptible to a CMV-infection.

In this study we failed to identify a herpes family virus in the inner ear of unselected patients and failed to find additional support for the theory of a reactivation of a latent herpes simplex infection in the inner ear as a cause of ISSHL. Despite this

study we feel that the clinical picture of sudden deafness closely resembles a sudden inflammatory "disease" and that a latent herpes infection remains a good candidate as a triggering mechanism. The high prevalence of herpes viruses in the general population is undisputed and therefore our failure to detect these viruses is probably due to methodological issues rather than absent virus.

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Chapter 4

The Treatment of Idiopathic Sudden Sensorineural Hearing Loss using Antiviral Therapy; a prospective, randomized, double-blind clinical Trial

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INTRODUCTION

Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) is characterized by sensorineural hearing impairment or deafness, which develops during a very short period in otherwise normally hearing persons. The hearing loss is frequently associated with vestibular disturbances, tinnitus and a pressure sensation in the ear.
In a majority of the cases ISSHL is unilateral but infrequently both ears are involved. Spontaneous hearing recovery is reported in 45-65% of the cases, although in a small majority of the cases hearing will recover to functional levels[1].

Although the precise etiology of ISSHL is still unknown Van Dishoeck first suggested a viral involvement in 1957, when he reported observations of an upper respiratory infection preceding the hearing loss [2]. This hypothesis is supported by reports of seroconversion of viral antibody titers for several viruses in patients with ISSHL [3]. MRI studies of the inner ear have shown labyrinth enhancement in patients with ISSHL [4]. Post-mortem cochlear histopathological changes seen in ISSHL patients closely resemble changes seen after viral labyrinthitis [1;5]. Especially a herpetic viral labyrinthitis provided a matching histopathological pattern of cochlear damage when compared to patients having suffered from ISSHL [6]. Herpes simplex type 1 (HSV-1) has been demonstrated to remain latent in healthy human spiral ganglia [7]. Experimentally induced HSV-1 labyrinthitis resulted in sudden hearing loss in guinea pigs and cochlear histopathology closely resembled cochlear histopathology seen in ISSHL [8].
As a result of these findings we have hypothesized that ISSHL is caused by a reactivation of a subclinical labyrinthine infection, possibly by HSV-1.
Therapy for ISSHL still remains unknown even though many drugs have been tried, ranging from vasodilators, plasma expanders, intravenous contrast agents, carbogen inhalation, corticosteroids or all of them together as "shotgun" therapy [9]. Treatments given depended on the believed cause of ISSHL or directed at all hypothesized causes of ISSHL. The only treatment that has proven more effective than placebo is the early application of corticosteroids [10;11]. Cochlear damage seemed to be limited by the anti-inflammatory properties of the corticosteroids.
In experimentally induced HSV-1 labyrinthitis a combination therapy consisting of aciclovir and corticosteroids proved more effective than either therapy alone in limiting cochlear damage and achieving earlier recovery [8]. This combination therapy

is also favored in other herpetic infections [12;13] but has not been reported in ISSHL. After 14 days it is clinically accepted that the viral replication stage has ended and the addition of aciclovir to steroids is no longer effective.

In this study we evaluated the treatment of ISSHL using aciclovir and corticosteroids versus corticosteroids alone in a prospective, double-blind, randomized clinical trial. The aim of the study and the preliminary data of the study evaluating the combination of antiviral treatment with acyclovir and corticosteroids in the treatment of ISSHL were published elsewhere [14].

PATIENTS AND METHODS

In- and exclusion criteria

Patients participating in the trial met the following criteria (1) sensorineural hearing loss of unknown etiology; (2) hearing loss of at least 30 dB HL for three subsequent one octave steps in frequency in the standard pure tone audiogram; (3) blank otological history; (4) hearing loss occurring within 24 hours. Exclusion criteria were (1) hearing loss occurring more than 14 days ago; (2) contraindications for the use of either prednisolone or acyclovir.

Diagnostic protocol

In order to exclude a known cause of hearing loss, the patients entered a diagnostic protocol that included complete history and physical examination, audiological and vestibular tests, MRI of the temporal bone and laboratory work-up. Evaluation and treatment of sudden sensorineural hearing loss was considered a medical urgency. Laboratory investigations were aimed at excluding the presence of an infectious, inflammatory or autoimmune process or coagulopathy. An extensive virus serological evaluation for HSV, VZV, CMV, Epstein-Bar, mumps, measles, influenza, parainfluenza, rubella and chlamydia, was performed using paired blood samples and nasopharyngeal swab or aspirate. Consults for ophthalmology and internal medicine were asked to exclude Cogan's Syndrome and systemic disease. After diagnostic samples had been taken, a provisional diagnosis of ISSHL was made and treatment was initiated. When a cause of sudden hearing loss could be identified later, patients were excluded from the study.

Informed consent

Before participation, patients were given oral and written information about the study. Patients were required to sign a written informed consent, designed according to European Good Clinical Practice regulations, before participation in the study.

Study design

The study was designed as a prospective, randomized, double-blind, placebo-controlled clinical trial. A multicenter approach was necessary because the low incidence of ISSHL makes inclusion of sufficient number of patients difficult. In each participating hospital, the Medical Ethics Committee approved of the trial protocol.

All patients who met the inclusion criteria but not the exclusion criteria were divided in two groups. Both groups were treated with intravenous prednisolone in a dose of 1 mg/kg bodyweight on day one, to be diminished in equal steps during 7 days to 0 mg. In addition one group received aciclovir 10 mg/kg bodyweight intravenously three times daily for seven days; the other group received placebo. The hospital pharmacist performed randomization and aciclovir or placebo was given in identical bottles labeled "ISSHL Trial". Outpatient follow-up consisted of four consultations, 1 week, 3, 6 and 12 months after discharge.

After completion of the study participating patients and treating physicians and investigators were told whether aciclovir or placebo had been given.

Audiometric and subjective parameters

The audiometric parameters used for determining recovery were pure-tone audiometry in dB HL Extended Fletcher Index (EFI = average of thresholds at 0.5, 1, 2, and 4 kHz) and speech audiometry. Pure-tone and speech audiometry were performed at inclusion and discharge, and repeated after 1 week, 3, 6 and 12 months. Our primary endpoint was hearing recovery after 12 months.

Subjective parameters that the patients were asked to judge semiquantitavely were hearing recovery, tinnitus intensity, pressure sensation and vertigo. Hearing could be categorized as improved, equal or worsened. Tinnitus, pressure sensation and vertigo could be categorized as absent, mild, moderate or severe. These parameters were recorded before and after hospitalization and during outpatient follow-up. These subjective parameters were our secondary endpoints.

Data collection and statistical processing

A Case Record Form (CRF) was used for data collection. For data processing a special spreadsheet program was designed to facilitate data entry. Statistical processing was performed using the statistical program SPSS 10. Data entry was controlled by frequency tables.

Power analysis: A 10 dB improvement in primary outcome was expected from the addition of aciclovir with an expected recovery in the placebo group of 35 dB. Alpha = 0.05 and beta = 0.2. We calculated the number of necessary patients with different sigma's. Sigma (SD) = 10 then N = 32; sigma = 15 then N = 72; sigma = 20 then N = 126.

Non-parametric data was analyzed using the Mann-Whitney test or Fisher's exact test. Parametric data were processed using *t*-tests for independent samples, and ☒2 analysis. A 5% significance level was used.

RESULTS

Patient characteristics

Between 1994 and 1999, 91 Dutch and Flemish patients were included in the study (age 12-80 years; mean age: 46.8 ± 16.8 years; median: 47 years). All patients were treated using the "intention-to treat-principle".

Forty-six patients received aciclovir with prednisolone (aciclovir group) and forty-five patients received placebo with prednisolone (placebo group). Four patients were excluded after randomization due to the results of the diagnostic protocol, which showed a known cause of their hearing loss (2 otosclerosis, 1 vestibular schwannoma, and 1 bleeding cerebral peduncle). 16 patients were excluded because of administrative problems (CRF not correctly documented). One patient refused further participation after randomization. The remaining patient group consisted of 70 patients; their characteristics are shown in Table 1.

Table 1. Patient characteristics

	Placebo (N = 33)	Aciclovir (N = 37)	p-value	Total patients (N = 70)
Gender (2)	23 M, 10 F	23 M, 14 F	0.616	
Age (mean ± SD) (1)	44.7 ± 17.6	45.9 ± 15.9	0.757	
Hearing loss in dB EFI at admission in unaffected ear (mean ± SD) (1)	21.2 ±20.7 dB HL	29.5 ± 33.2 dB HL	0.222	
Hearing loss in dB EFI at admission in affected ear (mean ± SD) (1)	83.6 ± 28.0 dB HL	62.9 ± 21.6 dB HL	0.002	
Virus infection in preceding month (2)	Neg = 25 pos = 8	Neg = 27 Pos = 9 unknown = 1	1.000	Neg = 51 Pos = 15
Prev Herpes labialis (2)	Neg = 26 Pos = 7	Neg = 29 Pos = 7 Unknown = 1	1.000	Neg = 55 Pos = 14
Delay in days (mean ± SD) (1)	4.2 ± 3.4	4.4 ± 3.9	0.844	

(1): T-test; chi square (2-tailed)
(2): Crosstabs; Fisher's exact test

Of the 70 patients 4 patients had missing audiograms at 12 months, but we were able to extrapolate their hearing loss and could therefore still use their data for analysis. Extrapolation was possible because their hearing loss had been stable for the last 2 outpatient follow-up consultations. Age and gender were equally divided between both groups.

The mean hearing loss at admission in the aciclovir group was 62.9 dB HL, while in the placebo group the mean hearing loss was 83.6 dB HL. This was statistically significant (p = 0.002).

The occurrence of previous infections was equally distributed between aciclovir- and placebo-treated patients (See Table 1). Time from onset to presentation was limited to 14 days by our study protocol, even though one patient was included in our protocol after 16 days. This only became apparent after recalculation. This was not considered of having a significant influence on the end result of the trial and the patient was not excluded from analysis. Average delay for the whole group was four days (See Fig. 1). There was no difference between the aciclovir and placebo groups. Median hearing loss for the whole group occurred in 2 hours and 23 minutes (range 1 minute to 23:40 hours). Almost 50% of the patients lost their hearing within one minute. This includes patients who first noticed their hearing loss on awakening (See Fig. 2). No seasonal influence could be established on occurrence of hearing loss in our patient group.

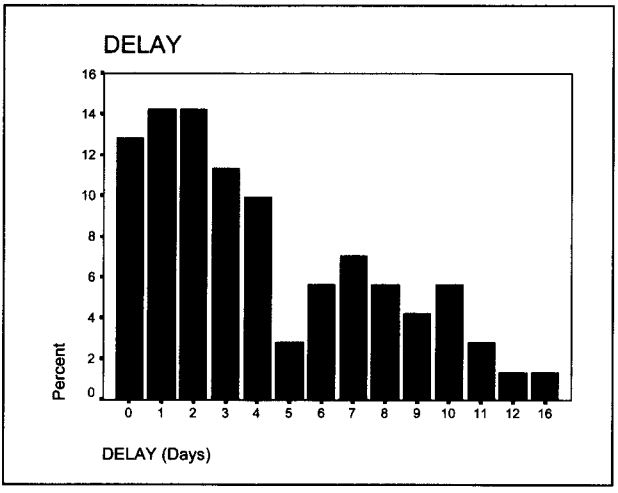

Figure 1. Patient Delay

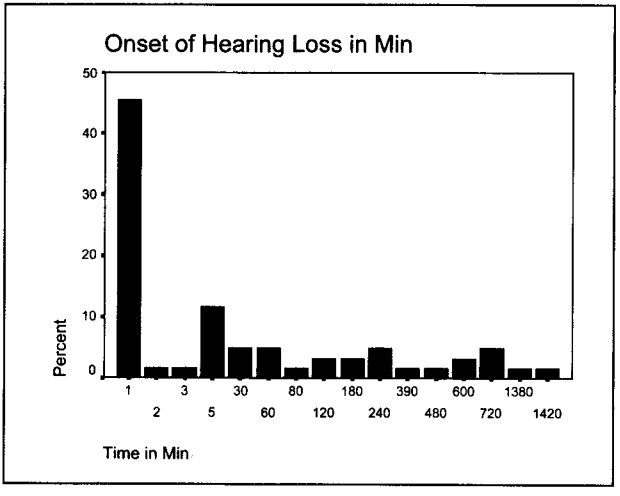

Figure 2. Onset of Hearing Loss

Side effects

All patients were able to tolerate both aciclovir/steroid and placebo/steroid schedule with only limited mild side effects. Mild side effects were transient and included slightly raised blood glucose, mild headache, palpitations and mild nausea. These side effects were interpreted to be the result of steroid therapy. No specific aciclovir side effects were observed.

Virus serology

An intensive effort was made to demonstrate the presence of systemic viral infection. Although none of the patients had clinical symptoms of viral infection, in 8/70 patient's serological signs of viral infection were present.

A raised IgM antibody titer against varicella zoster virus was found in one patient and a dubious IgM reaction against mumps virus existed in another patient.

Seroconversion against rubella occurred twice and a sign of an active non-primary Epstein-Bar virus infection was also demonstrated once.
Herpes simplex type 1 was cultured from the nasopharynx in two patients and parainfluenza type 3 was cultured in one patient. None of these last three patients had a concomitant rise in antibody titer.

Subjective data

Subjective parameters noted were hearing recovery, pressure sensation, vertigo and tinnitus. Subjective hearing recovery closely followed audiogram parameters (figure not shown). Pressure sensation had a good prognosis, decreasing from 35.1% to 15.6% after 12 months in the aciclovir group and from 45.5% to 10.3% in the placebo group (See Fig. 3a). In 12 months time, vertigo decreased from 32.4% to 12.5% and from 36.4% to 10.7% for aciclovir and placebo groups respectively (See Fig. 3b). Tinnitus, however, showed a poor prognosis. At inclusion 86.5% of patients in the aciclovir group and 72.7% of patients in the placebo group suffered from tinnitus. After 12 months this had decreased to 46.9% for the aciclovir group and to 55.2% for the placebo group (See Fig. 3c). There was no statistical difference between the aciclovir and placebo groups in initial presentation or recovery ($p > 0.05$) for these subjective parameters.

