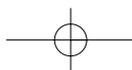
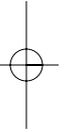




Morbidity in Meniere's disease;  
aspects on quality of life and triggering factors



*Benägne läsare,*

*Lägg märke till det ord med vilket jag anropar Er. Sanningen att säga, om Ni inte vore benägen och redo att välvilligt uppfatta de ord som uttalas och de handlingar som utförs (...), om Ni inte vore hågad att förlåta författaren (hennes) brist på emfas, moraliska syften osv osv, skulle jag inte tillråda Er att läsa vidare. Denna berättelse är skriven med tanke på ett litet antal läsare som jag aldrig råkat och förtretligt nog aldrig kommer att råka: det skulle ha varit ett sådant nöje att tillbringa aftonen med dem!*

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*Farväl, käre läsare och vän, se till att Ni inte ägnar Ert liv åt att hata och vara rädd.*

STENDHAL

Anne-Charlotte Hessén Söderman

## Morbidity in Meniere's disease; aspects on quality of life and triggering factors

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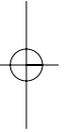
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## CONTENTS

Contents	5
Abstract	7
Acknowledgements	8
Abbreviations	11
Introduction	13
<i>Meniere's disease</i>	13
<b>Clinical presentation</b>	13
<b>Definition</b>	13
<b>Historical Background</b>	14
<b>Symptomatology</b>	14
Vertigo	14
Hearing loss	14
Tinnitus and aural fullness	14
<b>Natural course</b>	14
<b>Etiology and pathogenesis</b>	15
<b>Treatment</b>	16
Medical treatment	16
<i>Symptomatic treatment</i>	16
<i>Dietary salt restriction and diuretics</i>	16
<i>Vasodilators</i>	17
<i>"Immunological" treatment</i>	17
Pressure and oxygen treatment	17
Intratympanic treatment with aminoglycosides	17
Surgical treatment	18
<i>Endolymphatic sac surgery</i>	18
<i>Labyrinthectomy</i>	18
<i>Vestibular neurectomy</i>	18
<b>Epidemiology in Meniere's disease</b>	18
<b>Psychosomatic and somato-psychic aspects on Meniere's disease</b>	19
<b>Quality of life in Meniere's disease</b>	19
<b>Stress in Meniere's disease</b>	20
<i>Concepts integrated in the study</i>	21
<b>Health and quality of life</b>	21
<b>Stress and coping</b>	22
<i>Sense of coherence</i>	23
<b>Aims and objectives of the study</b>	24
<b>Material</b>	25
<i>Patients</i>	25
<i>Reference and comparison groups</i>	27

Methods	29
<i>Extended clinical examinations</i>	29
Questionnaires	29
Case-crossover method	32
Statistical methods	33
Results	35
Paper I	
<i>Surgical treatment of vertigo: The Karolinska Hospital policy</i>	35
Paper II	
<i>Patients' subjective evaluations of quality of life related to disease-specific symptoms, sense of coherence, and treatment in Meniere's disease</i>	36
Paper III	
<i>Factors influencing quality of life in Meniere's disease, identified by a multidimensional approach</i>	37
Paper IV	
<i>Stress as a trigger of Meniere's disease attacks. A case-crossover study</i>	40
Discussion	41
Methodological aspects	43
Clinical applications	44
Conclusions	45
References	46
Paper I-IV	55-103
Appendix	104

## ABSTRACT

Meniere's disease is an inner ear disorder of unclear origin, characterized by severe attacks of simultaneously appearing fluctuant hearing loss, vertigo, tinnitus and a feeling of aural fullness. The disease has a well-known natural course. In the early stage symptoms occur episodically, followed by complete remission, but during the course of the disease the hearing impairment progresses and becomes permanent, while the vertigo becomes less prominent with time. The sudden and unexpected attacks can cause a dramatic influence on the patient's quality of life, particularly as it is combined with increasing hearing loss and tinnitus. It is a well known clinical issue that stress might trigger the attacks, but so far the only correlation found has been a same day association between stress and attacks.

### AIMS OF THE PRESENT INVESTIGATION

1. To assess which of three different surgical treatments of vertigo (Endolymphatic Sac Surgery, ELS, intratympanic gentamicin injections or vestibular neurectomy) was most beneficial to patients with Meniere's disease. 2. To evaluate health-related quality of life issues from a general and disease specific perspective. 3 To find if stress can trigger attacks of Meniere's disease 4. To propose a policy for treatment of patients with Meniere's disease

### MATERIAL AND METHODS

1. 40 surgically treated patients with Meniere's disease were followed up with extended clinical tests, including vestibular and audiological tests, computerized postural tests, functional balance tests and a questionnaire. 2. 112 Meniere patients, both surgically treated and untreated, answered a battery of disease specific and generic quality of life questionnaires. The sense of coherence, which measures coping ability, was also evaluated. 3. In a case-crossover study, 46 Meniere patients answered questionnaires concerning the frequency of stress both in the period before an attack of Meniere's disease and in a period without attacks.

### RESULTS AND CONCLUSIONS

1. The outcomes with regard to vertigo were similar regardless of treatment modality. About 80% of the patients in each group reported a total or substantial improvement of vestibular symptoms, but the gentamicin treated patients had more adverse effects on hearing and vestibular neurectomy resulted in some surgical complications.

2. The patients rate their quality of life as being significantly poorer than reference groups of healthy subjects, in both the physical and the psychosocial dimensions. Vertigo impairs the physical dimension of quality of life, while tinnitus and hearing loss have influence on the psychosocial dimension. Strong sense of coherence seems to be an important predictor of the patient's evaluation of disease-specific as well as general quality of life, but the impact of the sense of coherence is stronger on psychosocial than physical aspects.

3. Being subjected to emotional stress increases the risk for an attack of Meniere's disease to occur one to three hours later. Mental stress has less impact on the risk for having a Meniere-attack and physical stress has not been found to trigger attacks of Meniere's disease.

4. When medical treatment has failed, ELS may be a useful first choice of surgery treatment modality in patients with serviceable hearing. Recent treatment regime with low dose gentamicin can be used if ELS has failed or if for some reason surgery in general anesthesia not is advisable. Vestibular neurectomy should be saved for special cases and performed in a limited number of patients. Considering the role of stress as a trigger of attacks it might be fruitful to test whether different kinds of stress management techniques could be taught to patients with the effect of reducing the number of attacks.

### KEY WORDS:

Meniere's disease, ELS, gentamicin, vestibular neurectomy, outcome assessment, health related-quality of life, sense of coherence, stress, case-crossover.

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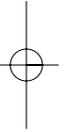
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## ABBREVIATIONS

AAO/HNS	American Association of Otolaryngology/Head and Neck Surgery
ELS	Endolymphatic Sac Surgery
FLS	Functional Level Scale
HAD	Hospital and Anxiety Depression Scale
HDHS	Hearing Disability Handicap Scale
HRQL	Health-Related Quality of Life
MCS-12	Mental Component Summary 12
PCS-12	Physical Component Summary 12
SF-12	Short Form 12
SF-36	Short Form 36
SIP	Sickness Impact Profile
SOC	Sense of Coherence
TSQ	Tinnitus Severity Questionnaire
VSS	Vertigo Symptom Scale

THIS THESIS IS BASED ON THE FOLLOWING PAPERS, WHICH WILL BE REFERRED TO IN THE TEXT BY THEIR ROMAN NUMERALS:

I

Hessén Söderman AC, Ahlner K, Bagger-Sjöbäck D, Bergenius J.  
Surgical Treatment of Vertigo-The Karolinska Hospital Policy  
American Journal of Otology (1996) Vol 17, No 1 93-98 Jan

II

Hessén Söderman AC, Bergenius J, Bagger-Sjöbäck D, Tjell C, Langius A.  
Patients' subjective evaluations of quality of life related to disease-specific symptoms,  
sense of coherence, and treatment in Meniere's disease  
Otology & Neurotology (2001) Jul;22(4):526-33.