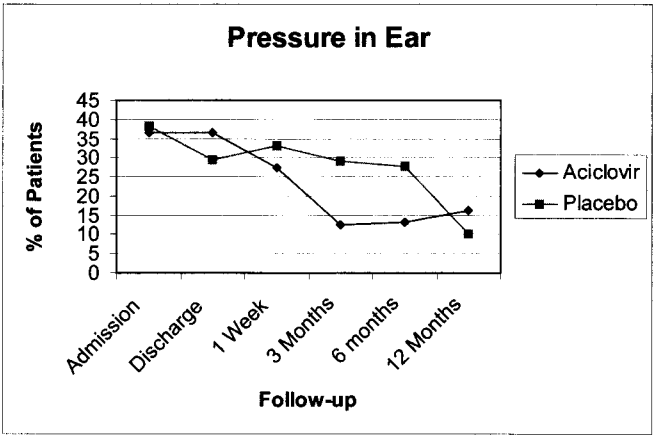

Figure 3a. Subjective parameters: Pressure sensation

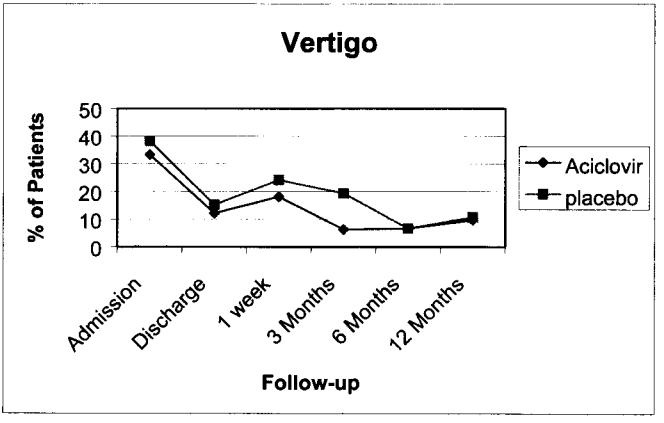

Figure 3b. Subjective parameters: Vertigo

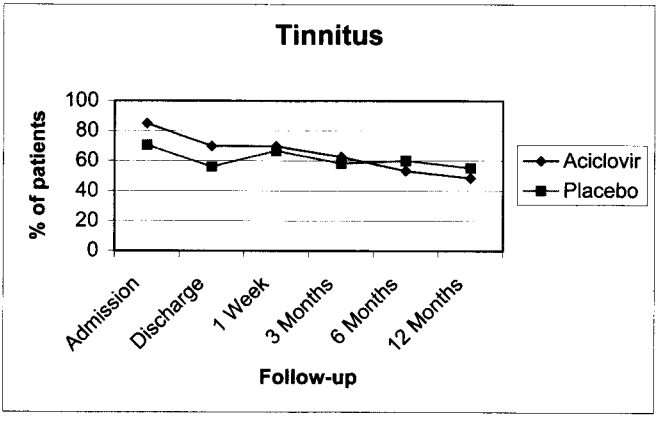

Figure 3c. Subjective parameters: Tinnitus

Audiometric data

Pure-tone audiometry in Extended Fletcher Index (EFI) was used to quantify hearing levels. At admission hearing loss for the whole group was 72.7 dB EFI. At 12 months endpoint hearing levels had improved to 45.5 dB EFI.

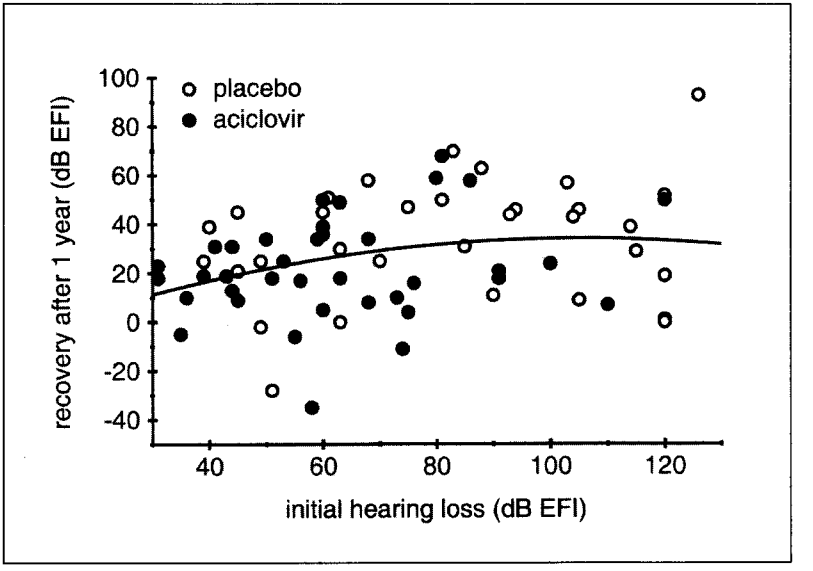

Figure 4. Hearing loss at 12 months versus initial hearing loss

The recovery 1 year after admission vs. initial hearing loss for the aciclovir and placebo groups is shown in a scatter plot (See fig. 4). The line drawn is a least squares fit with a quadratic curve. The average vertical distance to the curve for the aciclovir group is -3.1 dB (SD 20.5 dB) and for the placebo group + 3.5 dB (SD 24.4 dB). The placebo group shows a greater recovery after one year than the aciclovir group. However, the difference of 6.6 dB is statistically not significant. Figure 4 can therefore also be interpreted as the result for whole group of patients. There was no difference in recovery between aciclovir and placebo groups. Despite double blind randomization, more cases of profound hearing loss were allocated to the placebo group than to the aciclovir group. This however did not influence hearing recovery, as is shown in figure 4. An analysis comparing hearing recovery for patients with hearing loss less than 100 dB HL with patients with hearing loss larger than 100 dB HL showed no difference between the groups (Mann-Whitney Test, $p > 0.05$), thereby confirming the results in figure 4. Using the fitted line in figure 4 we calculated the hearing recovery for the

different initial hearing losses. The results are given in Table 2.
Pure-tone audiogram shape was difficult to categorize in our patients. We were not able to establish a relationship between hearing recovery prognosis and pure-tone audiogram shape.

Table 2. Calculated hearing recovery after 1 year

Initial hearing loss (dB EFI)	Recovery after 1 year (dB EFI)
40	17
60	26
80	32
100	34
120	33

ISSHL is often regarded as an otological emergency. It is assumed that when treatment is initiated in the very early phase of the hearing loss, hearing recovery prognosis might be better. To verify this assumption, additional analysis was performed. We divided our patients into two subgroups: one in which treatment had begun within 24 hours after occurrence of hearing loss (N=19), and the remaining patients (N=51). Hearing recovery prognosis turned out to be comparable in both subgroups ($p > 0.05$).

On average, a maximum speech discrimination score of 49% was achieved by patients when presenting with hearing loss. After 1 week of treatment, speech discrimination had improved to 59%, reaching 74% after six months. After 12 months speech discrimination score had reached 75%. Application of aciclovir had no effect on speech discrimination scores.
Figure 5 is a histogram that shows the distribution of the vertical distance of all the points to the curve drawn in Figure 4.
The distribution for the placebo group (not shown) is the difference between the total group and the aciclovir group. The standard deviation for the total group (the "width" of the histogram) is 22.4 dB. (This value can also be calculated from the already known SD's for the acyclovir and placebo groups) Clinically important is the speed of recovery. Figure 6 shows the time it takes patients to reach 80% of their total recovery. The data in this curve contain only those patients who have shown recovery, i.e. their initial hearing loss was greater than their hearing loss after 1 year (n=33 for the aciclovir group and n= 27 for the placebo group).

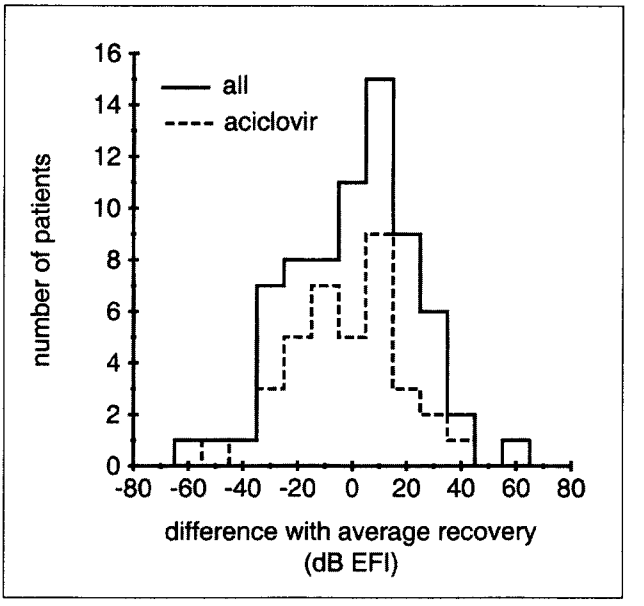

Figure 5. Distribution of average recovery

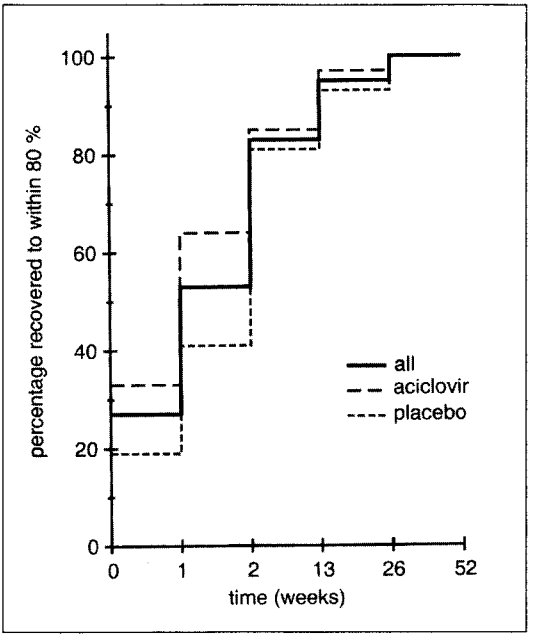

Figure 6. Speed of recovery

About half of the patients reach their 80% recovery after only 2 weeks. The aciclovir group with a fast recovery is larger than the placebo group with a fast recovery. The probability that both groups have the same speed of recovery is 20% (Mann-Whitney-Wilcoxon-test). This p-value (p=0.2) is so large that the difference between both distributions is not significant. On average a patient will reach 80% recovery in about seven weeks.

Discussion

Etiology and treatment of Idiopathic Sudden Sensorineural Hearing Loss (ISSHL) are still open to debate, even after 60 years of research [15]. It affects patients to the core of their existence and has serious repercussions on their social and professional functioning. Most ISSHL patients experience some hearing recovery after treatment with corticosteroids. The majority does so in the first two weeks after treatment. In our patient group we calculated expected hearing recovery for several different initial hearing losses (see Table 2). With a few exceptions there appears to be a limit of recovery for the cochlea of around 35 dB. In this study addition of aciclovir to corticosteroid therapy did not improve hearing recovery as compared to corticosteroid therapy alone.

Secondary endpoints (subjective parameters) such as vertigo and pressure sensation, which affect about one third of patients, have a good prognosis and also show recovery. A large proportion of patients suffer from tinnitus. This has a poor prognosis and this very often remains a lasting effect of ISSHL. Addition of aciclovir unfortunately did not improve any these subjective complaints.

In ISSHL, the delicacy of the structures involved makes elucidation of and interference with its pathophysiology difficult. In our experience, no truly successful treatment regimen can be offered to ISSHL patients, despite the mild beneficiary effect of corticosteroids. Although we have not been able to ascertain the therapeutic value from the application of aciclovir in ISSHL in this study, some methodological limitations are apparent which might explain our results in part.

In our study, a multicenter approach covering the entire Dutch language region (21.5 million inhabitants) was necessary to include our 91 patients. This group might still have been too small to achieve statistical significance. Almost every study concerning ISSHL suffers from this limitation, because of the low incidence of the condition,

especially when in- and exclusion criteria are strictly applied. Our definition of ISSHL was somewhat stricter than the definition used in Wilson or Moskowitz's study [10;11], but was similar enough to allow comparison between our patient group and patient groups reported in these and other studies. Secondly, to prove efficacy of any therapeutic modality in ISSHL, it has to perform significantly better than the high spontaneous recovery rate, reported to be between 40-65%. Thirdly, the range in hearing recovery was larger than we expected (SD) and therefore our sample size might still have been too small.
Fourthly, despite double-blind randomization, we failed to control for severity of initial hearing loss in this study. There was a statistical significant difference between aciclovir and prednisolone groups in severity of initial hearing loss of affected ear at admission. The hospital pharmacist randomized the patients in blocks of four. The only information the hospital pharmacist had prior to randomization was name, age and weight of patient. After analysis of the randomization procedure no explanation could be given as to the reason for this difference between both groups. The other relevant criteria were evenly distributed between the acyclovir and placebo groups.
The prognostic factors in ISSHL mentioned in the literature include vertigo or vestibular involvement, audiogram shape and severity of initial hearing loss. These factors can be used as an indication of the severity of the damage to the structures in the inner ear. In general, patients with mild to moderate hearing loss without vertigo, who are seen quickly after initial presentation of the hearing loss, have a better chance of recovery [16].

Prognosis of hearing loss with or without vestibular involvement was comparable in our patients. Vestibular involvement has been suggested to indicate more extensive damage to the labyrinth, with a relatively unfavorable prognosis as a result[17]. In our study vertigo had a relative good prognosis and did not influence recovery, consequently this could not be confirmed as an indicator of poor recovery.
Secondly, audiogram shape as a prognostic factor is often used to characterize severity and location of damage to the cochlea. Pure tone audiogram shape was difficult to categorize in our patients, therefore we could not correlate audiogram shape with recovery.
Thirdly, severity of initial hearing loss is used as an indication of more severe damage to the cochlea. This theoretically lowers the potential recovery. In our study absolute recovery in dB depended only weakly on initial hearing loss (see fig. 4 and table 2).

We hypothesized that the cochlea has a maximum potential recovery of around 35-45 dB. Depending on the severity of initial hearing loss, this would mean either full recovery, for losses up to 45 dB; limited recovery, for losses 45-80 dB; or no (functional) recovery for losses > 90-100 dB.

The failure to demonstrate the effectiveness of aciclovir for patients with ISSHL has forced us to readjust our theory regarding the etiology of ISSHL. The three main hypotheses concerning the etiology of ISSHL mentioned in the literature are a circulatory disturbance, a membrane rupture or a viral cause. Despite an extensive diagnostic protocol we could not identify a single etiologic cause. As ISSHL affects all age groups, is evenly distributed between sexes and no coagulopathy or autoimmune disorder could be demonstrated, we consider a circulatory disorder highly unlikely. The spontaneous occurrence of ISSHL without a history of (baro)trauma, even while asleep makes a membrane rupture doubtful. Histopathology suggests a viral etiology and the significant yet mild beneficiary effect of steroids at least suggests an inflammatory component. Although we could not prove a viral infection as a cause of ISSHL with serology techniques, this doesn't mean that there was no infection, be it a primary infection or reactivation. Testing perilymph or endolymph samples in patients with ISSHL for viral DNA using PCR (polymerase chain reaction) could prove this. This is ethically not feasible, as there would be a significant possibility of permanent hearing loss.

In conclusion we can say that circumstantial evidence still points to a viral infection, probably from a neurotropic virus such as herpes simplex as a cause for ISSHL. Although the combination of aciclovir combined with steroids is the preferred treatment for known herpetic infections, there seems to be no place for aciclovir in the treatment of ISSHL. Considering that the anti-inflammatory effect of corticosteroids is thought to play an important part in the recovery, a more powerful suppression of the immune system might enlarge or quicken the recovery in ISSHL. This could be achieved using high-dose glucocorticoid therapy (pulse therapy). Pulse therapy combines a large anti-inflammatory effect with limited side effects[18]. Pulse therapy has shown positive results for diseases as diverse as rheumatoid arthritis, optic neuritis, multiple sclerosis, and pemphigus vulgaris. [18-22].

Proof of effectiveness of new therapeutic initiatives must be studied in large trials for proper evaluation. Only then can evidence based medicine contribute to a better understanding or to a more effective treatment of ISSHL.

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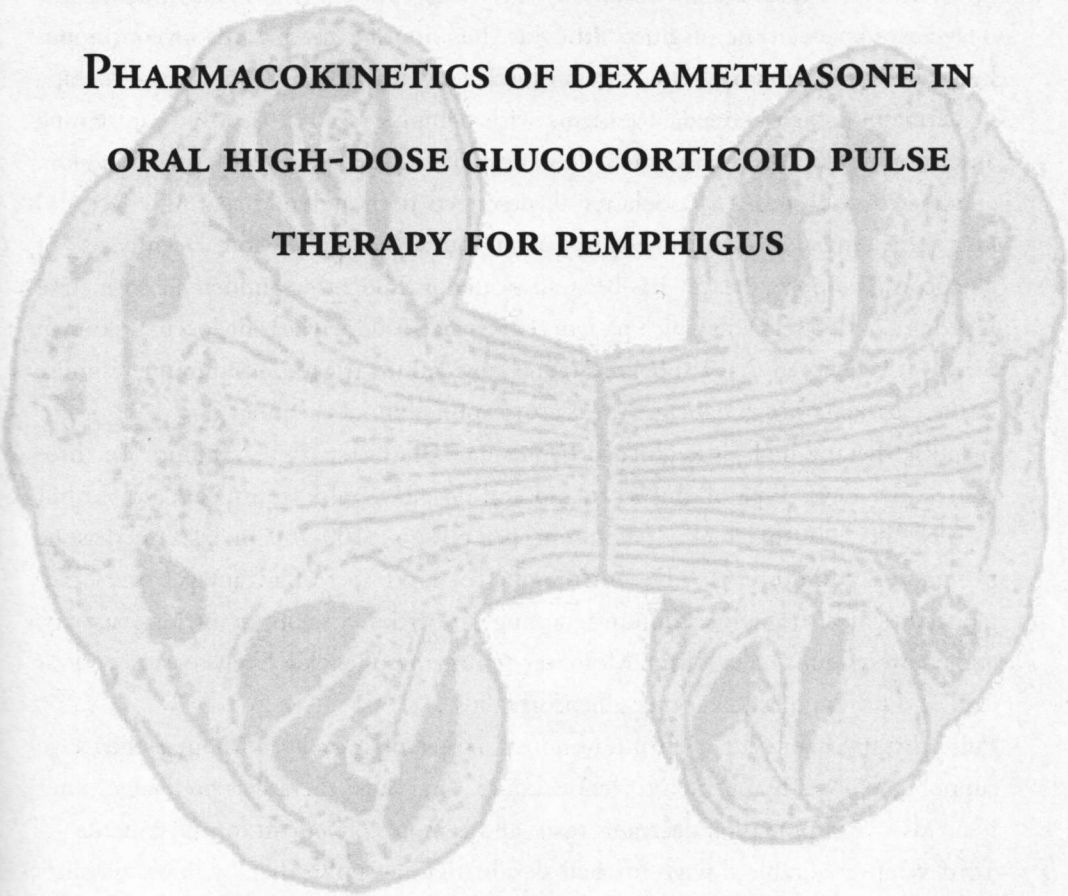
Chapter 5

Pharmacokinetics of dexamethasone in oral high-dose glucocorticoid pulse therapy for pemphigus



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INTRODUCTION

High-dose glucocorticoid pulse therapy aims at periodically strong immunosuppression[2]. As adjuvant in chronic inflammatory disorders, pulse therapy may reduce the daily maintenance dose of glucocorticoids thus limiting the hazards of continuous long-term steroid intake. The largest experience with glucocorticoid pulse therapy in dermatology is obtained in patients with pemphigus vulgaris, a life-threatening autoimmune skin disease in which autoantibodies cause loss of epidermal cohesion, and therefore blistering. Pasricha et al. described both a steroid-sparing effect and long-term remission of up to 9 years, using pulse therapy [2]. More recently use of glucocorticoid pulse therapy has been advocated in Idiopathic Sudden Sensorineural Hearing Loss (ISSHL), in which patients experience a sudden hearing loss of unknown origin. It is believed that a subclinical viral labyrinthitis triggers an immune response in these patients which damages the sensory epithelium of the inner ear [3, 4].

In pulse therapy high-dose glucocorticoids are administered every month on three consecutive days. Type of glucocorticoid and dose per pulse is not standardised but usually 500-1000 mg methylprednisone per pulse or 100-200 mg dexamethasone per pulse is administered [5]. Dexamethasone has a number of advantages over other glucocorticoids: negligible sodium-retaining properties, a stronger intrinsic activity, and no presystemic metabolism. Moreover dexamethasone is less likely to cause serious cardiac dysrhythmias than other glucocorticoids [6].

Pulse therapy is mostly given intravenously rather than orally, without evidence to support the necessity of the intravenous route. Oral pulse therapy is preferable, since it avoids a vena-puncture, decreases costs, and is more convenient for the patient.

To develop a suitable dosage for oral dexamethasone pulse therapy, bioavailability of high-dose dexamethasone had to be determined. A recent study reports the bioavailability of oral high-dose dexamethasone (100 mg capsules) of 63.4%. Dexamethasone 300 mg per os is therefore equivalent to approximately 200 mg dexamethasone iv, the standard iv. pulsed dose [1].

In this study, the pharmacokinetics of a new dexamethasone formulation was studied, namely 50 mg tablets for oral use in pulse doses of 300 mg. If the results of this study is satisfactory, these tablets will be used in two prospective multicenter double-blind randomised clinical trials, in which the effect of oral high-dose dexamethasone pulse therapy will be evaluated in patients with pemphigus vulgaris or ISSHL.

MATERIAL AND METHODS

Subjects

Four patients with pemphigus vulgaris were enrolled in this study, three males with an average age of 46 years (range 33-57), and a 54 year old female. One of the male patients suffered from diabetes.

Patients were admitted for their monthly pulse therapy. Prior to pulse therapy safety parameters in blood (full blood count, electrolytes, liver and kidney functions and glucose) and urine (sediment, reduction) were measured. On two consecutive days patients were given 200 mg dexamethasone intravenously, and 300 mg dexamethasone orally. During pulse therapy heart rate and blood pressure were monitored. Clinical effects were not studied.

Drug administration

For intravenous administration dexamethasone phosphate was used. Tablets containing 50 mg dexamethasone were produced in our hospital pharmacy, since high-dose dexamethasone tablets are not available in the Netherlands. The dexamethasone (Eur. Pharm) was hydrophylised with methylcellulose 15 MPA-s (Eur. Pharm). The tablets were prepared by direct compression using cellulose microcrystalline (Eur. Pharm, Avicel pH101), and magnesium stearate (Eur. Pharm).

In vitro control of content uniformity of 50 mg dexamethasone proved more reliable than a 100 mg dosage, as dexamethasone is practically insoluble in water. For the planned clinical trials a charge of 30.000 units was produced, which is in our setting easier to produce in tablets than in capsules. Furthermore correction of taste is easier in tablets.

Tablets were white, diameter 7 mm, thickness 3.5 mm, and no inscription. Mean tablet weight (n=12) was 201.7 mg with coefficient of variation of 1.04% (requirement <3% n=10). Tablets satisfied the tests for tablets according to BP 1998. The dissolution test showed a dissolution of 38.3 % of dexamethasone after 45 minutes, uniformity of content was 103.3 % (requirement 85-115%). Tests on identity, uniformity of mass, uniformity of content, disintegration and purity were all conform requirements.

Sample collection

Blood samples were drawn in non-heparinised tubes, after intravenous administration at times 0; 1; 2; 3; 4; 6 and 24 hours and after oral administration at times 0; 1; 2.5; 3;

3.5; 4; 8 and 24 hours. Serum was obtained after centrifugation (at 1500 g, at ambient temperature then stored at –20°C until analysis.

Analysis

Serum samples were analysed by a validated suitable selective high performance liquid chromatography procedure.

Chromatographic separation was performed using a Chromsphere 5C18 analytical column (250 x 4.6 mm I.D.) after a guard column (Chrompack R.P. 10 x 2.1 mm). A high pressure pump (spectroflow 300 solvent delivery system) and an autosampler (Merck-Hitachi, model AS-2000) were used. For detection, we used a diode array-UV detector (Gynkotek) at 244 nm with computer software to achieve data handling and peak integration. The mobile phase was a mixture of phosphate buffer (0.067 M; pH 6.9), tetrahydrofurane and ultra pure water (1:2:5 v/v/v) at a flow rate of 1.25 ml/min. During analysis the mobile phase was stirred. The samples were purified by a liquid-liquid extraction. Betamethasone (10 mg/L) was used as internal standard.

To one ml of serum, 100 µL of internal standard solution and 6 ml of diethylether were added. After shaking for 15 minutes and centrifugation at 1500 g for 5 minutes, the water layer was frozen at -40°C.

The organic layer was carefully decanted into clean centrifuge tubes and was evaporated to dryness at 35°C under nitrogen. The residue was dissolved in 100µL of mobile phase and 50 µL of aliquot was injected into the chromatograph. From recorded peak heights, the ratios of drug to internal standard were calculated. The analytical procedure has been validated [7]. Linearity (range 20-750 µg/L), precision and accuracy have been proven. In testing the method it appeared to give a linear response to at least 3400 µg/L. Samples with concentrations above 3400 µg/L were re-analysed after a validated dilution step. The day to day coefficients of variation were 13.6% (C=20.0 µg/L) and 2.0% (C= 99.9% µg/L) respectively (n=15). The day to day inaccuracy varied between 97.5 to 102.1%. The lower limit of quantitation was 20 µg/L. In the previous study using dexamethasone capsules (100mg) the same analytical procedure and extraction were used [1].

For pharmacokinetic analysis the computer program MW/PHARM (Mediware, Groningen, the Netherlands) was used. This program calculates a set of pharmacokinetic parameters that best fits the measured serum concentrations in time. In the curve fitting module Kinfit the optimal compartment model is fitted. In the module Kinbes bioavailability of oral administered dexamethasone was calculated using AUC (area

under the serum concentration-time curve) ratios with trapezoidal rule. In Kinbes bioavailability is calculated using the following equation [8]:

$$F = (AUC_{oral} \times dose_{iv}) / (AUC_{i.v.} \times dose_{oral}) \times 100\%$$

Kinbes corrects the outcome of this formula for differences in elimination constants that are determined for oral and intravenous administration. AUC_{oral} and $AUC_{i.v.}$ is the area under the serum concentration time curve of the oral and intravenous administration respectively. For both oral and intravenous administrations the time course of dexamethasone serum concentrations was characterised by peak concentration (C_{max}), time of reaching peak concentration (t_{max}), area under the curve (AUC) and elimination half-life ($t_{1/2}$). These parameters were calculated in the module Kinbes.

Results

Bias of measured concentration of the quality control samples with respect to the true concentration was calculated. For the lower quality control sample (335 µg/L) a mean bias of −1.69 % was calculated. None of the outcomes exceeded 20%. For the high quality control sample (3464 µg/L) a mean bias of 4.82 % was calculated with also none of the results exceeding 20 %. All runs were accepted.

Figure 1 shows the mean serum concentration-time curve for both oral and intravenous administration of dexamethasone. The serum concentration-time curves corresponding to these administrations were best described by a tri-exponential equation.

Table 1 summarises all pharmacokinetic parameters. Mean bioavailability of the tablets was 55.8 % (range 43-65%). Mean peak concentration after 200 mg dexamethasone iv. was 5040 µg/L, after 300 mg dexamethasone per os 2580 µg/L. Mean time to peak concentration is 2.25 hours for oral administration.

Little variation in peak concentration was found among the four patients. Mean peak concentration after oral administration is 51.2 % of the mean peak concentration after intravenous administration.

In patient D dexamethasone was quantifiable 21 hours after intravenous administration (83 µg/L). Dexamethasone was also quantifiable 24 hours after oral administration (101 µg/L). These results were confirmed by reanalysing the corresponding samples using LC-MS with APCI interface. Hydrocortisone-3D was used as an internal standard

replacing betamethasone (a stereoisomer of dexamethasone). In the MS-spectrum an obvious peak corresponding to dexamethasone was seen, thereby confirming the presence of dexamethasone in these samples.
Side-effects in the four patients were limited to facial flushing, and sleeping disturbances the first night after administration.

Table 1: Pharmacokinetic parameters of dexamethasone after intravenous and oral administration of 200 and 300 mg respectively

Therapy	Patient A	Patient B	Patient C	Patient D	Mean	SD
* 200 mg iv.						
- AUC(mg/l/h)	17.36	9.52	17.45	21.76	16.52	5.10
- C_{max} (mg/l)	4.44	4.72	5.99	5.00	5.04	0.67
- $t_{1/2}$ (h)	2.15	1.39	2.92	3.78	2.56	1.03
* 300 mg p.o.						
- AUC (mg/l/h)	15.88	6.64	14.67	24.74	15.48	7.41
- C_{max} (mg/l)	2.79	1.84	2.34	3.35	2.58	0.64
- t_{max} (h)	3.5	3.5	1.0	1.0	2.25	1.44
- $t_{1/2}$ (h)	2.84	1.52	3.05	4.39	2.95	1.17
- F (%)	61	43	54	65	55.8	9.64

Discussion

The mean bioavailability of high-dose dexamethasone tablets was 55.8 % (range 43-65%). The dose of 358 mg dexamethasone per os is therefore equivalent to 200 mg dexamethasone iv..
Bioavailability does not differ significantly when 50 mg tablets (58.8%) or 100 mg capsules (63,4%) are used for high-dose dexamethasone pulse therapy (6). When tablets of 50mg were used mean dexamethasone peak concentration (C_{max}) was 52% (range 37-66%), which is lower than after administration of the capsules (mean 72.3%; range: 67-79%) (6).
Since it is unknown whether the effects of pulse therapy are due to C_{max} or AUC and the bioavailability (AUC) of the tablets was comparable to capsules we concluded that 300 mg oral dexamethasone in 50 mg tablets can be used as oral pulse therapy. Therapeutic effects of the oral pulse therapy will be studied separately [9].
The elimination half-life for one patient was large compared to the other patients, possibly due to interindividual variation in pharmacokinetics. This prolonged half life would not cause any risk for the patient in terms of side effects, since the serum

concentration was extremely low compared to the peak concentration. Besides pulse therapy is only administered on 3 consecutive days, once a month.

Oral pulses, instead of iv, reduce patient inconvenience, increases cost-effectiveness, and are more acceptable in placebo controlled trials. Tablets are preferable instead of capsules, for better *in vitro* control of content uniformity and better taste correction. Intake of tablets is more convenient than of capsules for the patient.

The new dexamethasone tablets have reliable pharmacological and technical characteristics, and appear to be safe. They can be safely used for high-dose pulse therapy, and are suitable for use in the planned clinical trials, in which the therapeutic effect of oral high-dose dexamethasone pulse therapy is evaluated.