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Hallqvist J.  
Stress as a trigger of Meniere's disease attacks. A case-crossover study  
In manuscript

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## INTRODUCTION

### *Meniere's disease*

#### Clinical presentation

Meniere's disease is an inner ear disorder of unclear origin. It is characterized by attacks of simultaneously appearing vertigo, hearing loss, tinnitus and a feeling of aural fullness. The pathologic correlate is hydropic distension of the endolymphatic system. The attacks occur in well-defined, often prostrating, episodes, frequently accompanied by nausea and sometimes vomiting, and persist for 20 minutes up to 24 hours. Erect posture often becomes impossible and movement of the head aggravates the balance disorder and nausea. The attack often starts suddenly, and once an attack is underway, the patient is compelled to remain as still as possible. There might be various adjunctive spells between the definite attacks, such as motion intolerance, positional vertigo, drop attacks, etc, but the diagnosis is not applicable unless the patient is free of symptoms between the definite attacks. During an attack hearing in the affected ear becomes impaired and tinnitus increases, remaining so for a variable time after the attack. It is highly likely that the patient's quality of life can be severely impaired. One important issue is the fright and insecurity caused by the sudden and completely unexpected attack of vertigo, which might result in a reaction of intense anxiety and often panic [1]. The attacks occur episodically, and it is not possible to establish a timetable. An episode may be followed by a period of a year or more without symptoms, or attacks may cluster over a brief period of time. Such uncertainty in predictably increases the patient's general level of anxiety [2].

#### Definition

The American Academy of Otolaryngology-Head and Neck Surgery (AAO/HNS) committee on Hearing and Equilibrium has, since 1972, given three versions of guidelines for diagnosis and evaluation of treatment in Meniere's disease. The last version of the guidelines was published in 1995. According to the 1995 guidelines, Meniere's disease is defined as recurrent, spontaneous episodic vertigo, hearing loss, aural fullness and tinnitus [3]. The committee also concluded, "For reporting purposes, Meniere's disease is a clinical disorder defined as the idiopathic syndrome of endolymphatic hydrops", i. e. the committee has chosen a simplified definition and accepted that there is no consensus on the underlying pathogenesis.

Even though the AAO/HNS definition is accepted world-wide, there are still unresolved issues on the definition of the disease, particularly regarding the duration, the presence of bilateral disease and the necessity of presence of aural fullness if tinnitus is absent. These matters have recently been discussed in a thesis from the Netherlands [4], which includes a diagnostic protocol for clinical purpose and an extended protocol for scientific analysis.

## Historical Background

The French physician, Prosper Ménière, who gave name to the disease, first described the condition in 1861. Meniere's impressive achievement was to identify the specific disease out of a group of neurological disorders, at the time known as "apoplectiform cerebral congestion". Meniere, in Atkinson's translation [5], states that "when these symptoms (vertigo, dizziness arising suddenly and giving rise to a state of syncope, to nausea and vomiting) are accompanied by a buzzing in the ears, by continued and variable head noises, and above all when there arises rapidly a notable diminution of hearing, then the trouble has its seat in the labyrinth and more particularly in the semicircular canals." For the first time the inner ear was pointed out as the site of origin in balance disorders. The term Meniere's disease appeared in the literature in 1867, after Meniere's death, in a publication by Adam Politzer [6]. The next significant contribution to the understanding of Meniere's disease was published in 1927, when Guild described and discussed the longitudinal flow of endolymph [7]. That same year Portmann described the surgical treatment of Meniere's disease using an endolymphatic sac operation [8], and Dandy simultaneously discussed vestibular neurectomy for treating vertigo [9]. In 1938 Yamakawa [10] in Osaka and Hallpike and Cairns [11] in London independently discovered endolymphatic hydrops in post-mortem studies on temporal bones from Meniere disease patients.

## Symptomatology

According to the guidelines from AAO/HNS' Committee of Hearing and Equilibrium [3] the three major symptoms are shortly described as follows:

### Vertigo

The definite spell of Meniere's disease is a spontaneous rotational vertigo, lasting at least 20 minutes (commonly several hours), often prostrating, and it is accompanied by dysequilibrium, which may last for days. Consciousness is not lost. During the definite episode, horizontal or horizontal rotatory nystagmus is always present.

### Hearing loss:

1. The average of hearing thresholds at 0.25k, 0.5k and 1 kHz is 15 dB or more than the average of 1, 2 and 3 kHz.
2. In unilateral cases, the difference between the average of the thresholds values at 0.25k, 0.5k and 1 kHz is 20 dB or more when comparing the ear in question with the ear on the opposite side.
3. In bilateral cases, the average of the thresholds values at 0.25k, 0.5k and 1 kHz is greater than 25 dB in the studied ear.

### Tinnitus and aural fullness

Tinnitus and aural fullness are not defined in the guidelines; the guidelines only state that these are difficult to quantify independent from the hearing loss and the vertigo.

## Natural course

The natural course of the disease has been described by Friberg et al [12] using a retrospective material, which consisted of 161 Meniere patients. The patients were followed for 9 years or more, and the hearing-impairment, the caloric response, the vertigo and the

ability to work were analyzed. The authors showed that after about 5–10 years duration of disease, the initial cochlear hearing loss evens out at a hearing level of 50–60 dB and the vestibular loss at a caloric response which is about 50% of the normal. In addition the frequency of vertigo attacks decreases after approximately two decades. The impact of vertigo on capacity to work during the course of disease was described as moderate. The risk for developing bilateral disease is considerable. Figures for bilaterality ranges from 10% [13] to 45% [14].

### Etiology and pathogenesis

The etiology of Meniere's disease is still unknown. Numerous hypothetic etiologic factors have been studied. Paparella proposed a developmental anomaly of the endolymphatic sac and duct due to multifactorial heredity [15]. Allergy as a possible etiologic factor has been the subject to many studies [16–18] since the first report by Duke in 1923 [19]. Meniere's disease has also been proposed to be an autoimmune disease and studies have both supported and rejected the theory [20–23]. Viral infections [24–26] and disturbance of the glycoprotein metabolism [27, 28] are other proposed etiologic factors. Alternative theories concern the roles of hormones [29–33] and enzymes [34], acting in the inner ear.

One invariable finding in Meniere's disease patients is the presence of endolymphatic hydrops, even though it also can be found in other afflictions of the labyrinth. An imbalance between secretion and resorption of endolymph has been suggested to be the pathophysiologic mechanism. One theory is based on Guilds work on the circulation of endolymph, known as the "longitudinal flow theory" [7]. According to this theory, the endolymph is produced in the scala media, passing through the ductus reuniens, saccule and endolymphatic duct to reach the endolymphatic sac where the absorption takes place. An alternative theory, the "radial flow theory", proposes that the production of endolymph enmates from perilymph which should occur in each cochlear section independently [35]. The fluid transport takes place through Reissner's membrane, with an ion exchange being carried out by the stria vascularis. Probably the longitudinal and radial flows are complementary and occurs simultaneously [34, 36].

Endolymphatic hydrops may explain the chronic symptoms in Meniere's disease. A reduced resorption of endolymph in the endolymphatic sac may produce endolymphatic hydrops. The ensuing endolymphatic overpressure may alter the cochlear amplifier by decoupling of the tectorial membrane from the sensory hair bundles. This mechanism may contribute to chronic sensorineural hearing loss and tinnitus, but not to the acute Meniere's attacks [37].

Schuknecht in 1963 proposed the membrane rupture theory [38] in order to explain acute attacks. According to this theory, transitory endolymph leakage can occur in Reissner's membrane or in the reticular lamina, and may be produced by ruptures or transitory junctional leakage of the distended endolymphatic system. The repair of the membranes between attacks is a prerequisite for this concept. Healed membranes have also been reported in studies of post mortem human material, but the observed ruptures have been regarded mainly as artefacts.