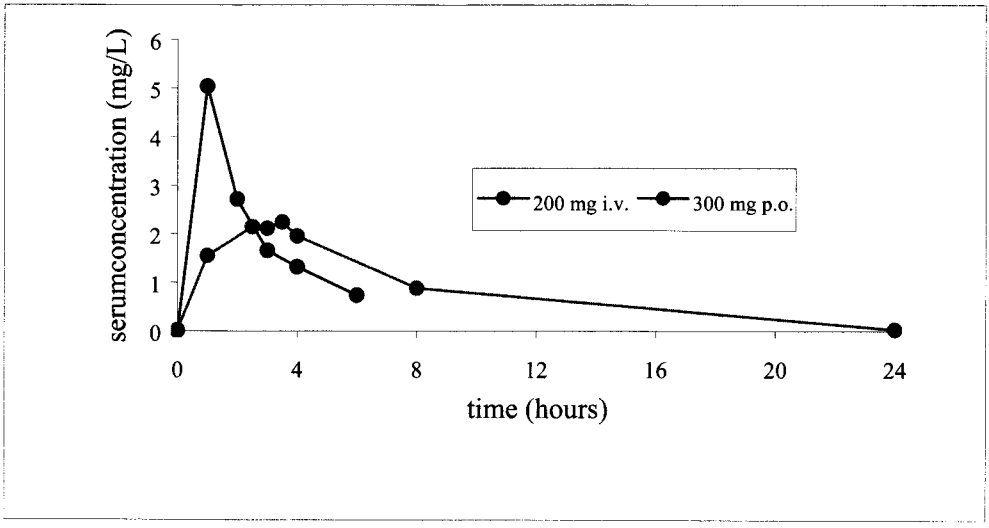

Figure 1. Mean dexamethasone serum concentrations (mg/L) in all patients as a function of time (hours)

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Chapter 6

The treatment of Idiopathic Sudden Sensorineural Hearing Loss using pulse therapy; a prospective, randomized, double-blind clinical trial

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Conflict of interest statement

The authors have no financial or personal relationships with other people or organizations that might (inappropriately) influence this paper.

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The funding source had no role in the study design, in the collection, analysis or interpretation of data, in the writing of the report or in the decision to submit the paper for publication.

Introduction

Sudden deafness is characterized by sensorineural hearing loss of 30 dB HL or more over at least 3 sequential 1-octave frequency steps in the standard pure tone audiogram, which develops over a period ranging from a few hours to three days in otherwise normally hearing, healthy individuals. It affects between 5 and 20 persons per 100,000 annually. The hearing loss is usually unilateral and frequently associated with vestibular disturbances, tinnitus and a pressure sensation in the ear [1]. Most studies report spontaneous partial recovery in 45% to 65% of patients, although hearing will recover to functional levels in only a small number of patients.

Although sudden deafness is a well-recognized condition, no standard definition or treatment protocol has been accepted. In addition, despite extensive evaluation, an etiological factor can only be found in 10-15% of patients [2]. Viral infections [3], disturbances in the microcirculation [4] and cochlear membrane ruptures [5] are all entities that have been hypothesized as causes of idiopathic sudden sensorineural hearing loss (ISSHL).

The two main theories concerning the aetiology of ISSHL are disturbances in the microcirculation and a viral infection of the inner ear.
A disturbance in the inner ear microcirculation is unlikely because sudden deafness occurs in individuals of all ages, is evenly distributed among sexes and no coagulopathy

can be found in patients with ISSHL. Furthermore, experimentally induced hearing loss of vascular origin is irreversible and vaso-active therapy has yet to show a positive effect on hearing improvement.

Viral infections such as measles, mumps, rubella and herpes can cause sudden hearing loss. Moreover, the histories of around 30% of sudden deafness cases include infections of the upper respiratory tract [2]. Magnetic resonance imaging studies of the inner ear have shown labyrinth enhancement in patients with sudden deafness [6]. Post-mortem cochlear histopathological changes seen in patients with ISSHL closely resemble changes seen after viral labyrinthitis [7]. Liao et al. [8] suggest a virally-mediated immune response causing the cochlear damage, and thus the hearing loss, as a possible pathophysiology for ISSHL. The immune response can provoke the degeneration of the organ of Corti, stria vascularis and spiral ganglion [9].

The only form of treatment that has shown some effect in improving hearing after ISSHL is the administration of corticosteroids as quickly as possible after the onset of hearing loss [10]. The mechanism of steroid action in the inner ear remains open to speculation; they reduce the cytotoxic immune response, increase the microvascular blood flow in the cochlea and decrease the onset of endolymphatic hydrops [11]. Considering that the anti-inflammatory effect of corticosteroids is thought to play an important part in the recovery from ISSHL, a more powerful suppression of the immune system might enhance or quicken recovery. This could be achieved with high-dose corticosteroid therapy (pulse therapy). Pulse therapy combines a large anti-inflammatory effect with limited side effects [12]. Pulse therapy is the discontinuous administration of corticosteroids in very high doses. The pulse doses are not standardized but usually range between 10 and 20 mg/kg for methylprednisone and between 2 and 5 mg/kg for dexamethasone. A dose of 500 mg methylprednisone or 100 mg dexamethasone roughly equals 625 mg prednisone [12, 13].

The present study was based on an earlier study which evaluated whether the addition of acyclovir to prednisone leads to better hearing recover than prednisone alone [14]. In this study we evaluate whether pulse therapy or high dose dexamethasone leads to better recovery of hearing in ISSHL patients than our standard treatment with prednisone.

MATERIALS AND METHODS

Inclusion and exclusion criteria

Patients participating in the trial met the following criteria: 1) perceptive hearing loss of unknown aetiology; 2) hearing loss of at least 30 dB hearing level (HL) for 3 subsequent 1-octave steps in the standard pure tone audiogram (PTA); 3) Hearing loss occurred within twenty-four hours; 4) blank otologic history of the affected ear. Patients were excluded if the hearing loss had occurred more than fourteen days before evaluation, had fluctuating hearing loss or if they had contraindication to the use of high-dose steroids. (Table 1: Contraindications for Pulse Therapy).

Table 1. Contraindications for the use of Pulse Therapy

A. serious infections: herpes simplex oculi, active tuberculosis
B. hypertension (diastolic > 110 mg Hg, systolic > 180 mmHg; treated or untreated)
C. manifest decompensatio cordis
D. cardiac arrhythmias, with the exception of atrial fibrillation
E. low serum potassium (below patient's own hospital's reference value)
F. severe osteoporosis
G. Cushing syndrome
H. badly regulated insulin-dependent diabetes mellitus
I. ulcer
J. pregnancy
K. oral anticoagulants (cumarin derivatives)
L. use of corticosteroids

Diagnostic protocol

In order to exclude known-causes of hearing loss, we submitted patients to a diagnostic protocol. This included a complete history and physical examination, audiological and vestibular tests, magnetic resonance imaging of the temporal bone and cerebellopontine angle, and laboratory work-up. Laboratory investigations were aimed at excluding the presence of an infectious, inflammatory, autoimmune process or coagulopathy. An extensive serological evaluation for HSV, varicella-zoster virus, cytomegalovirus, Epstein-Barr virus, mumps, measles, influenza, parainfluenza, rubella, Borrelia, chlamydia and syphilis was performed on paired blood samples and with a nasopharyngeal swab or aspirate. Consulting specialists in opthalmology

and internal medicine were asked to exclude Cogan's syndrome and systemic disease, respectively. After diagnostic samples were taken, a provisional diagnosis of ISSHL was made and treatment was initiated. In cases where a cause of sudden hearing loss was identified later, patients were excluded from the study.

Informed consent

Before participation, patients were given oral and written information about the study. Before participating in the study, patients were required to sign a written informed consent form, designed in line with the European Good Clinical Practice regulations. Patients had to be 18 or older to be eligible for participation.

Study design

The study was designed as a prospective, randomized, double-blind clinical trial. A multicentre approach was necessary because the low incidence of ISSHL makes the inclusion of sufficient numbers of patients difficult. Patients were recruited from April 2000 to October 2004. Each participating hospital's respective Medical Ethics Committee approved the trial protocol.

Medication

Patients were randomly allocated to pulse therapy or control treatment. Pulse therapy consisted of 300 mg dexamethasone for three consecutive days followed by four days of placebo. Control treatment consisted of 70 mg prednisone per day tapered in steps of 10 mg per day to 0 mg. The treatment lasted seven days for both groups. Each patient took 7 tablets for the first three days, then 4 tablets on day four and 3 tablets on the last three days. Outpatient follow-up consisted of 4 consultations at 1 week, 6 weeks, 6 months and 12 months after discharge.

The trial medication was pre-packaged and supplied in identical sterile packaging with a label specifying the days of the regimen.

All trial medication was prepared at the University Medical Centre Groningen dispensary to ensure stable pharmacodynamics and pharmacokinetics. The hospital dispensary performed randomization.

The medication was randomized per block and was given a serial number. The order of the serial number determined the order of dispensing. Once an ISSHL patient had been included in the study, the pre-packaged trial medication was delivered to the patient's physician. In order to ensure that the medication was given as quickly as

possible, a supply of ten pre-packaged medication packages was stored at each of the participating academic hospitals.

Audiometric and subjective parameters

The primary endpoint was recovery of hearing measured after 12 months. Recovery of hearing was defined as the difference between hearing loss on presentation and after 12 months. Hearing loss was measured with pure tone audiogram (PTA) and speech audiogram. The Extended Fletcher Index (EFI) was used to calculate hearing loss. EFI is mean hearing loss at (500+1000+2000+4000) Hz. PTA and speech audiometry were performed at inclusion and discharge and were repeated after 1 week, 6 weeks, 6 months and 12 months. We believe that after 12 months no further recovery can be expected.

Subjective parameters that the patients were asked to judge semi-quantitatively were hearing recovery, tinnitus, pressure sensation and vertigo. Hearing could be categorized as improved, equal or worsened. Tinnitus, pressure sensation and vertigo could be categorized as absent, mild, moderate or severe. These parameters were recorded at inclusion and discharge and were repeated during outpatient follow-up. These subjective parameters were our secondary endpoints.

Data collection and statistical analysis

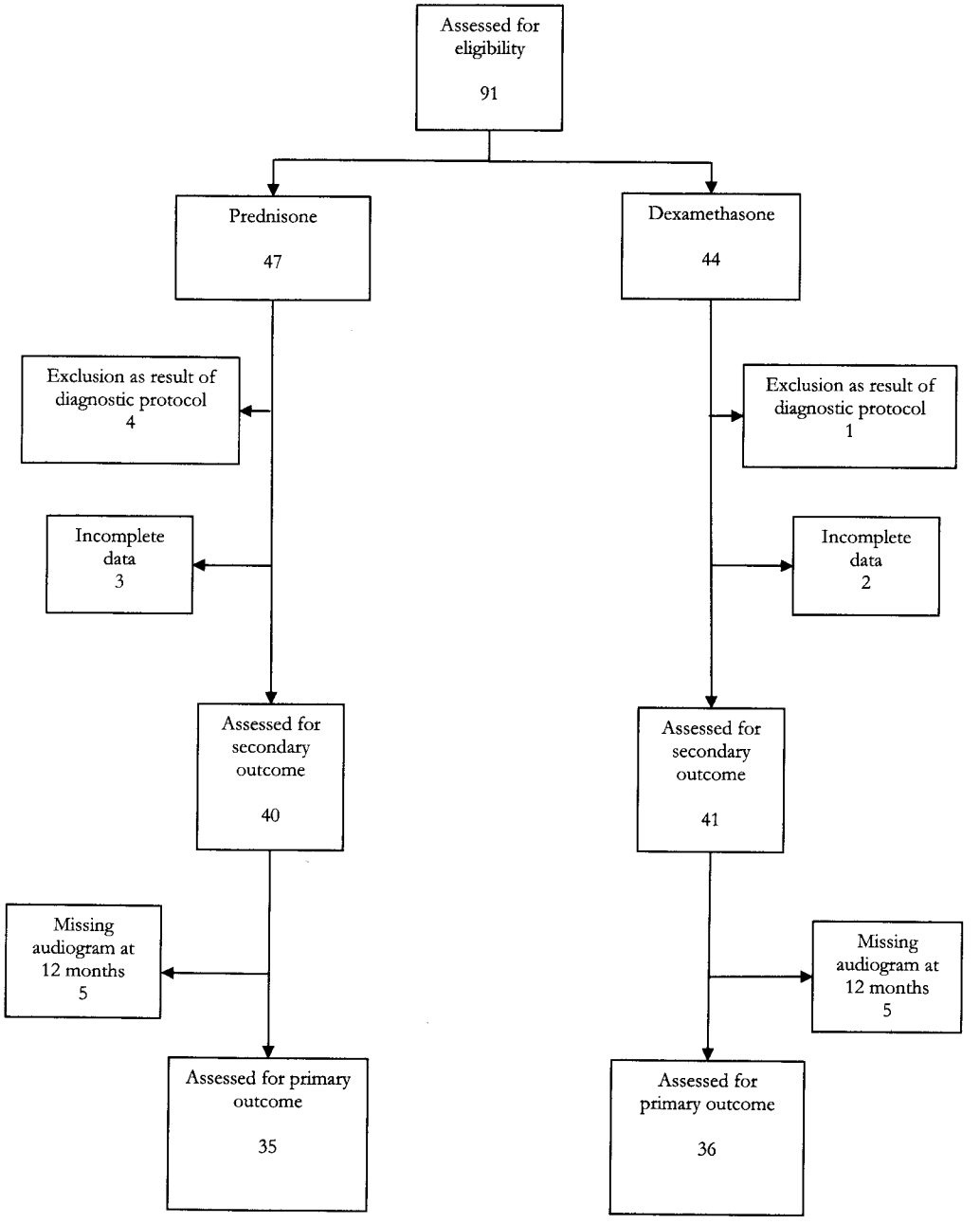
A case record form was used for data collection. For data processing, a special spreadsheet programme was designed to facilitate data entry. Statistical processing was performed using the statistical programme SPSS12. Data entry was controlled by frequency tables.

A 10 dB improvement in primary outcome was expected from pulse therapy with an expected recovery in the control group of 45 dB (alpha 0.05, Beta = 0.2). The N's were forced to be equal.

Two-sample T-test power analysis calculated that 51 patients per group were required. The total number of patients needed therefore was 102.

All quantitative variables and the changes between groups were calculated with the student's T-test. Qualitative variables were assessed with the $\chi 2$ –test.

Table 2: Trial Profile



RESULTS

General characteristics

Between 2000 and 2004, 91 Dutch and Flemish patients were included in the study. The hospital pharmacy randomly allocated 47 patients to the prednisone group and 44 to the dexamethasone group. See table 2 for the trial profile. After completing the diagnostic protocol, 5 patients were excluded owing to known causes of their hearing loss being identified (prednisone group: 1 positive IgM for Borrelia, 1 active herpes zoster oticus, 1 paraneoplastic hearing loss and 1 patient who had psychiatric hearing loss; 1 patient in the dexamethasone group had bleeding in the cochlea, as identified on the MRI-scan). Five patients were excluded because of incomplete data. The remaining patient group consisted of 81 patients and their characteristics are shown in table 3. All these patients were included for treatment.