Hydrophilic glycoproteins have been proposed playing a role in Meniere's disease. Gibson's and Arenberg's drainage theory of erratic endolymphatic sac function states that irregular production of these glycoproteins could cause hydrops and sudden changes in

endolymphatic flow, and also stagnation of endolymphatic fluid and backflow [39].

Attacks may also be mediated through stress-induced changes in the levels of hormones that influence the inner ear [33, 40]. This mechanism will be discussed later.

## Treatment

The major problem when evaluating treatment results of Meniere's disease is to account for the natural course of the disease, as well as for the placebo effect. In a retrospective analysis Torok [41] concluded that the various therapies in Meniere's disease all produced a remission rate in 60-80% of the patients. In 1989 Silverstein [42] published a long-term follow-up of 50 patients who had declined surgery after failure of medical treatment. After two years 59% of the patients reported complete control of vertigo, increasing to 70% after eight years.

There are almost no published results from evidence-based studies on the treatment of Meniere's disease. Thorp and co-workers systematically reviewed 128 publications in 2000 [43], out of which only three were randomised controlled trials and a further three were well-designed controlled studies without randomisation. The majority of the remaining articles concerned non-experimental clinical descriptive studies or case series. The six studies with good design are accounted for under each individual treatment modality subheading.

### Medical treatment

#### SYMPTOMATIC TREATMENT

Vestibular suppressant drugs have been used for a long time to control vertigo. These drugs have variable sedative, anticholinergic and antiemetic properties. The site of action in the vestibular system is however unknown, and there is little data on their effect in Meniere's disease [44], except for one study by Storper et al, who in a randomised controlled trial could show that glycopyrrolate is a useful vestibular suppressant in patients with Meniere's disease [45].

#### DIETARY SALT RESTRICTION AND DIURETICS

Diuretics and dietary salt restriction have been considered one of the primary treatments of cochlear hydrops for many years. The hypothesis is that these drugs can alter the fluid balance in the inner ear. The Furstenberg regimen, including low-sodium diet and diuretics was developed and promoted in the 1930's [46]. The Furstenberg group concluded that the tissues involved in Meniere's disease have an increased avidity for sodium ions or an unusual sensitivity to them. Dietary treatment of Meniere's disease is still very popular, even though there is no evidence of treatment effects [47]. The last evaluations of the regimen were published in the 1970's [46, 48]. Boles et al conclude, based on clinical experience, that the Furstenberg regimen has been quite satisfactory in relieving the most disturbing symptoms in the vast majority of cases, but no control group is presented and the natural course of the disease is not discussed. According to Snively, salt restriction is only effective when it contains the amount of sodium recommended on the physicians order and the patient is taught by a dietician. A moderate salt restriction means 1/4 teaspoon of salt daily, including bread and butter as well as the natural amount of salt in foods such as meat, fish cheese etc. These foods must be restricted or specially prepared to remove the salt.

There are two placebo controlled double blind studies on diuretics. Klockhoff et al [49,

50] studied 30 patients who had been treated with either hydrochlorthiazide or placebo for two 4-months periods. A two-months observation period preceded the remedy, which was followed by second two-months observation period. The authors concluded that vertigo and tinnitus as well as the patient's general condition improved during the active treatment period. The second double blind study on diuretics (hydrochlorthiazide and triamterene) by van Deelen and Huizing [51] showed improvement on vertigo scores, but not on hearing or tinnitus. In this study however the placebo-treated patients also reported improvement, so the selective effect of diuretics remains unclear.

#### VASODILATORS

The use of vasodilators is based on the hypothesis that endolymphatic hydrops results from ischaemia in the stria vascularis. The drugs are intended to improve metabolism in the affected inner ear. Thus we encounter the paradox that histamines and antihistamines are both used to treat the same condition [44]. Two double-blind studies [52, 53] on the histamine analogue betahistine (Betaserc®) have indicated some short-time effect on vertigo, hearing loss and tinnitus. On the other hand, a randomised controlled trial by Schmidt and Huizing suggests that betahistine has no effect on tinnitus and hearing loss when compared with placebo [54]. This trial found no effect on imbalance, but did not assess rotational vertigo.

#### IMMUNOLOGICAL TREATMENT

"Immunological" treatments include administration of steroids, systemically or intratympanically, as well as immunoglobulin injections and plasmapheresis. Only intratympanic dexamethasone has been the subject of a prospective randomised controlled study, which did not show that dexamethasone was superior to placebo [55].

#### Pressure and oxygen treatment

In 1974 Tjernström observed that ambient pressure changes were related to inner ear function [56]. Based on these findings, pressure chamber treatment for Meniere's disease has been tried and positive effects on quality of life have been reported [57]. Unfortunately this was study design without a control group. Oxygen treatment has also been used, with reported improvement on the incidence and intensity of vertigo attacks, as well as hearing thresholds and tinnitus when compared with a non-treated control group [58].

Ödkvist et al studied local over-pressure treatment in the affected ear. In their placebo-controlled study, improvement on inner ear symptoms could be demonstrated, even though study time only was two weeks [59].

#### Intratympanical treatment with aminoglycosides

Schuknecht first introduced ototoxic drugs, administered intratympanically, in 1957 [60]. The treatment have since then been advocated by several authors, based on results from large series of patients [61–66]. In the early studies, high doses of aminoglycosides were used, with a high incidence of adverse cochlear effects as a result. In recent years a very low titration technique has been accounted for [67]. The exact dosage varies between studies, but improvement of vestibular symptoms in 80–90% of the patients with preserved hearing has been achieved [66]. In a review of eighteen articles, Blakley concluded that at present no single technique of gentamicin injection has a significant advantage over the

others [68]. At Karolinska Hospital the first patients, treated in the 1980's, received much higher doses (up to 17 injections) than the recently treated patients, who only received 2-4 injections.

### Surgical treatment

#### ENDOLYMPHATIC SAC SURGERY

Even though endolymphatic sac surgery (ELS) has been seriously criticized [69], it is still a common procedure, with low rate of complications [70, 71]. Portmann first proposed drainage of excess endolymph into the mastoid through an opening in the endolymphatic sac in 1927 [8]. Several variations of this technique have been developed [72], such as endolymphatic sac decompression and endolymphatic-mastoid shunt procedures. At the Karolinska Hospital the operation is performed by inserting a small silastic shunt into the sac, draining it into the mastoid.

#### LABYRINTHECTOMY

In the 1950's otologists began to carry out labyrinthectomy. This procedure did cure the vertigo and was associated with little risk to the facial nerve and other adverse effects. The major drawback to the procedure was the unavoidable loss of hearing [73]. However, it is a rapid and safe procedure for patients with non-serviceable or borderline hearing [74].

#### VESTIBULAR NEURECTOMY

When medical and non-destructive surgical procedures have failed, as well as intratympanic gentamicin injections, vestibular neurectomy is the last treatment alternative to offer the patient, particularly if the hearing is to be preserved. Success rates with abolition of the vertiginous attacks from 85-100% have been reported in different materials [75]. It is a neurosurgical procedure that requires long surgical experience, and even in skilled hands the risk for serious complications is considerable. The middle fossa, the retrolabyrinthine and the retrosigmoid approaches are the surgical approaches used. In the 1990's more than 90% of the vestibular nerve sections in the USA were performed through a posterior fossa approach (retrolabyrinthine, retrosigmoid or a combination of these) [76]. At the Karolinska hospital the middle fossa approach, according to Haid's description [77] is used, as it is regarded to provide better exposure of the internal auditory canal.

### Epidemiology in Meniere's disease

Reliable data about the epidemiology of Meniere's disease are scarce, even though the disease has been subject to many epidemiological investigations. There are studies of the geographic, ethnic and socio-economic distribution as well as of the incidence in the general population.

Okafor conducted a study in Nigeria [13], and he proposed that improved facilities would demonstrate that racial factors are of no importance in Meniere's disease, even though in early studies the incidence was believed to be lower among blacks than among Caucasians.

Celestino and Ralli reported an unexpectedly high occurrence of Meniere's disease in doctors, nurses and hospital employees [78]. They concluded that the level of health awareness and the ease with which it is possible to obtain medical help are factors that gre-

atly increase the number of diagnosed cases. Watanabe reports similar findings from Japan: an apparently higher incidence of Meniere's disease among technicians or "white-collar" workers [79].

A slight female [80] or male [81] predominance have been reported among Meniere disease patients, as well as equal sex distribution [79]. Friberg concludes that most probably there is no difference between sexes, and that the slight differences reported could be attributed to different principles in patient selection or to local social factors [14].

A number of incidence and prevalence figures from different countries have been published, but comprehensive statistics on the incidence are lacking, depending on the lack of a well-defined population at risk, lack of adequate diagnostic criteria, and failure to make a distinction between relative frequency, prevalence ratio and incidence rate of the disease, as has been pointed out by Wladislavosky-Waserman [80]. Available incidence figures ranges from 82 cases per  $10^6$  inhabitants in Italy [78] to 1.570 per  $10^6$  inhabitants in Great Britain [81]. In Sweden an incidence of 460 cases per  $10^6$  inhabitants has been reported [82].

### Psychosomatic and somato-psychic aspects on Meniere's disease

Some diseases are identified as psychosomatic since there seems to be specific mental factors implicated in one or more phases of a disorder. Meniere's disease used to be referred to as a psychosomatic disorder. Clinical and case studies as well as systematic assessment with standardized tests seemed to provide evidence that psychological factors have a significant role in the development of the disease [1, 83, 84]. In 1977 Cray and Wexler [2] challenged these conclusions. They demonstrated that when Meniere patients were compared with a non-vertiginous group, differences in psychopathology emerged. However, when these patients were compared with patients with organic ear diseases, who were also vertiginous, the differences vanished. Their conclusion was that the psychopathology noted in the previous studies was a response to, rather than a cause of, the disease.

Hägnebo et al have performed a retrospective study [85] using questionnaires about somatic sensations and psychological state before and during an attack. Situational characteristics surrounding an attack were also investigated. The analysis of the psychological state showed an energy/awareness factor and a negative emotional factor. Two factors were found surrounding an attack: emotional disturbances and stressful conditions.

In a study on Meniere's disease patients Groen found that psychosomatic factors ("conflictogenic environment") had impact on the fluctuating course of the disease [1].

Takahashi et al performed an analysis of lifestyle and behavioral characteristics in patients with Meniere's disease [86] and concluded that the behavioral characteristics of the Meniere patients are more stress-causative than in normal controls, and may be important in the pathogenesis of endolymphatic hydrops.

### Quality of life in Meniere's disease

Recently the Meniere patient's subjective view on the health-related quality of life has been taken in account in several studies. In 1995 Cohen et al, using quality of life questionnaires, found that the most disabling symptom is vertigo, followed by hearing loss [87]. Hägnebo et al showed that all the prominent symptoms of Meniere's disease, i.e. vertigo, hearing impairment and tinnitus had negative influences on the daily life [88].

Kinney et al used both disease-specific and global quality of life instruments [89] in the long-term follow-up of a group of Meniere patients. Their results showed that the health handicap was greater for emotional distress than for physical ability, and by using the disease-specific quality of life instruments, no significant differences between medical and surgical treatment were found. Kinney's study is so far the only study to compare the patient's own evaluation of the Meniere's disease specific symptoms with different treatment regimes. Smith and Pyle [90] have used a global quality of life instrument (Short Form-36, SF-36) as well as both the A-F classification and the Functional Level Scale (FLS) of the AAO/HNS criteria, to evaluate the results of ELS. According to the SF-36 the Meniere patients preoperatively scored significantly lower function than norms on the role-physical and social functioning subscales. Postoperatively, patients that were classed as class A or B (total or substantial control of definite spells) scored significantly better function on the role-physical, social functioning and role-emotional subscales of the SF-36 than the patients classed as class C-F (unchanged or increased number of definite spells postoperatively or secondary treatment because of treatment failure). Several patients who reported good outcomes on the FLS scored below norms on the SF-36, possible indicating that the SF-36 is more sensitive to changes than the FLS.

A quality of life questionnaire specific to Meniere's disease, the MD-POSI, has also been published [91, 92]. Neither results using the MD-POSI nor tests of validity or reliability have been presented as yet.

In the 1995 guidelines from the AAO/HNS – the "golden standard" when presenting results of treatment of Meniere's disease – a single-question item is included concerning the effect of vertigo on daily life activities [3]. This 6-point scale, The Functional Level Scale (FLS) can be regarded as a rough inclusion of quality of life aspects in the evaluation of treatment results. It must however be pointed out that even if the AAO/HNS classification and FLS are worldwide accepted and used, no tests of validity or reliability of the scales have been published.

### Stress in Meniere's disease

Except for anecdotic case reports, three studies on stress as a triggering factor of Meniere's disease attacks have been published. Crary and Wexler conducted a study where patients with Meniere's disease kept diaries to record stress and vertigo [2]. Most attacks of vertigo occurred in the absence of stress. Their data also showed that the occurrence of stress within 5 days prior to (proportion of cases=0.075) as well as within 5 days after an attack (proportion of cases=0.068) was almost equal to the stress that occurred on the same day as an attack of vertigo (proportion of patients=0.084). They interpreted the findings as if the occurrence of stress was equal in the three periods. However, because of the different time spans, these results can be interpreted as if the occurrence of stress was in fact five times higher the day of an attack or vertigo.

In a prospective study Andersson et al [93] showed concurrent (same day) associations between stress and Meniere attacks by means of a time-series analysis. However in their report the information is not detailed enough to conclude whether "the same day stress" preceded or followed an attack.

Sawada et al [94] used a retrospective stress questionnaire in a study on the effect of antidiuretic hormone on Meniere's disease. They found that 78% of the 46 cases were con-

scious of stress before an attack of vertigo. Their questionnaire is without any details concerning the time span between stress and attack, and includes stressors as "social conflicts", "economical problems" and "living alone", which are complicated to evaluate as triggers of the onset of an acute attack.

In these three studies the temporal resolution in the exposure information is too inexact to determine whether stress occurring on the day of the attack came before or after the onset of the attack. Although none of the studies actually conclude that stress the same day precedes the attacks this might well have been the case.

## *Concepts integrated in the study*

### Health and quality of life

THE WHO DECLARES (95):

*Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.*

A medical conception of health is freedom from disease and abnormalities; a sociological conception can be defined in terms of the possession of acceptable levels of mental and physical fitness, in order to perform one's role in society. There is also a humanistic view of health in which optimal autonomy, personal strength and the positive meaning of life are central components [96].

Health status is increasingly referred to as quality of life, and quality of life is therefore increasingly referred to as health-related quality of life (HRQL).

HRQL – like subjective health status - is patient based, but focuses more on the impact of a perceived health than on the ability to live a full life. It is important to remember that HRQL is distinct from quality of life as a whole, which would also include other factors such as adequacy of housing, income and perceptions of immediate environment [96]. Wilson and Cleary have presented a conceptual model for linking clinical variables with HRQL [97]. According to this model, measures of health can be thought of as existing on a continuum of increasing biological, social and psychological complexity. At one end of the continuum are biological measures and at the other are more complex and integrated measures as physical functioning and general health perceptions. Five levels can be distinguished on the continuum: biological and physical factors, symptoms, functioning, general health perceptions and overall quality of life.