Table 3. Patient characteristics

	Prednisone (N = 40)	Dexamethasone (N = 41)	Total patients (N = 81)
Sex	19 M, 21 F	25 M, 16 F	81
Age (y; mean ± SD)	49 ± 16	46 ± 15	81
Hearing loss at admission in unaffected ear (dB HL EFI; mean ± SD	19 ± 20	16 ± 16	81
Hearing loss at admission in affected ear (dB HL EFI; mean ± SD)	75 ± 28	71 ± 27	81
Delay in days	3 ± 3	4 ± 4	81
Virus infection in preceding month	Negative 31 (38%) Positive 8 (10%) Unknown 1 (1%)	Negative 28 (34%) Positive 11 (14%) Unknown 2 (2%)	81
Previous herpes labialis	Negative 27 (33%) Positive 12 (15%) Unknown 1 (1%)	Negative 33 (41%) Positive 6 (7%) Unknown 2 (2%)	81

Adverse effects

All patients were able to tolerate the medication with only limited, mild side effects. These included mild headache, palpitations, euphoria and mild nausea. All patients showed transient increase in their blood workup (day 3) of blood glucose and white blood cell count. All values returned to normal and, more importantly, during the therapeutic stage of the trial there was no difference in reaction between prednisone and dexamethasone.

Serological evaluation

An extensive effort was made to demonstrate the presence of an infectious, inflammatory or autoimmune process or coagulopathy. Two patients were excluded because of active infection; one patient had positive IgM for Borrelia and one patient had clinical herpes zoster oticus (varicella-zoster virus) with concomitant rise in antibody titer. Two patients had a raised IgM titer for influenza A, two had raised CMV IgM titers and one patient had a raised IgM for mycoplasma pneumoniae. Positive IgG titers were much more common, especially for EBV (41 patients), Rubella (37 patients), VZV (16 patients) and HSV (13 patients). Cultures from the nasopharynx were all negative.

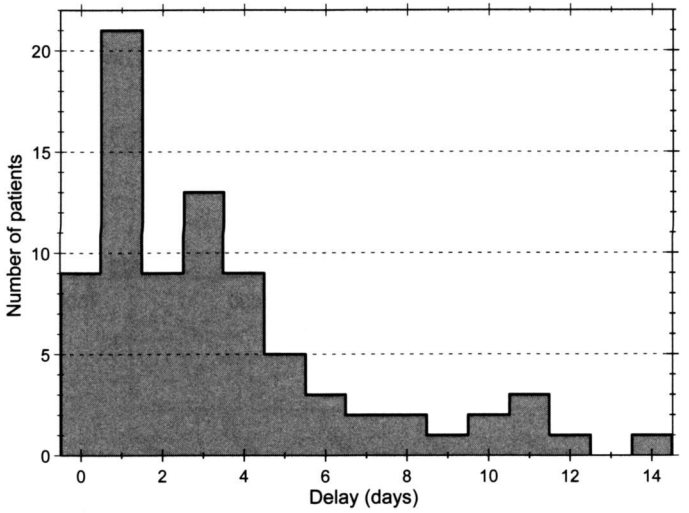


Figure 1. Patient delay. Delay from onset of the hearing loss until presentation at the clinic.

Patient characteristics

As shown in table 3, patient groups were comparable in age, gender, hearing loss in the affected ear and hearing loss in the unaffected ear. The occurrence of previous upper respiratory infections or previous herpes labialis was equally distributed between the prednisone and dexamethasone groups. Time from onset to presentation was limited to 14 days by our protocol. Figure 1 shows the distribution for the whole group. The average patient delay for the prednisone group was 3 days and 4 days for the dexamethasone group. The hearing loss usually developed rapidly, with almost 60% of patients losing their hearing in the first minute. This figure includes patients who first noticed their hearing loss on awakening.

The median time for patients to lose their hearing across the whole group was 2 hours, 32 minutes (range: 1 minute to 22 hours, 30 minutes) (Figure 2). No seasonal influence could be established on the occurrence of hearing loss in our patient group.

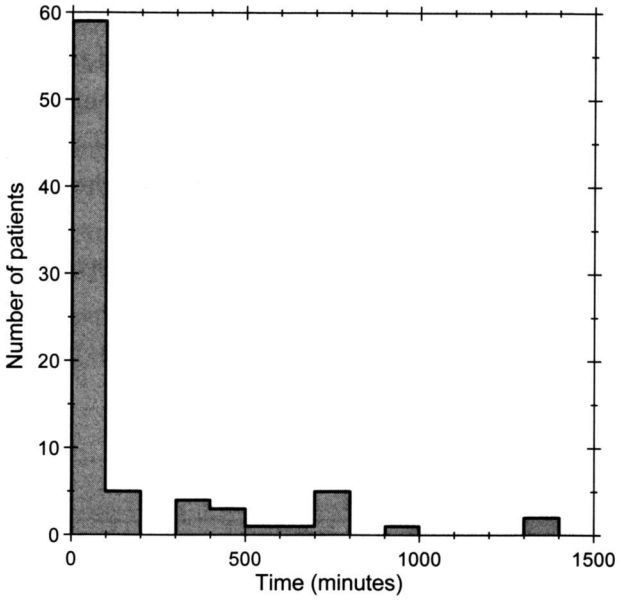


Figure 2. Development of the hearing loss: onset in minutes.

Subjective data

The subjective parameters noted were hearing recovery, pressure sensation, vertigo and tinnitus. Subjective hearing recovery closely followed audiogram changes (data not shown). In 12 months, pressure sensation and vertigo had a good prognosis but tinnitus did poorly, only decreasing from 85% to 69% in dexamethasone-treated patients and from 95% to 58% in prednisone-treated patients. This remains one of the lasting and most burdensome side effects of ISSHL (Figure 3A). Vertigo had a good prognosis, decreasing from 26% to 13% in the dexamethasone group and from 37% to 10% in the prednisone group (Figure 3B). Pressure sensation in the affected ear had the best prognosis in this study, decreasing from 46% to 9% in the dexamethasone group and from 54% to 16% in the prednisone group (Figure 3C). There was no statistically significant difference between the study groups in subjective parameters.

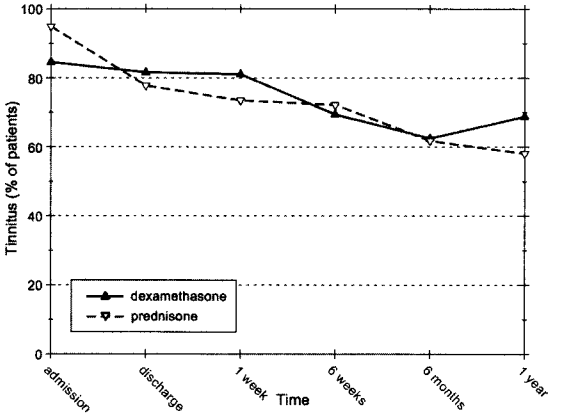


Figure 3a. Subjective parameters: Tinnitus. The percentage of patients suffering from tinnitus, for both patient groups.

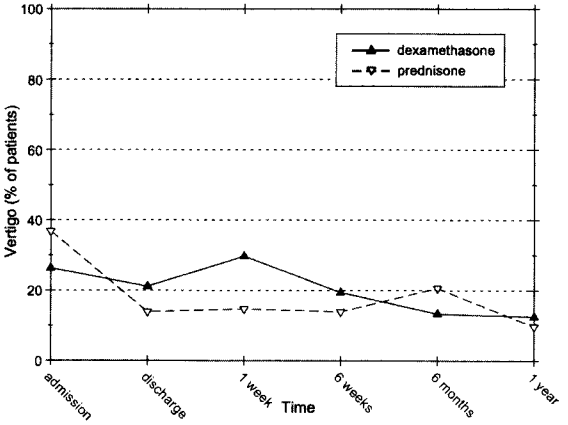


Figure 3b. Subjective parameters: Vertigo. The percentage of patients suffering from vertigo, for both patient groups.

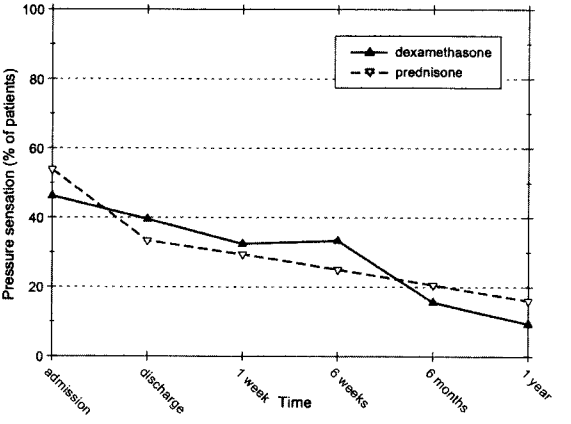


Figure 3c. Subjective parameters: Pressure sensation. The percentage of patients suffering from pressure sensation, for both patient groups.

Audiometric data

Pure tone audiometry using the Extended Fletcher Index (EFI) was used to calculate hearing loss and recovery. Maximum speech discrimination was defined as the maximum percentage of words that patients recognized at their optimal sound level. Of the 81 patients, 10 had missing audiograms at 12 months (5 in the prednisone group, 5 in the dexamethasone group). As these audiograms could not be retrieved, the primary endpoint was calculated using the remaining 71 patients. Age, gender, hearing loss at inclusion and hearing loss in the unaffected ear were equally divided between these groups and the 'loss' of 10 patients did not influence mean audiometric or maximum speech discrimination.

In a 12-month period, average hearing for the whole group improved from 72 dB HL to 39 dB HL and speech discrimination improved from 42% to 78%. If the study groups are considered separately, hearing improved from 71 dB HL (SD 27 dB) to 36 dB HL (SD 28 dB) in the dexamethasone group and from 75 dB HL (SD 28 dB) to 42 dB HL (SD 29 dB) in the prednisone group ($p>0.05$). Figure 4 shows the hearing loss in EFI for both groups as a function of time. It shows the median and the interquartile range for dexamethasone and prednisone.

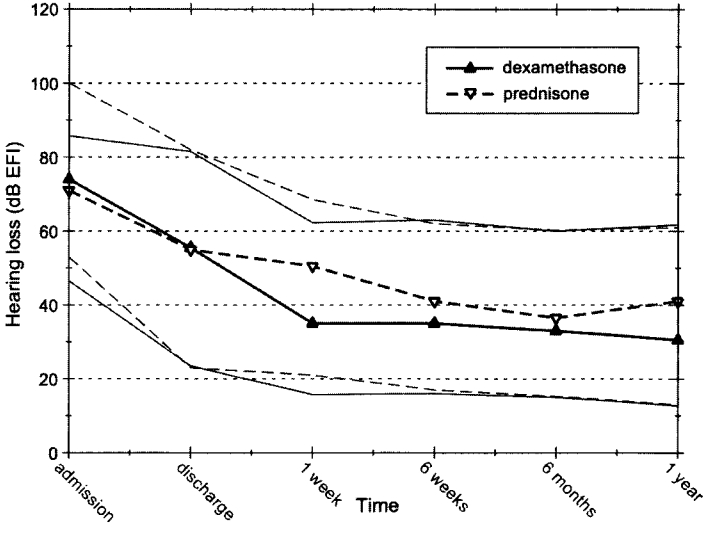


Figure 4. Hearing loss as a function of time, for both patient groups. Thick lines indicate the median, thin lines the 25th and 75th percentile.

Hearing loss after a year as a function of initial hearing loss is shown in a scatter plot for the dexamethasone and prednisone groups in figure 5. There is no significant

statistical difference between the two groups (p>0.05). Lines are added that show 'no recovery' and 'normal hearing', with normal hearing being defined as 20 dB EFI hearing loss or less. Figure 5 can therefore also be interpreted as the result for the whole group of patients.

Further analysis was conducted to evaluate whether patients had regained symmetrical hearing, i.e. an interaural hearing difference of less than 20 dB HL.

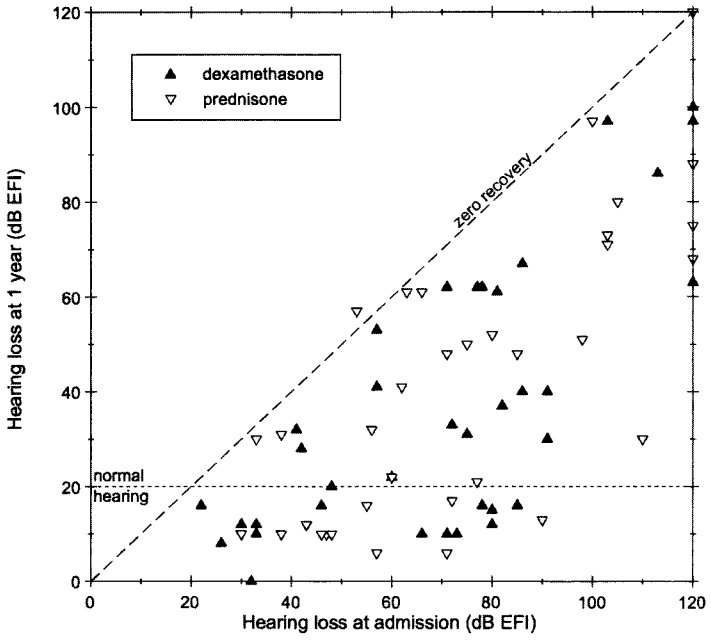


Figure 5. Hearing loss at 12 months compared to hearing loss at admission, for all patients. The boundaries for patients showing no recovery, as well as for patients regaining normal hearing are indicated.

In the dexamethasone group, 22/36 patients (61%) regained symmetrical hearing and 19/35 patients (54%) in the prednisone group (p>0.05), thereby confirming the results in figure 5. Despite there being no difference, this does mean that 41/71 patients (57%) regained symmetrical hearing in both groups. Another way of looking at recovery is to define recovery as a more than 50% decrease in hearing loss at 12 months when compared to initial hearing loss. Accordingly, in the dexamethasone group, 21/36 patients (58%) attained a 50% decrease, while 14/21 patients (40%) recovered 50% of their hearing loss (p>0.05) in the prednisone group.

An analysis comparing recovery in patients whose initial hearing was less than 100 dB HL with those whose hearing loss was greater than 100 dB showed no difference.

ISSHL is often regarded as an otological emergency. It is assumed that when treatment is initiated at a very early phase of the hearing loss, the prognosis for recovery might be better. To verify this assumption we divided our patients into two subgroups: patients for whom treatment had started within 24 hours after the occurrence of hearing loss (N = 24) and the remaining patients (N = 47). Hearing recovery turned out to be comparable. The mean speech discrimination score at presentation was 41% for the whole group (39% for the dexamethasone group and 42% for the prednisone group), after 12 months this had increased to 78% (dexamethasone and prednisone groups both reached 78%). The percentage of patients reaching 100% speech discrimination scores is shown in figure 6. The dexamethasone group did slightly better than the prednisone group, 64% reached 100% as compared to 57% ($p>0.05$). It was remarkable that the discrimination scores kept improving even after the audiograms stopped changing.

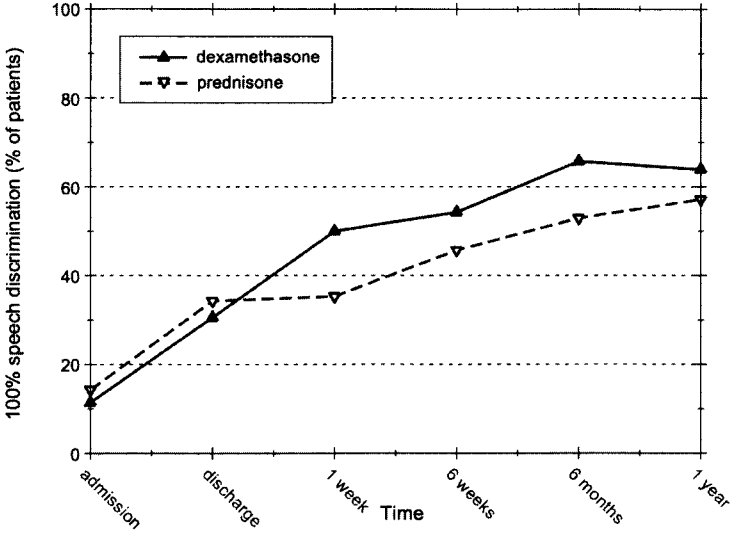


Figure 6. 100% speech discrimination scores, as a function of time. The percentage of patients with maximal speech discrimination, for both patient groups.