THE WHO HAS ALSO PROVIDED A DEFINITION OF QUALITY OF LIFE:

*Quality of life is defined as an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad ranging concept affected in a complex way by the person's physical health, psychological state, level of independence, social relationships, and their relationships to salient features of their environment. (WHO Quality Of Life Group 1993b [98]).*

Cella and Tulsky have presented a similar definition of quality of life, which also takes the individual's perception of and relationship to the environment into account: "Quality of life refers to patient's appraisal of and satisfaction with their current level of functioning as compared to what they perceive to be possible or ideal" [99]. They suggest that,

when the assessment of quality of life is operationalized to cover cancer patients, it should include physical concerns (symptoms and pain), functional ability, family well-being, emotional well-being, spirituality, treatment satisfaction, future orientation, sexuality and intimacy, as well as social and occupational functioning. Even though this definition is intended for cancer patients, the same aspects are applicable for patients with Meniere's disease as well as other disorders.

As quality of life is a multidimensional concept, it is difficult to measure. The use of multiple instruments covering different research questions of presumed importance to a certain study sample may facilitate the obtaining of adequate answers concerning the patients' perceived quality of life in connection with their disease and treatment [96, 100].

Quality of life instruments are mainly of two types, disease-specific and generic [101]. Disease-specific instruments focus on problems associated with the specific diagnoses (as cancer) or specific symptoms (as hearing loss), while generic instruments point to general health, functional status or well-being.

### Stress and coping

Throughout life, human beings are confronted with a variety of stressful situations, some of which may threaten the individual's life, health or quality of life. It is important to recognize that stress is not necessarily bad for the individual [102–104]. It has been suggested that there are three forms of stressors [102].

Primarily, chronic stressors, which are beyond the control of the individual, such as the historic era, the cultural surroundings or a natural disaster.

Secondly, major life events, such as death or birth in the family, divorce, retirement or suffering from a disease.

Thirdly, daily hassles or everyday problems, as having an argument, being late for work, queuing or feeling lonely.

Different models concentrate on different types of stress, such as physiological or psychological stress.

According to the stimuli-response-based model, a stressor is explained as the demand that invades the body, and consequently stress is the individual's response to these demands. Selye, "the father of stress", developed this model, called the General Adaptive Syndrome (GAS), more than 60 years ago [103]. He suggested that stress, no matter if it is evoked by physical or psychological demands, results in the same general reactions in the individual's body.

The transactional model of stress, suggested by Lazarus [102], views the person and the environment in a dynamic, mutually reciprocal relationship. A stressor can be defined as a stimulus, which "poses a demand to which one has no ready-made immediately available and adequate response". Coping can be viewed as a strategy to deal with and attempt to overcome problems and difficulties. In recent years, there has been great scientific interest in the phenomenon of coping as related to stress, illness and health. Both Lazarus and Antonovsky [104] use the transactional model to state that the coping process starts when an individual is affected by a stimulus (stressor) and appraises the situation as benign/positive, irrelevant or stressful. According to Antonovsky's theory it is the individual's prerequisites that decide whether the stimulus is benign, irrelevant or stressful,

while according to Lazarus the two perspectives supplement each other [105].

The physiologic response to stress depends on in which fashion a person perceives a situation, and the person's general state of physical health, which is determined not only by genetic factors but also by behavioural and lifestyle choices [107]. Allostatic (adaptive) systems enable the response to the physical state and the coping with external challenges. Allostasis can be defined as the ability to achieve stability through changes, and the allostatic load as the physiologic response to stress.

The allostatic load on the human being can arise in four different ways:

The first way is frequent stress.

The second is when adaptation to a repeated stressor of the same type is lacking, resulting in prolonged exposure to stress hormones.

The third is an inability to shut off allostatic responses after a stress is terminated.

The fourth type of allostatic load is when inadequate responses by some allostatic systems trigger compensatory increases in others.

Other factors can contribute to allostatic load, as anticipation, worry, isolation or work strain and consumption of drugs such as tobacco and alcohol [107]. Most of the studies on allostatic load concern the cardiovascular system and the brain.

### Sense of coherence

Antonovsky has introduced the concept of sense of coherence (SOC) as a prerequisite for the coping capacity of an individual [108]. The SOC was derived from a theoretical model designed to explain the maintenance or improvement of one's position on a health-ease/disease continuum [108]. Antonovsky wanted to identify the person that copes successfully with stressor from a "salutogenic" as the opposite of pathogenic point of view. What are the characteristics of the person who is capable of playing an active independent part of managing prevention, illness and recovery? Except from enabling the clinician to integrate the strengths of patients into the therapeutic process, it would enable identification of those patients with fewer of these strengths and hence in need of particular support [109].

The SOC is defined as a relatively stable, enduring and generalized orientation to one's world; it characterizes a person through adulthood. Antonovsky assumes that the SOC is developed during childhood and young adulthood. It is seen from the period of early adulthood, showing only minor and temporary fluctuations when radical changes in life occur. The SOC comprises three components, comprehensibility, manageability and meaningfulness in life. According to Antonovsky the SOC is "a global orientation that expresses the extent to which one has a pervasive, enduring though dynamic feeling of confidence the stimuli deriving from one's internal and external environments in the course of living are structured, predictable and explicable; the resources are available to one to meet the demands posed by these stimuli; and these demands are challenges, worthy of investment and engagement." [108].

Some time after introducing the concept of SOC, Antonovsky developed an instrument for measuring the SOC, and he has conducted several studies using the instrument [110], where he could show that the stronger the SOC, the more likely a person will cope successfully with stressful situations. A strong SOC has shown to be positively related to self-rated health and quality of life [110, 111].

## AIMS AND OBJECTIVES OF THE STUDY

As the etiology is not fully understood, Meniere's disease still remains a challenge to the clinician and scientist. The epidemiology and natural course are unclear and treatments aim on reducing symptoms, not cure. There is a quite satisfactory knowledge of how to evaluate the patient's medical status and "objective" treatment results, but there is a limited knowledge in the patients' subjective view on the treatment results and the impact by the disease on the HRQL. From a clinical experience it is well known that these patients in their contact with the health care often express frustration with unplanned spells of vertigo which may occur at all times of the day and at most unexpected and inconvenient situations. The few previous studies on HRQL in Meniere's disease have, not surprisingly, shown a considerable impact on quality of life by the disease. Still few details have been given and few predictors, except for treatment, to the results have been presented, even though the impact of stress on the condition has been pointed out.

Previous studies on stress and Meniere's disease have demonstrated an increased occurrence of stress on the same day as the attack of vertigo, but none of the studies could conclude if the stress precede or came as a result of the vertigo attack. When the case-crossover method became available, it was an obvious tool to use, to see if better temporal resolution could answer the question.

The goal with of this thesis was to assess the HRQL in a group of patients with Meniere's disease, and to identify factors that might trigger attacks of the disease. In order to assess of the HRQL it was necessary to incorporate instruments measuring the functional status, the presence and seriousness of disease specific conditions and as well as the general health. Coping capacity and the impact of stress on the symptoms of Meniere's disease were also studied. A secondary objective was to formulate a treatment policy, based on the findings in the separate studies.

### THE SPECIFIC OBJECTIVES WERE:

To assess which of three different surgical treatments of Meniere's disease that was the most beneficial to the patient

To examine determinants of general and disease specific HRQL in patients with Meniere's disease

To find if stress can trigger attacks of Meniere's disease

To propose a policy for treatment of patients with Meniere's disease

## MATERIAL

### *Patients*

All included patients fulfilled the criteria for definite Meniere's disease according to the AAO/HNS' guidelines for the diagnosis and evaluation of treatment in Meniere's disease [3]. The only exception is in Paper I, where 4 (10%) of the patients had a peripheral vestibular disorder that did not fulfil all criteria.

The material in the first study (Paper I) consisted of 40 consecutive patients, treated at the Karolinska Hospital with ELS, gentamicin or vestibular neurectomy, or a combination of these, during the period 1984 to 1990. In patients with serviceable hearing, ELS was primarily offered. In loss of cochlear function and if ELS had failed, gentamicin injections were chosen. If the other treatment modalities had failed, vestibular neurectomy was recommended.