Discussion

This prospective, randomized, double-blind clinical trial, comparing high dose dexamethasone and prednisone in the treatment of ISSHL, was the result of a unique co-operation among all academic hospitals in the Netherlands and a great many

regional hospitals. Faced with a disease entity like ISSHL, where no clear aetiology or consensus of treatment exists, all participating centres set aside their differences and made this study possible.
Our results showed that in the treatment of ISSHL, dexamethasone showed no clear advantage over "standard" dose prednisone.
Our secondary endpoints, such as tinnitus, vertigo and a pressure sensation, all improved. Tinnitus, which affected 85% to 90% of patients in our study group, has a poor prognosis and remains a lasting disturbing consequence of ISSHL. Pulse therapy had no extra beneficial effect on the prognosis for tinnitus. Pressure sensation and vertigo reacted more favourably to treatment.

Corticosteroids are pleiotropic hormones that at pharmacological doses prevent or suppress inflammation and other immunologically mediated processes [15]. Corticosteroids may play a role in the regulation of ionic and fluid dynamics in the inner ear, since the sodium, potassium and Na, K-ATPase sites of the lateral wall of the inner ear are modulated in accordance with the presence or absence of circulating glucocorticoids. Corticosteroid administration correlates with increased levels of Na, K-ATPase in the inner ear [9].
Inhibition of leukocyte traffic and cellular immune responses require lower doses of glucocorticoids, higher doses of these agents are needed to suppress the functions of leukocytes and the humoral immune response [15]. Higher doses of systemic glucocorticoids can be administered for less than a week with relative safety, although the same dose of drug administered for a more extended period will result in predictable, clinically significant morbidity. The aim of pulse therapy is to suppress both the humoral and cellular immune response in relative safety.

In ISSHL, the delicacy of the structures involved makes elucidation of and interference with its pathophysiology difficult. In our opinion, no truly successful treatment regimen can be offered to patients with ISSHL, despite the mildly beneficent effect of corticosteroids. Although we have not been able to ascertain an advantage of pulse therapy over 'standard' prednisone therapy in this study, some methodological limitations are apparent that might explain our results in part.
We hypothesized that we would need 102 patients to detect a 10 dB hearing recovery difference between our study groups. Even with a multicentre approach we included only 91 patients over four years, before being forced to stop because of logistical reasons.

This group may still have been too small to achieve statistical significance, especially when you consider the large range (SD) of both hearing loss at admission and after 12 months. Second, for any therapeutic technique in ISSHL to show efficacy, its success rate would have to significantly exceed the high spontaneous recovery rate reported of between 40% and 65% [1]. Third, ISSHL is probably multifactorial in origin and the failure as a group to benefit from Pulse Therapy does not exclude the possibility that a subgroup is highly responsive to this treatment.

Conclusion

This study showed that pulse therapy is equally effective and safe as standard-dose prednisone. Pulse Therapy suppresses both humoral and cellular immune responses and therefore should have a wider anti-inflammatory effect.

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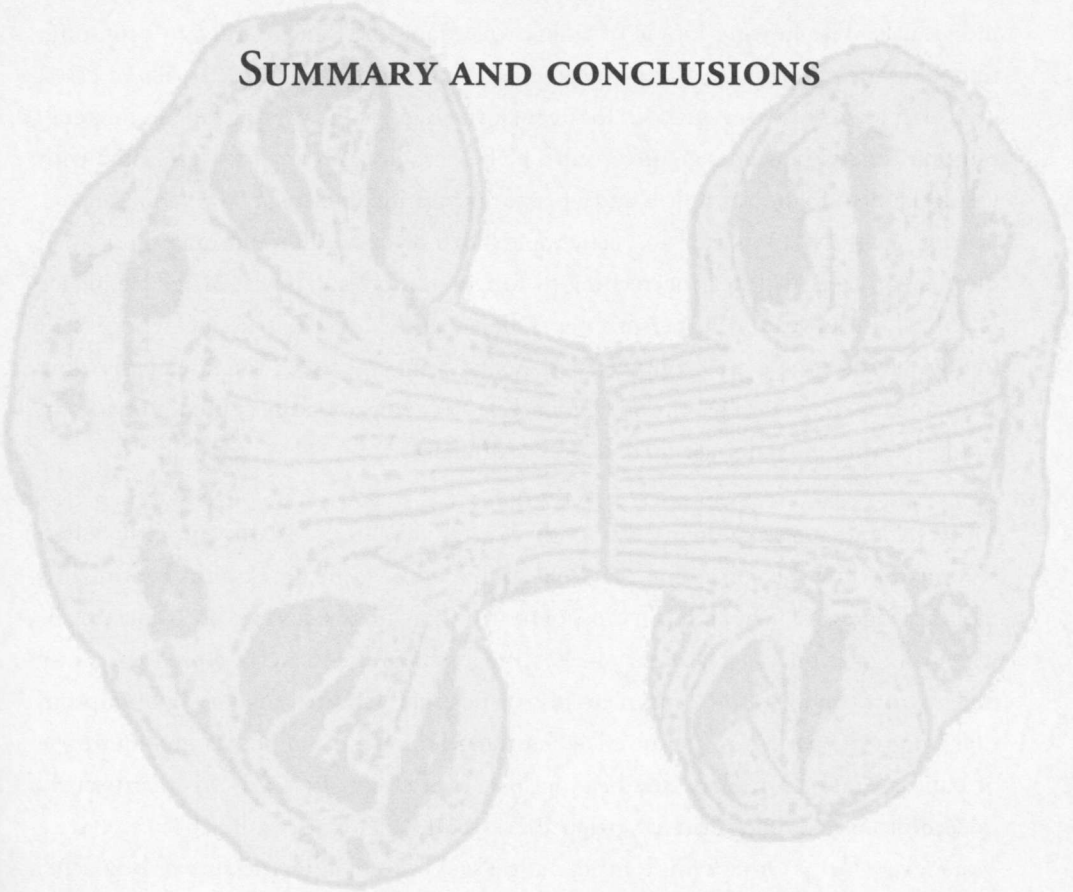
Chapter 7

Summary and conclusions



Summary

Idiopathic sudden sensorineural hearing loss (ISSHL) is characterized by sensorineural hearing loss that develops within 24 hours in otherwise healthy, normally hearing individuals. The hearing loss is of unknown origin and can be mild to profound, temporary or permanent. A known cause can be identified in only 10-15% of cases, even after an extensive evaluation. In the majority of cases the hearing loss is unilateral, but on occasion both ears are involved. The hearing loss is frequently associated with vestibular disturbances, tinnitus and a pressure sensation in the ear. Some spontaneous hearing recovery is reported to occur in 45-65% of cases, although only in a small number of cases will hearing recover to functional levels. The estimated incidence of ISSHL is between 5-20 persons per 100,000 annually. The true incidence is not known because there are groups of patients who may not seek treatment following spontaneous recovery. There is no gender difference or geographical predominance in sudden hearing loss, nor are there seasonal influences.

Most patients present themselves with hearing loss that occurs instantly, often accompanied by the perception of a loud sound, while some develop the hearing loss rapidly progressive. The subjective loss of hearing may first be noticed on awakening or when using the phone. There may be hearing loss in all frequencies, a predominantly high or low tone loss, or a complete loss of hearing. Tinnitus may be the symptom that brings the patient to the physician's office. This symptom occurs in about 80% of patients and can precede the hearing loss. It often persists and can be extremely uncomfortable. A mild form of vertigo affects 40% of patients, while 10% can have a more severe form. Other symptoms include a sensation of aural pressure or headache. Vertigo and a pressure sensation have a good prognosis, in only 10% of the population do these symptoms persist. An upper respiratory infection occurs in about 30% of cases preceding the hearing loss.

Prognostic factors in ISSHL mentioned in the literature include vertigo, the shape of the audiogram, and the severity of the initial hearing loss. In general, patients with mild to moderate hearing loss without vertigo who are seen (and treated) quickly after the initial onset of the hearing loss will have a better chance of recovery.

Of the patients presenting sudden hearing loss, a cause will be found in 10-15% of

cases. The remaining 85-90% has true idiopathic loss. There are four main theories regarding the aetiology: viral infection, disturbances in the microcirculation, inner ear membrane leaks and immunopathological processes. The difficulties in elucidating the aetiology, therefore also the therapy, of ISSHL might be attributed to three factors. The condition's low incidence, especially when inclusion and exclusion criteria are strictly applied, makes the inclusion of sufficient patients to evaluate new therapies difficult. The biggest problem, however, is the closed delicate compartment formed by the inner ear, which does not permit diagnostic samples to be taken. Furthermore, evaluation of treatment is hampered by the lack of a definition of ISSHL, which makes comparison of trials difficult, and the tendency for spontaneous recovery, which makes the contribution of therapy to hearing recovery difficult to assess.

In this thesis the definition of ISSHL is: 1) a perceptive hearing loss of unknown aetiology; 2) hearing loss of at least 30 dB hearing level (HL) for 3 subsequent 1-octave steps in the standard pure tone audiogram (PTA); 3) Hearing loss occurred within twenty-four hours; 4) blank otologic history of the affected ear.

Chapter 2 reviews the literature on the aetiology and therapy of ISSHL. The main theories concerning the aetiology of ISSHL are (1) vascular disturbances, (2) sub clinical viral labyrinthitis, (3) inner ear membrane leaks and (4) immunopathological processes. Each theory is evaluated and relevant treatment modalities compared.
After 60 years of research, aetiology and treatment are still unproven. It even remains uncertain whether ISSHL is a symptom or a disease. All trials suffer from poor design and (too) small patient populations. Even when well designed, no true placebo has been tested. A high-dose steroid is the only therapy to yield some improvement in hearing recovery, although even this is not universally accepted. Vasoactive therapy shows only minor advantages in a small subset of parameters. Our theory that ISSHL is most probably the result of a (sub clinical) viral infection of the inner ear which leads to an immune response, as a result of which the hearing loss occurs, still stands.

Chapter 3. A viral cause of ISSHL was hypothesized because clinical observations reported an upper respiratory infection preceding ISSHL in about 30% of cases. This led to the supposition of a viral cochlear labyrinthitis to cause ISSHL. Reports of seroconversion of herpes antibody titers and the presence of latent neurotropic herpes viruses in the spiral ganglia of asymptomatic individuals have drawn attention

to the possible role of this virus family in causing ISSHL. A possible mechanism could be a latent virus infection and its reactivation. Herpes simplex virus type 1 and 2, varicella zoster virus and cytomegalovirus(HSV-1, HSV-2, VZV, CMV) all have a strong neurotropism and have been detected in human post mortem spiral, geniculate, trigeminal and vestibular ganglia.

In this study, specimens from fresh nervous tissue of the inner ear of 21 unselected patients were taken during operations in which access had to be gained to the cerebellopontine angle. Samples of the inner ear were analyzed by polymerase chain reaction analysis (PCR) for HSV-1, HSV-2, VZV and CMV. Under the hypothesis that ISSHL is the result of a reactivation of a herpes family virus, latent virus should be present and detectable in a proportion of the "normal" population.
In our patient group we detected only two positive PCR-reactions for CMV and three dubious positives for VZV and CMV. None of the samples were positive for HSV. The failure to detect a herpes simplex virus in our series and the very low incidence of CMV and VZV was unexpected. Worldwide, more than 90% of people are seropositive for HSV-1 by their fourth decade of life. The high prevalence of herpes viruses in the general population is undisputed and therefore our failure to detect these viruses is probably due to methodological issues rather than absent virus.

Chapter 4 presents a prospective, randomized, double-blind clinical trial. This study was based on the theory that a viral infection of the inner ear, probably a herpes simplex virus, is the cause of ISSHL.

The therapeutic value of the anti-herpetic drug acyclovir was evaluated by studying the hearing recovery in 91 patients with ISSHL who also received prednisone. The audiometric parameters included pure tone and speech audiometry. Subjective parameters studied included hearing recovery, a pressure sensation in the affected ear, vertigo and tinnitus. A one-year follow-up was obtained. Hearing recovery for the whole group averaged about 35 dB and was independent of initial hearing loss or vestibular involvement. Tinnitus, occurring in a majority of patients, had a poor prognosis. There was no difference in hearing recovery, speech discrimination or subjective parameters between the acyclovir and the prednisone group. We conclude on the basis of this study that no beneficial effect from combining acyclovir with prednisone can be established in patients with ISSHL.

In **Chapter 5** the bioavailability of a new 50 mg dexamethasone tablet was assessed for use in four patients with pemphigus vulgaris. This was a co-operation with the departments of Dermatology and Otorhinolaryngology.
A pulse of 300 mg dexamethasone in the form of six 50 mg tablets was administered orally. Serum concentrations of dexamethasone were measured by high-performance liquid chromatographic procedure with diode-array UV detection. The mean bioavailability of oral high-dose dexamethasone was about 60% of 200 mg dexamethasone administered intravenously. We conclude that dexamethasone in a 50 mg tablet formula is suitable for oral high-dose glucocorticoid pulse therapy.

Chapter 6. A new study was designed where our hypothesis was that a sub clinical virus infection of the inner ear triggers an immune response which in turn causes the hearing loss. A strong suppression of the immune reaction by pulse therapy with high dose dexamethasone, should lead to better hearing recovery as compared to "standard" dose prednisone. In a randomized, prospective, double-blind, multicentre clinical trial, we recruited 81 patients with ISSHL. Patients were randomly allocated to pulse therapy (300 mg dexamethasone for 3 consecutive days followed by four days of placebo) or control treatment (prednisone 70 mg per day tapered in steps of 10 mg per day to 0 mg). The primary outcome was hearing recovery as measured by pure tone audiometry and speech audiometry after 12 months. The secondary outcomes were subjective parameters like hearing recovery, tinnitus, vertigo and a pressure sensation. Overall improvement of pure tone thresholds and speech discrimination scores was slightly but not significantly better in patients given dexamethasone than those given standard prednisone. Hearing improved from 71 dB HL to 36 dB HL in the dexamethasone group and from 75 dB HL to 42 dB HL in the prednisone group. Speech discrimination scores of 100% were attained by 64% of dexamethasone-treated patients and 57% in the prednisone group.
We conclude that Pulse therapy is as least as effective and safe as standard-dose prednisone.

Conclusions

The results of the treatment of ISSHL remain unsatisfactory. In this thesis, two systematic studies have evaluated different aspects of the etiology, and therefore treatment, of ISSHL. Both studies compared the experimental treatment with "standard" dose prednisone. Based on the literature when the studies were performed, prednisone had a small but positive effect on hearing recovery. We felt it was unethical to withhold our patients this treatment, therefore no placebo was used. The first study was based on the theory that a viral labyrinthitis, probably a herpes virus, is the cause of the hearing loss. The addition of acyclovir however, did not improve hearing recovery. The second study was based on the theory that a (viral) infection or reactivation of a viral infection in the inner ear causes an immune reaction which in turn causes the hearing loss. Pulse therapy is used to suppress both the humoral and cellular immune reaction. Suppression of this immune reaction should lead to better hearing recovery. This study did not show a difference between the study groups.