The patients in the second study (Papers II and III) were recruited from two groups of registered Meniere patients. One group originated from the Departments of Otolaryngology and Audiology in the Karolinska Hospital in Stockholm, Sweden and a second group from the Department of Otolaryngology in the Central Hospital in Skövde in western Sweden. Of 124 non-consecutive patients asked to participate, 112 (90%) were included in the study, 84 patients from the Karolinska Hospital and 28 patients from the Central Hospital in Skövde. The reasons for denying to participate in the study were not asked for. The patients were recruited regardless if they had been subjected to surgical treatment or not.

In the third study (Paper IV) patients were recruited during regular visits at the Departments of Otolaryngology and Audiology in Stockholm, Sweden. Patients who had at least one attack of Meniere's disease during the last year were asked to participate. Those waiting for active treatment with gentamicin injections or ELS were also offered to participate in the study, until surgery was performed. Sixty-three non-consecutive patients were enrolled and 46 (73%) of these participated throughout the study. Two patients discontinued because of ELS. A third patient emigrated and had trouble returning the questionnaires. Two did not think the questions were relevant to their symptoms and the remaining 12 patients did not give a specific reason for discontinuing. The 46 patients who completed the study participated for 7–21 months, mean time 18.8 months.

Demographic data for the patients in Papers I–IV are accounted for in the respective tables (Tables 1–3).

*Table 1.* Descriptive data of the patients in Paper I. Characteristics of each sample according to treatment.

	ELS	Gentamicin	Neurectomy
n	18	17	11
<b>Mean age (years)</b>	50	60	50
Range	34–66	36–76	35–60
<b>Sex f/m</b>	10/8	9/8	3/7
<b>Mean duration of disease</b>			
(years)	5	9	7
Range	0,5–17	1–27	2–25
<b>Follow up time (years)</b>	3,5	4	2,5
Range	2,5–8	2,5–8	2–3,5

*Table 2.* Descriptive data of the patients in Papers II–III. Characteristics of each sample according to treatment.

	Gentamicin	ELS	Untreated	Total
n (%)	26 (23)	59 (53)	27 (24)	112
<b>Marital status</b>				
Married	20 (77)	49 (83)	22(81)	91 (81)
Single	5 (19)	9 (15)	5 (18)	19 (17)
Living with relative	1 (4)	1 (2)	0 (0)	2 (2)
<b>Working status</b>				
Working	11 (42)	39 (66)	14 (52)	64 (57)
Retired	10 (38)	10 (17)	6 (22)	26 (23)
Sick leave	4 (15)	6 (10)	3 (11)	13 (12)
Other	1 (4)	4 (7)	4 (15)	9 (8)
<b>Sex</b>				
Men	14 (54)	24 (41)	16 (59)	54 (48)
Women	12 (46)	35 (59)	11 (41)	58 (52)
<b>Education</b>				
Lower education	18 (69)	26 (44)	18 (67)	62 (55)
College	3 (12)	5 (8)	2 (7)	10 (9)
University	5 (19)	26 (44)	7 (26)	38 (34)
Other	0	2(3)	0	2 (2)
<b>Mean age years (range)</b>	63 (42–83)	53 (28–75)	52 (30–74)	56 (28–83)

*Table 3.* Descriptive data of the patients in Paper IV, divided by presence or absence of attacks during the study.

	Attacks	No attacks	Total
n %	24	22	46
<b>Mean age, years</b>	55	50	53
Range	27-71	24-75	24-75
<b>Sex</b>			
Men	6 (25)	11 (50)	17 (37)
Women	18 (75)	11 (50)	29 (63)
<b>Marital status</b>			
Married	15 (62)	15 (68)	30 (65)
Single	9(38)	7 (32)	16 (35)
<b>Working status</b>			
Working	11 (46)	12 (55)	23 (50)
Sick leave	4 (17)	0	4 (9)
Retired	4 (17)	4 (18)	8 (17)
Other	5 (21)	6 (27)	11 (24)
<b>Mean duration of disease (years)</b>	11	7	11
Range	1-45	1-44	1-45

### *Reference and comparison groups*

A randomly selected sample consisting of 268 individuals from the population of Stockholm County was used as reference group for the SOC scores [112] (Papers II and III). Another sample consisting of 145 individuals from the population of Stockholm County and served as the reference group for the Sickness Impact Profile (SIP) scores [109] (Paper III).

A sample of 99 patients with peripheral vestibular disorders (of which 22% were diagnosed with Meniere's disease) was used as comparison group for the SOC scores (Papers II and III), the SIP scores and the Hospital Anxiety and Depression Scale (HAD) scores [113] (Paper III).

For the Short Form 12 (SF-12) the Swedish reference material was used [114] With regard to the groups, the total values of the samples were used, as the group of Meniere patients consisted of both sexes with a similar age distribution (Paper III).

The results of the three generic instruments were compared with published results from other groups of patients:

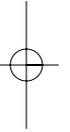
For the HAD a Swedish population sample [115], a group of patients who had survived Hodgkin's lymphoma for more than 5 years as well another sample of a healthy Swedish population (Wettergren, personal communication).

For the SF-12 the same group of Hodgkin lymphoma survivors (Wettergren, personal



communication), a group of patients with spinal cord injuries [116] and a group of patients studied after myocardial infarction [117]

For the SIP a group of uremic patients in the predialys stage [118], patients with oral cancer 12 months after surgery [119] and a group of women with rheumatic disorders [120].



## METHODS

### *Extended clinical examinations*

In the first study (Paper I, the follow up of the surgically treated patients was performed with clinical routine examinations (including vestibular tests and pure-tone audiometry), supplemented by a questionnaire. Dynamic and static posturography were performed, in which body sway was tested in four situations (1. eyes open, platform stable. 2. eyes closed, platform stable. 3. eyes open, platform moving 4. eyes closed, platform moving) recorded and automatically analyzed by a computer system (Chattex Balance System B30). A physiotherapist performed a functional test of postural control, where the degree of unsteadiness at certain body movements was judged according to a standardized procedure.

### *Questionnaires*

Three symptom-specific questionnaires concerning vertigo (VSS), hearing loss (HDHS) and tinnitus (TSQ) were chosen because they have shown reliability and validity in earlier studies and in addition are available in Swedish. Only patients who reported that the respective symptom still was present were asked to answer the symptom-specific questionnaires.

Three generic instruments were chosen to view the quality of life from different aspects: functional status (SIP), emotional distress (HAD) and general health status (SF-12).

The SIP was selected because it has shown reliability, validity, and sensitivity to changes of functional status and clinical utility in different diagnostic groups. It has been translated and validated in Swedish [120] and Swedish reference values have been obtained from a healthy population [111].

The HAD was selected because previous studies have shown it to possess a good screening ability and a high level of agreement between patient scores on HAD and structured psychiatric interviews. It also has a high positive predictive value [121, 122].

Finally, the SF-12 was chosen because it is widely used, and has proven validity and reliability in several languages including Swedish. Reference values from a Swedish population samples are available [114].

Beyond these six questionnaires, all patients answered questions about socio-demographic data and disease history. Questionnaires concerning disease specific quality of life items were constructed for Papers I and II, and case-crossover questionnaires for Paper IV. All patients in Papers II and III were asked to answer the SOC scale. The patients who had been submitted to surgical treatment (Papers I, II and III) were also asked

to answer the AAO/HNS questionnaires (Table 4).

Six questionnaires according to the AAO/HNS classification and FLS could not be analyzed as they were incompletely answered. One patient did not fill in the SOC, HAD, SF-12 or SIP. A few patients left out single items.

Table 4. Questionnaires used in the different papers.

Paper	I	II	III	IV
1 Demographic data	X	X	X	X
2 Disease-specific items	X	X		
3 VSS		X	X	
4 HDHS		X	X	
5 TSQ		X	X	
6 AAO/HNS	X	X	X	
7 SOC		X	X	
8 SF-12			X	
9 SIP			X	
10 HAD			X	
11 Case-crossover questionnaires				X

#### CONTENTS OF THE INDIVIDUAL QUESTIONNAIRES:

1. DEMOGRAPHIC DATA, such as age, gender, education and working status.

2. DISEASE SYMPTOM-SPECIFIC ITEMS In Paper I the patients were asked to grade their present degree of hearing loss, tinnitus and unsteadiness when moving, if any, on a visual-analogue scale. They were also asked if, and in what direction, the tinnitus or hearing loss had changed after surgery. In Paper II the questions concerned the presence of vertigo, hearing impairment and or tinnitus respectively. The patients' general quality of life and the duration of disease were also investigated.

3. THE VERTIGO SYMPTOM SCALE (VSS), measures the frequency of symptoms such as dizziness, spinning, nausea, vomiting and also somatic anxiety symptoms such as sweating, feeling of pressure in the head and or heart pounds [123]. The short version (15 items) was used. It is divided in two sub-scales, the Vertigo Severity Scale (8 items) and the Somatic Anxiety Scale (7 items) [124]. In Paper III only the Vertigo Severity Scale was used.

4. THE HEARING DISABILITY HANDICAP SCALE (HDHS) is a shortened and modified version of the Hearing Measurement Scale [125-127]. The HDHS consists of 20 hearing-related items. The HDHS has four sub-scales: Speech Perception, Non Speech Sounds, Interpersonal Distress and Threat to Self-image. In Paper III only the Speech Perception subscale was used.

5. THE TINNITUS SEVERITY QUESTIONNAIRE (TSQ) has been developed in Sweden for clinical use and includes 10 items [128] concerning the severity of tinnitus. For the purpose of Paper III a new subscale was constructed, where the items measuring tinnitus severity symptoms were chosen (items 3-7 in the questionnaire), while items measuring anxiety or depression caused by tinnitus were excluded. Cronbach's alpha for this new subscale was 0.91, indicating high internal consistency.

#### 6. THE AMERICAN ACADEMY OF OTOTOLOGY – HEAD AND NECK SURGERY'S, AAO/HNS, CRITERIA.

According to the AAO/HNS-guidelines for evaluating results of treatment of Meniere's disease [3] a numerical value ( $X/Y \times 100$ ) was calculated between the average number of definitive spells per month for the six months 18 to 24 months after treatment (X) and the average number of definite spells per months for the six months before treatment (Y). Numerical value 0 (no attacks postoperatively, complete control of definitive spells) is designated as Class A, numerical value 1–40 (substantial control of spells) as Class B, 41–80 as Class C, 81–120 as Class D, >120 as Class E and secondary treatment due to disability from vertigo as Class F (Papers I and II). In Paper III the single-question six-point functional level scale (FLS) was used, which aims to assess the effects of vertigo on daily activities. The scale was compressed to four levels, from 1 (No limitations in daily life activities) to 4 (I was unable to work because of my dizziness).

#### 7. THE SENSE OF COHERENCE, SOC, SCALE

was developed by Antonovsky to measure overall capacity to cope with stressful life situations [108]. The shorter SOC scale, used in this study, includes 13 items measuring the three components comprehensibility, manageability and meaningfulness [110, 112]. The items were arranged on a seven-point Likert scale with two anchoring responses (e.g. very often and never). Higher score represents stronger sense of coherence.

#### 8. SHORT FORM 12, SF-12.

The SF-12, is a 12-item version of the Short Form 36 (SF-36) [129]. The SF-36 was aimed to be a short, generic, psychometrically sound measure of subjective health status that could be applied in a wide range of settings. The SF-12 uses one third of the SF-36 items and yields two summary measures, the Physical Component Summary (PCS-12) and the Mental Component Summary (MCS-12). Higher scores indicate better self-rated health.

#### 9. SICKNESS IMPACT PROFILE, SIP.

Developed in the USA in the early 1970:s the SIP is a measure of sickness-related dysfunction [130]. It includes 136 statements, summarized in 12 subscales, each of which represents a functional area. Three of the subscales are condensed into a physical dimension and four other subscales into a psychosocial dimension. The remaining subscales are independent. The 12 subscales, when merged, form an overall functional status. The lower the score, the less the perceived dysfunction.

#### 10. HOSPITAL AND ANXIETY AND DEPRESSION SCALE, HAD

was developed by Zigmond and Snaith in 1983 [131]. It is a brief assessment of anxiety and depression. It consists of 14 items divided into one sub-scale for anxiety (7 items) and one for depression (7 items), with no items concerning somatic symptoms. Lower scores indicate a lower level of anxiety or depression.

#### 11. CASE-CROSSOVER QUESTIONNAIRES (IV) (Appendix 1.).

Two different questionnaires were constructed for the study. The first questionnaire, the "Control Period Questionnaire", contained questions about the frequency of stress during a period without an attack. The second questionnaire, the "Attack Questionnaire" contained the same questions as the Control Period Questionnaire, but was filled in immediately after a Meniere's disease attack. The time period asked for was 48 hours before point zero. The respective zero points were the exact time the attack began in the Attack Questionnaire and the minute for starting writing the answers in the Control Period Questionnaire. The trigger studied was stress, sub-divided into emotional stress, mental

stress and physical stress, according to the definition used by Andersson and Yardley [132]. The patients were asked to give the exact time of any occasions of stress during the 48 hours. A maximum of three different exposures for each kind of stress during each of the two 24 hour periods could be entered.

### *Case-crossover method*

A recently described epidemiological technique, the case-crossover design, was used in Paper IV. Maclure first published the case-crossover design in 1991 [133]. According to Maclure the design resembles a retrospective non-randomised crossover study, but differs in having only a sample of the base population-time. The design was invented for studying transient exposures with short induction times, which might trigger an event, as for example a myocardial infarction. The basic idea is simple. When comparing two different types of periods, the patient serves as his or her own control (self-matching). The case-crossover design is based on the assumption that most people in their daily life cross over between short periods of exposure to hypothetical triggers and much longer periods of unexposed time. Three types of information are needed: the time of disease onset; knowledge of whether the trigger was present during a defined period immediately before onset; and the usual frequency of trigger exposure [134]. The hazard period is the period before disease onset before disease onset, during which the trigger has effect. Whether a case is exposed to the trigger or not during the hazard period determines the case information and makes it possible to calculate the observed exposure odds.

The frequency of exposure in an interval before the disease onset (the case window) is compared with the frequency of exposure during a control period (or the control window). Each patient contributes his or her own control information. The case and control windows are arbitrary units of observation. These are the windows one chooses to look into, when one is stating a hypothesis, designing questions or exploring the data. The length of the case window should correspond with the assumed hazard period. Terminology of the case-crossover method is accounted for in Table 5.

In the present study the case window of each attack was first compared with a control window from the control questionnaire answered before the attack and a control window from the control questionnaire answered some time after the attack (1:2 matched pair analysis). Case windows and control windows were of equal length. The windows were also matched regarding the time of the day. Depending on the patient's answer the case window and the control windows were classified as either exposed or unexposed.