Where does this leave us? Is treatment of ISSHL necessary? Which treatment gives the best results? These are fundamental questions to which there are no easy answers. Additional obstacles in the study of ISSHL are an absence of a clear definition of the disease and recovery, the low incidence and the high rate of spontaneous recovery. These factors greatly contribute to the general low quality of available studies.

As far as the etiology is concerned there are still two main theories left; one is the theory concerning vascular disturbances in the inner ear, the other is the labyrinthitis / immunopathological group. This last theory is often presented as two different theories but I think we must conclude that they represent a spectrum of similar pathophysiologies. Both main theories, however, might well be interrelated and influence each other.

In accordance with the Cochrane collaboration, a few advises can be given.

First it is imperative that a clear and internationally accepted definition of ISSHL is formulated. Second it is important that an accepted definition of recovery is defined. These two factors will greatly improve the comparison of different studies.

So far, the treatment of ISSHL has been unsatisfactory. Small successes have been reported, but on the whole, results have been disappointing. The need for systematic reviews of existing studies and methodically well executed new studies, always comparing the experimental treatment with a placebo, seem to be the route towards elucidating a better treatment option. Due to the low incidence, multicenter studies

are necessary. Furthermore, all patients must undergo a diagnostic protocol to rule out any known causes of hearing loss.
In the University Medical Center Groningen all patients with an unexplained hearing loss follow a diagnostic protocol: this includes a complete history and physical examination, audiological and vestibular tests, magnetic resonance imaging of the temporal bone and cerebellopontine angle, and laboratory work-up. Laboratory investigations are aimed at excluding the presence of an infectious, inflammatory, autoimmune process or coagulopathy. This includes viral and bacterial serology. After the provisional diagnosis ISSHL is made, all patients are treated with the dexamethasone pulse therapy. This is based on our belief that the immune reaction plays a large role in the hearing loss and recovery. Furthermore, pulse therapy has a theoretical wider anti-inflammatory effect compared to standard dose prednisone and a three days of pulse therapy is equally effective as a seven day course of tapered prednisone.

FUTURE PERSPECTIVES

The next step should be a methodologically sound trial comparing prednisone and placebo, although some might think this is unethical. However, first this should, once and for all, close the discussion about the effectiveness of prednisone. Secondly, a meta-analysis is underway by the Cochrane Collaboration evaluating the effectiveness of vasoactive treatment. Further studies of vasoactive treatment should also compare with a placebo. If, and only when positive results have been found, should vasoactive treatments be compared with prednisone. A combination of vasoactive treatments and prednisone might have a synergistic effect, but this can only be concluded after each separate treatment has been tested against a placebo.
Overcoming the inherent difficulties in the study of ISSHL poses major problems, but they should be solvable. This is what we owe to our patients, who come to us seeking help, when they have become suddenly deaf in one ear.

Chapter 8

Nederlandse samenvatting

INLEIDING

Idiopathisch plots perceptief gehoorverlies (Engels: Idiopathic Sudden Sensorineural Hearing Loss, ISSHL) wordt gekenmerkt door een perceptief gehoorverlies dat binnen 24 uur ontstaat in verder gezonde, normaal horende personen. Na uitgebreid onderzoek kan in slechts 10 -15% van de gevallen een onderliggende oorzaak gevonden worden. Het gehoorverlies kan mild of ernstig zijn, tijdelijk of permanent. Bij een overgrote meerderheid van de patiënten treedt het gehoorverlies slechts aan één oor op, zelden aan beide oren. Het gehoorverlies kan gepaard gaan met evenwichtsstoornissen, oorsuizen of een drukgevoel in of rond het oor. Bij 45-65% van de patiënten is er sprake van spontaan herstel, hoewel dit bij de meeste patiënten niet volledig is. ISSHL komt bij 5-20 personen per 100,000 mensen per jaar voor. Het precieze aantal personen met ISSHL is onbekend omdat sommige personen geen dokter bezoeken als het gehoor in de tussentijd hersteld is. Er zijn geen seizoens-, geslachts-, of geografische invloeden op het krijgen van ISSHL bekend. Wel is in 30% van de gevallen sprake geweest van een bovenste luchtweg infectie in de maand voorafgaand aan het gehoorverlies.

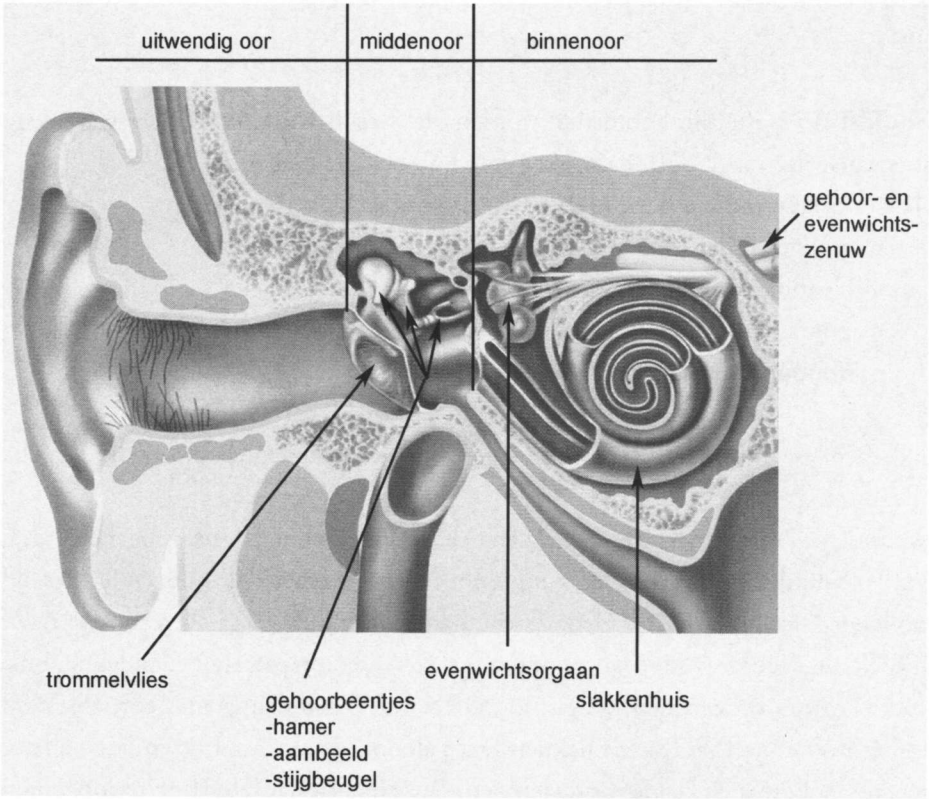
Patiënten kunnen zich presenteren met een plots ontstaan volledig gehoorverlies, of met een snel verergerend gehoorverlies. Het gehoorverlies wordt vaak bij het opstaan of telefoneren bemerkt. Het gehoorverlies kan zich op alle toonhoogtes voordoen, soms alleen voor de hoge of de lage tonen, soms totaal. Naast het gehoorverlies is oorsuizen een veelgenoemde hinderlijke klacht. Oorsuizen treedt op in ongeveer 80% van de gevallen en kan aan het gehoorverlies voorafgaan. Bij 60% van de patiënten met oorsuizen verdwijnen deze klachten niet.
Een milde vorm van duizeligheid treedt bij ongeveer 40% van de patiënten op, bij 10% zijn de klachten zo hevig dat het onmogelijk is om rechtuit te lopen. Een derde van de patiënten heeft last van een drukkend gevoel in of rondom het oor. Echter, evenwichtstoornissen en drukklachten hebben een gunstige prognose. Slechts 10% van de patiënten blijft hier last van houden.

Voorspellende factoren voor het herstel zijn de aan- of afwezigheid van evenwichtsstoornissen, het soort gehoorverlies en de ernst van het gehoorverlies. In het algemeen hebben jonge patiënten met een mild tot matig gehoorverlies zonder duizeligheid, die snel worden behandeld na het begin van het gehoorverlies, de beste kans op gehoorherstel.

Werking van het oor

Voor het begrip van de verschillende theorieën over het ontstaan van ISSHL is het belangrijk om iets over de werking van het gehoororgaan uit te leggen.
In Figuur 1 is een tekening van het gehoororgaan weer gegeven. Geluid is een trilling die via de oorschelp binnenkomt, waarna het trommelvlies deze trilling via drie kleine gehoorbeentjes doorgeeft aan het slakkenhuis (het binnenoor).

Hier wordt de geluidstrilling door speciale zintuigcellen omgezet in een elektrisch signaal dat dan via de gehoorzenuw naar de hersenen gaat. Gehoorsverlies dat optreedt vanaf de oorschelp tot aan de cochlea wordt een geleidingsslechthorendheid genoemd. Gehoorverlies dat optreedt in het traject vanaf de cochlea tot aan de hersenen wordt perceptieve slechthorendheid genoemd. ISSHL is een vorm van perceptieve slechthorendheid.



Figuur 1.

Drie eigenschappen van ISSHL bemoeilijken het onderzoek naar de oorzaak en behandeling ervan. Ten eerste komt ISSHL weinig voor, waardoor het heel moeilijk is om genoeg patiënten mee te laten doen om nieuwe behandelmodaliteiten te onderzoeken. Om wetenschappelijk verantwoorde conclusies te kunnen trekken is het noodzakelijk dat de patiëntengroepen groot genoeg zijn. Ten tweede is het binnenoor zeer kwetsbaar en moeilijk toegankelijk voor onderzoek. Als er een monster uit het binnenoor wordt genomen, wordt het oor doof. Dit is ontoelaatbaar bij een ziekte waar in 45 tot 65% van de patiënten het gehoor in meer of mindere mate herstelt.
Verder wordt het onderzoek gehinderd door het ontbreken van een duidelijke definitie van ISSHL en de al eerder genoemde neiging tot spontaan herstel, waardoor de effectiviteit van de behandeling moeilijk aan te tonen is.
De definitie van ISSHL, zoals gebruikt in dit proefschrift, is 1) een perceptief gehoorverlies van onbekende herkomst; 2) gehoorverlies van ten minste 30 dB voor drie opeenvolgende octaven in het standaard toonaudiogram; 3) het gehoorverlies ontstaat binnen 24 uur; 4) blanco otologische voorgeschiedenis aan het aangedane oor.

Hoofdstuk 2. In dit hoofdstuk worden de vier belangrijkste theorieën over de ontstaanswijze van ISSHL besproken met hun behandelingen.
De vier belangrijkste theorieën die ISSHL proberen te verklaren zijn:
- een onopgemerkte virale ontsteking van het binnenoor,
- doorbloedingsstoornissen van het binnenoor,
- een spontane membraanruptuur van het binnenoor en
- een immuunstoornis van het binnenoor.

Elke theorie wordt geëvalueerd en de verschillende behandelopties worden naast elkaar gelegd.
Na zestig jaar onderzoek zijn oorzaak en behandeling nog steeds niet opgehelderd. Het is zelfs onduidelijk of ISSHL een symptoom of een ziektebeeld is. Alle publicaties lijden aan tekortkomingen in de onderzoeksmethoden en te kleine aantallen patiënten. Zelfs in goed uitgevoerde studies wordt niet vergeleken met een placebobehandeling. Enkele studies wijzen op een beperkt gunstig effect van behandeling met corticosteroïden op het herstel na ISSHL. Medicijnen tegen doorbloedingsstoornissen laten alleen in beperkte subgroepen kleine voordelen zien. Onze theorie dat ISSHL een onopgemerkte virale ontsteking van het binnenoor is, met als gevolg daarvan een immuunreactie die

de schade aan het binnenoor veroorzaakt, en dus ook het gehoorverlies, staat nog steeds.

Hoofdstuk 3. In dit hoofdstuk wordt een studie besproken waarin onderdelen van het binnenoor worden onderzocht op bepaalde virussen met behulp van PCR-analyse (aantonen van DNA van de verschillende virusdeeltjes). Delen van het binnenoor werden onderzocht op de aanwezigheid van het herpes simplexvirus (HSV) type 1 en 2, cytomegalovirus (CMV) en varicella zostervirus (VZV). Een virale oorzaak van ISSHL werd geopperd als hypothese omdat uit klinische observaties bleek dat er sprake was van een bovenste luchtweginfectie in ongeveer 30% van de patiënten met ISSHL. Daarnaast werden in het bloed aanwijzingen gevonden voor seroconversie voor herpesvirussen.

Herpes simplex type 1 en 2, varicella zostervirus en cytomegalovirus (HSV-1, HSV-2, VZV en CMV) zijn allemaal aangetoond bij postmortem onderzoek in menselijk ganglion spirale, geniculate, trigeminale en vestibulaire. Een mogelijk mechanisme hiervoor zou een latente virus infectie met reactivatie kunnen zijn. Het is bekend dat een groot gedeelte van de "normale" populatie besmet is met een van bovengenoemde virussen en deze virussen zouden dan ook verantwoordelijk kunnen zijn voor de onopgemerkte virale ontsteking van het binnenoor, met ISSHL als gevolg.
In deze studie werd bij 21 patiënten, die aan de brughoekregio werden geopereerd en waarbij het binnenoor moest worden opgeofferd, vers zenuwweefsel verzameld en onderzocht op bovengenoemde virussen door middel van PCR-analyse.

De hypothese was dat als ISSHL het resultaat is van de reactivatie van een latent herpes virus in het binnenoor, deze ook moest kunnen worden aangetoond in ongeselecteerde individuen.
In onze patiëntgroep kon in slechts 2 binnenoormonsters CMV worden aangetoond, in 3 binnenoormonster kon zeer beperkt CMV en VZV worden aangetoond. In geen van binnenoormonsters kon HSV worden aangetoond. De afwezigheid van HSV en de zeer beperkte aanwezigheid van CMV en VZV kwam als een verrassing. Wereldwijd is meer dan 90% van de populatie besmet met HSV vanaf het veertigste levensjaar. Deze hoge aanwezigheid van HSV is onbetwist en wij denken dan ook dat in onze studie er eerder een probleem is geweest met het verzamelen van de binnenoormonsters dan dat deze populatie niet besmet zou zijn geweest met deze virussen.

Hoofdstuk 4 presenteert de resultaten van een prospectief, gerandomiseerd dubbelblind klinisch onderzoek. Dit onderzoek ging uit van de theorie dat ISSHL wordt veroorzaakt door een virale ontsteking van het binnenoor, waarschijnlijk door een herpes virus. In deze studie werd de toevoeging van het antiherpetische medicijn aciclovir vergeleken met een placebo op het gehoorherstel bij 91 patiënten met ISSHL beschreven. Beide groepen kregen daarnaast ook de standaardbehandeling met prednison. Het primaire eindpunt was het gehoorherstel gemeten met toon- en spraakaudiometrie. De subjectieve parameters die onderzocht werden zijn het gehoorherstel, drukgevoelens in het oor, evenwichtsstoornissen en oorsuizen. De follow-up bedroeg 1 jaar. Het gemiddelde gehoorherstel voor de hele groep was ongeveer 35 dB en was onafhankelijk van de mate van het gehoorverlies of de aanwezigheid van evenwichtsstoornissen bij inclusie van het onderzoek. Oorsuizen, dat voorkwam bij een meerderheid van de patiënten gaf een slechte prognose. Er was geen verschil in gehoorherstel, spraakaudiometrie, of subjectieve parameters als we beide behandelingsgroepen vergeleken met elkaar. De conclusie was dat toevoeging van aciclovir aan prednison geen toegevoegde waarde heeft bij de behandeling van ISSHL.

In **hoofdstuk 5** werd de biologische beschikbaarheid onderzocht van een nieuw dexametasontablet van 50 mg in de behandeling van 4 patiënten met Pemphigus Vulgaris. Dit was een samenwerkingsverband tussen de afdelingen Dermatologie en Keel-, Neus-, en Oorheelkunde. 300 mg dexametason werd als pulstherapie gegeven in de vorm van 6 tabletten van 50 mg.
De biologische beschikbaarheid bedroeg 60%. Hieruit concludeerden we dat de nieuwe dexametasontabletten van 50 mg geschikt zijn voor toepassing in een orale, hooggedoseerde, corticosteroïd pulstherapie.

Hoofdstuk 6. In een nieuw prospectief, gerandomiseerd, dubbelblind, multicenter klinisch onderzoek werden 81 patiënten met ISSHL gerekruteerd. Onze theorie naar de etiologie was aangepast na de teleurstellende resultaten van het aciclovironderzoek. Een (sub)klinische virale ontsteking zou nog steeds ISSHL kunnen veroorzaken, maar vooral omdat de virusontsteking een immuunreactie oproept die verantwoordelijk is voor het gehoorverlies. Een sterkere onderdrukking van het immuunsysteem zou dus een betere kans op herstel moeten geven.

Patiënten werden gerandomiseerd waarbij de ene groep pulstherapie kreeg (300 mg dexametason per os gedurende drie opeenvolgende dagen gevolgd door 4 dagen placebo) en de andere groep de standaardtherapie (prednison 70 mg per os, in een afbouwschema van 10 mg per dag tot 0 mg). Ook hier was de primaire uitkomst het gehoorherstel na 1 jaar, zoals gemeten met toondrempel- en spraakaudiometrie. Secundaire uitkomsten waren subjectieve parameters als gehoorherstel, drukgevoelens, duizeligheid en oorsuizen. Het gehoorherstel in de pulstherapie groep was iets beter, maar niet significant, dan in de controlegroep. Het gehoor herstelde van 71 dB HL naar 36 dB HL in de dexametasongroep en van 75 dB HL naar 42 dB HL in de prednisongroep. 100% spraakdiscriminatiescore werd gehaald in 64% van de patiënten in dexametasongroep en in 57% van de patiënten in de prednisongroep.

Pulstherapie is daarmee net zo effectief en veilig als standaarddosering prednison. Pulstherapie remt zowel de humorale als de cellulaire immuunreactie en heeft daardoor theoretisch een breder werkingsspectrum dan de "standaard" dosering prednison.

Conclusies

De resultaten van de behandeling van ISSHL zoals beschreven in dit proefschrift blijven onbevredigend. In dit proefschrift zijn twee prospectieve, dubbelblinde, multicenter klinische studies beschreven die systematisch een onderdeel van de behandeling hebben onderzocht. Beide studies vergeleken met een "standaard" behandeling met prednison, omdat ten tijde van de start van het onderzoek er een klein maar significant beter gehoorherstel was gevonden bij patiënten die waren behandeld met prednison. Wij vonden het daarom onethisch om geen prednison te geven. De eerste studie was gebaseerd op de theorie van een virale labyrinthitis, meest waarschijnlijk een herpesvirus, als oorzaak van de ISSHL. De toevoeging van acyclovir gaf geen beter gehoorherstel. De tweede studie was gebaseerd op de theorie dat weliswaar een virale labyrinthitis het begin was, maar dat vooral de immuunreactie hierop de grootste schade aan het binnenoor gaf. Pulstherapie geeft een bredere onderdrukking van het immuunsysteem dan prednison en zou daardoor een groter gehoorherstel moeten geven. Pulstherapie gaf een vergelijkbaar gehoorherstel als de standaarddosering prednison.
En nu? Moeten we ISSHL wel behandelen? Zo ja, waarmee?
Dit zijn de fundamentele vragen die na 60 jaar onderzoek nog steeds niet zijn opgelost.

Problemen bij het onderzoek naar de etiologie en behandeling van ISSHL zijn het gebrek aan een internationaal erkende definitie van het ziektebeeld en van herstel, de lage incidentie en het hoge spontane herstel. Deze intrinsieke factoren zijn een belangrijke reden voor de algemeen lage kwaliteit van beschikbare studies.

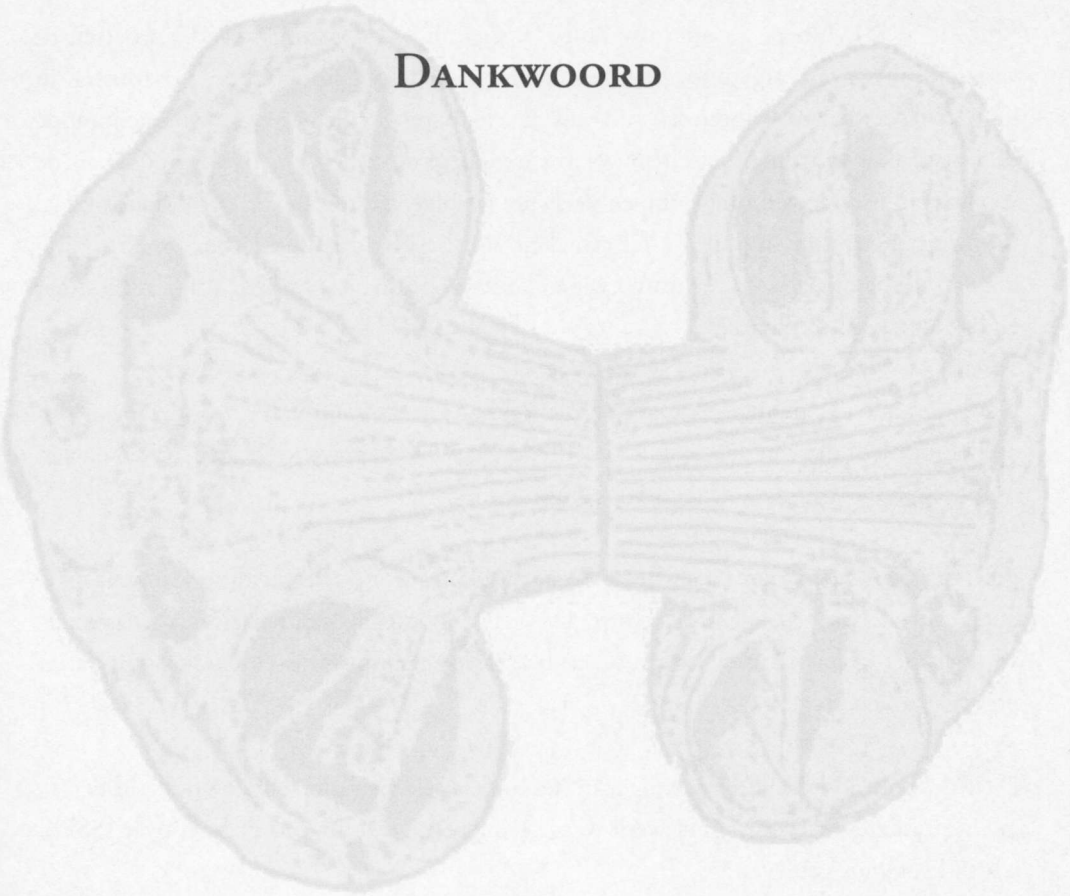
Wat betreft de etiologie zijn 2 theorieën overgebleven: een doorbloedingsstoornis van de cochlea en een labyrinthitis / immuunstoornis van de cochlea. Het is niet ondenkbaar dat deze hoofdtheorieën elkaar beïnvloeden. De laatste theorie wordt vaak gepresenteerd als twee gescheiden theorieën, echter het is waarschijnlijk dat er een grote onderlinge samenhang bestaat.

Evidence Based Medicine, zoals uitgedragen door de Cochrane Collaboration, biedt wel aanknopingspunten voor verder onderzoek. Ten eerste moet een algemeen geaccepteerde definitie van ISSHL worden gevonden. Ten tweede moet er een definitie van herstel komen en een manier waarop dit moet worden berekend. Alleen al het beschikbaar komen van deze twee definities zal bijdragen aan de kwaliteit en vergelijkbaarheid van toekomstige studies.
De behandeling van ISSHL blijft onbevredigend. Kleine successen worden gemeld, maar in het algemeen zijn de resultaten niet beter dan het spontane herstel. Systematische reviews en methodologisch juist uitgevoerde studies die altijd vergelijken met een placebo lijken wél de manier om een antwoord te vinden. Multicenter onderzoek lijkt onontkoombaar gezien de lage patiëntaantallen.
In het Universitair Medisch Centrum Groningen worden alle patiënten met een plotseling gehoorverlies volgens een richtlijn behandeld. Zij doorlopen allemaal een diagnostisch protocol dat gericht is op het uitsluiten van een bekende, en mogelijk behandelbare, oorzaak van het gehoorverlies. Dit houdt in: anamnese en onderzoek, audiometrie en vestibulaire testen, MRI van de brughoek en laboratoriumonderzoek. Het laboratoriumonderzoek is gericht op het uitsluiten of aantonen van een infectieus, inflammatoir, of auto-immuunproces, of een stollingsstoornis. Hieronder valt ook uitgebreide virus- en bacteriële serologie. Nadat de werkdiagnose ISSHL is gesteld worden alle patiënten behandeld met dexamethason pulstherapie.
Dit is gebaseerd op onze theorie dat de immuunreactie een grote rol speelt in het gehoorverlies en gehoorherstel en pulstherapie een theoretisch breder werkingsprofiel heeft dan de "standaard" dosering prednison. Verder blijkt de pulstherapie in drie dagen net zo effectief te zijn als een afbouwschema van 7 dagen met prednison.

Toekomstperspectieven

De volgende stap in het onderzoek naar ISSHL zou een methodologisch goed uitgevoerde trial moeten zijn waarbij prednison (of pulstherapie) wordt vergeleken met een placebo. Dit lijkt misschien onethisch, maar hiermee moet duidelijk worden of een behandeling met prednison zinvol is. De Cochrane Collaboration is nu bezig met een systematische review naar de effectiviteit van behandelingen tegen doorbloedingsstoornissen van de cochlea. Behandelingen van doorbloedingsstoornissen van de cochlea moeten (hierna) ook worden vergeleken met een placebobehandeling. Alleen wanneer positieve resultaten worden gevonden kunnen beide behandelingen met elkaar vergeleken worden. Een combinatie van vasoactieve therapieën en prednison zouden zelfs synergistisch kunnen werken, echter dit is alleen met zekerheid te zeggen nadat beide behandelingen afzonderlijk zijn vergeleken met een placebo.
Het onderzoek naar de etiologie en behandeling van ISSHL is nog lang niet afgerond. Zoals gebruikelijk levert dit proefschrift dan ook meer vragen dan antwoorden op. Het systematisch toetsen van ideeën en behandelingen is een langzame weg, waar ook negatieve resultaten bijdragen aan een toenemende kennis van het ziektebeeld Sudden Deafness. Het overwinnen van alle hindernissen in het onderzoek naar ISSHL kost veel tijd, geld en energie. Dit is wel een moeite die we moeten nemen voor al onze patiënten, die plotseling doof zijn geworden aan één oor.

Dankwoord



De totstandkoming van dit proefschrift was een langdurig proces. Een aantal mensen wil ik in het bijzonder bedanken, zonder wiens hulp dit mogelijk niet volbracht had kunnen worden.

Prof. dr. F.W.J. Albers. Zonder uw hulp, begeleiding en coaching was dit proefschrift waarschijnlijk nooit afgerond. Uw steun gedurende de opleiding en uw vertrouwen in mij dat ik beide zou volbrengen zijn van onschatbare waarde geweest. Ook gedurende de laatste fase van dit proefschrift waarin u zich terug trok, deels ten gevolge van de verandering in uw werkomgeving en deels ten gevolge van uw ziekte, dat u helaas fataal is geworden, en het mij alleen liet afmaken zijn bepalend geweest voor de afronding hiervan. Ik had graag nog veel van u willen leren. Voor dit alles zal ik u altijd onthouden en ben ik u zeer dankbaar.

Dank aan alle deelnemende patiënten die hebben meegewerkt aan dit onderzoek. Om op het moment dat een deel van de zekerheden van dit leven wegvalt, mee te werken aan wetenschappelijk onderzoek getuigt van grote moed.

Prof. dr B.F.A.M van der Laan, Beste Bernard. Dank voor de begeleiding van de laatste, doch cruciale fase van dit proefschrift. De laatste loodjes wegen het zwaarst zeggen ze, en nu is het klaar. Als beëdigd professor ben ik je eerste promovendus, ik hoop dat er nog vele zullen volgen.

Dr. R.J. Stokroos. Als jouw opvolger in het onderzoek naar plotselinge doofheid ben ik jou zeer erkentelijk voor al het werk wat je hebt gedaan. Jouw proefschrift over ISSHL is altijd een gids gebleven.

Prof. dr. ir. H.P. Wit. Zonder uw kennis van statistiek en de mogelijkheden om dit visueel te presenteren was dit proefschrift nooit zo helder geworden.

Dr. ir. E de Kleine, Beste Emile. Jouw nuchtere kijk op statistiek heeft mij behoedt voor al te enthousiaste voorspellingen die ik niet kon waarmaken. Dankzij jou zijn de conclusies ook wetenschappelijk verantwoord en in goed Nederlands verwoord.

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Yo sista, there can only be one.

Lieve Daniëlle. Jij hebt mij gegeven wat ik zocht en nodig heb. Samen met jouw kan ik de hele wereld aan. Door jouw keuze om jouw lot te verbinden aan het mijne heb je mij alle vrijheid gegeven om te kiezen. Het rotsvaste vertrouwen dat ik de juiste keuze zal maken betekent meer voor mij dan je beseft.

Floortje, je vrolijkheid doet wonderen. De wereld ligt aan je voeten.

Hasse, nieuwste Westerlaken telg. Alle wijsheid en liefde die ik kan geven, krijg je.

Boris Olivier Westerlaken

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Curriculum Vitae

Boris Olivier Westerlaken was born on October 18th 1970 in Utrecht, the Netherlands. At the age of eight his family moved to Tokyo, Japan, where he spent his next five years at Nishimachi International School. Upon returning to Holland he went to the Lorentz Lyceum and graduated in his last year at the Eckart College both in Eindhoven. He studied Medicine from 1990 to 1998 at the University of Groningen. Research efforts during his study were made in experimental thorax surgery in Lund, Sweden.

In August 1998 he began his research for this thesis at the department of Otorhinolaryngology at the University Hospital Groningen. He started his residency in 2001 which was completed in 2006. Currently he works as an ENT-surgeon at the Department of Otorhinolaryngology in the Medisch Spectrum Twente in Enschede. He lives together with Daniëlle van der Heide and they have two daughters, Floortje and Hasse.