Table 5. Case-crossover terminology

<i>Induction time</i> = the time between the cause and effect of an individual, the time between a momentary trigger and the onset of the triggered outcome
<i>Effect period</i> = the time between the minimum and maximum induction times in the population (When the minimum induction time is zero, the effect period=the maximum induction time)
<i>Hazard period</i> = a time interval after the trigger begins (such as a road hazard) when a population experiences an increased risk of the outcome (such as a car accident) caused by the trigger
<i>Exposure window</i> = an arbitrary unit of observation, that one chooses to look into when one is stating the hypothesis, designing the questions or exploring the data.
<i>Case window</i> = the window in which one hypothesizes that an excess of triggers will be seen
<i>Case time</i> = the thing one observes while peering into the case window.
<i>Control window</i> = The window one chooses to collect information of trigger exposure from, when an event has not occurred

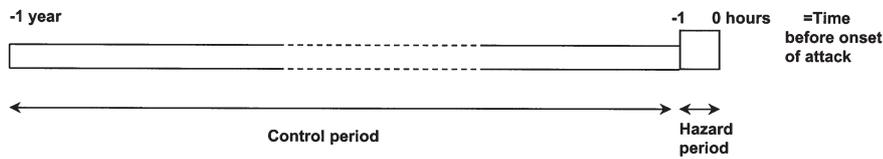
Secondly, to take advantage of the full information in the study, we also conducted an analysis in which each case window of all attacks was compared with control windows, matched on for the time of the day, from all available control questionnaires of the same patient (1:n-matched pair analysis). Thirdly we used the so called usual frequency approach in which we compared the observed exposure odds in the case window with an expected exposure odds, calculated from all available control questionnaires of the same patient. A usual usual frequency of trigger exposure was derived from all episodes of exposure during the 24 hours before answering the questionnaires and the total number of control questionnaires. The expected exposure odds were based on the proportion of exposed time of in relation the total time. The principal designs of the matched-pair and usual frequency approaches are illustrated in Figure 1 and the collection of data in Figure 2.

### Statistical methods

Student's t-test was used to test differences between the study populations and reference groups in Papers I, II and III.

Parametric methods were used in Papers II and III as the procedure of summated scales is based on these methods. Differences between the treatment groups were tested using one-way Analysis of Variance (ANOVA) with subsequent Bonferroni-Dunn tests for post-hoc analyses. Differences in proportions were assessed with the chi-square test. Correlation matrixes were computed between the variables in Papers II and III. In order to estimate the effects of the significant variables multiple regression analyses were per-

**A. "Usual frequency approach"**



**B. "Pair-matched interval approach"**

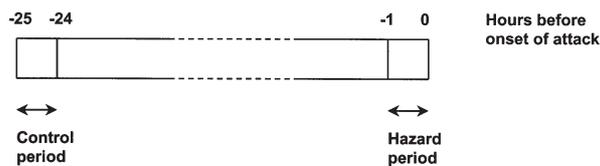


Fig. 1. Two methods of sampling control information in the case-crossover design.

formed. The significance level was set at  $p < 0.05$ .

In Paper IV the effect of trigger exposure was measured as a relative risk, estimated by the ratio between the observed exposure odds at the time of disease onset and the expected exposure odds.

Fig. 2. Collection of data

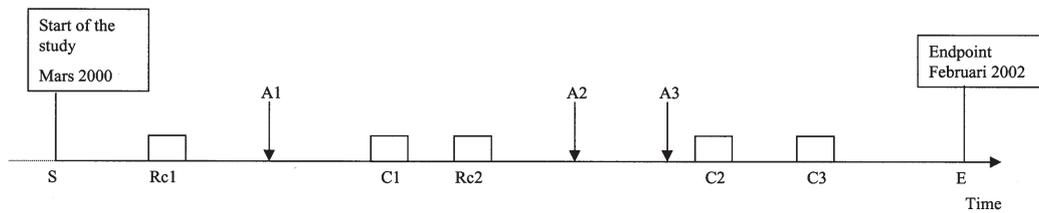


Fig. 2. Schematic presentation of the data collection from one individual patient with three reported attacks. S = starting point of the study: background questionnaire and an initial control questionnaire were answered. A1, A2 and A3 indicate the onset of consecutive attacks of Meniere's disease. An attack questionnaire was answered after each attack. Rc1-Rc2 = randomly chosen control periods, when control questionnaires were answered. C1-C3 = a date 22 days after an attack of Meniere's disease when control questionnaires were also answered. E = end of the study when a final control questionnaire was answered. Three different ways of selecting control windows were used: 1). 1:2 matched pair analysis: from the two control questionnaires before and after each attack (In this case for attack A1 control questionnaires Rc1 and C1, for attack A2 control questionnaires Rc2 and C2 and for attack A3 control questionnaires Rc2 and C3) 2). 1:n matched pair analysis: for each attack control windows were taken from all control questionnaires available for the patient (different numbers for each patient) (In this case for all attacks A1-A3 control questionnaires S, Rc1-Rc2, C1-C3 and E). The control windows for each attack were matched by time of day. analysis based on the usual frequency approach: the usual frequency of exposure was calculated for each attack from all available control questionnaires using the 24 hours before the filling in as the control window. It was expressed as an expected exposure odds based on the proportion exposed time of the total time.

## RESULTS

### *Paper I*

#### *Surgical treatment of vertigo: The Karolinska Hospital policy*

The only difference between the groups concerning demographic data was that the gentamicin treated patients were significantly older than patients in the two other groups.

After ELS, 9 of the 18 patients (50%) were completely free of vertigo attacks (Class A) and 3 had substantial control (Class B). However 3 patients reported no attacks of vertigo but constant unsteadiness. These are according to the AAO/HNS classification Class A patients, so in summary 15/18 ELS patients (83%) had total or substantial control of vertigo. Of the 18 patients, three were subjected to gentamicin and one to vestibular neurectomy because of reoccurring or persisting vestibular symptoms and the results are accounted for later.

After gentamicin injections, 8/17 patients (47%) were classed as Class A and 4 as Class B. Three patients reported constant unsteadiness, which in one patient was intense, but no attacks of vertigo. If the patient with intense unsteadiness (but no attacks) is classed as Class E, 14/17 (82%) had total or substantial control of vertigo. If the patient with intense unsteadiness but no attacks is classed as Class A (which he according to the AAO/HNS criteria should be) the result is 88% Classes A and B. The patient with intense unsteadiness and the two patients with unchanged numbers of vertigo attacks after gentamicin treatment were subjected to vestibular neurectomy and are accounted for in the next paragraph.

After vestibular neurectomy 5/11 patients were relieved of vertigo symptoms and 4/11 patients had substantial control of vertigo, i.e. 82% reported a total or substantial loss of vestibular symptoms. Two patients did not experience any change in their vestibular symptoms.

The outcomes with regard to vertigo were similar regardless of treatment modality. About 80% of the patients in each group reported a total or substantial loss of vestibular symptoms. The rate of complications differed however. After ELS one patient became deaf 10 days after surgery. After gentamicin injections, 12 of the 14 patients with preoperatively measurable hearing had significantly decreased hearing. No other complications were reported in this group. After vestibular neurectomy 5 of 11 patients had complications in form of hearing loss, infections or transient facial paralysis.

No effects on tinnitus were seen after any of the treatments.

The balance was evaluated in three different ways: first the patient's subjective evaluation of the degree of unsteadiness, secondly the body sway measured by computerized posturography and third, the evaluation made by a physiotherapist of the patients' degree of unsteadiness at certain body movements. Results from the computerized posturograp-

hy showed significant differences between normal subjects and the ELS and vestibular neurectomy groups in test situation 4. After gentamicin treatment, significant differences were found in test situations 2–4 compared with normal subjects. According to the physiotherapist, 37/40 patients performed normally in their postural control. The functional evaluation, made by the physiotherapist, was found to mirror the patients' subjective view of their state of balance better than the computerized posturography.

As some of the patients were subjected to more than one surgical treatment, a final outcome was assessed after the final surgical treatment. Out of the 40 patients included in the study, it was found 38 patients (95%) reported total or substantial loss of vestibular symptoms.

## *Paper II*

### *Patients' subjective evaluations of quality of life related to disease-specific symptoms, sense of coherence, and treatment in Meniere's disease*

Fifty-five percent of the patients had all three symptoms, (vertigo, hearing loss and tinnitus), at the time of the study, and none was symptom-free. The patients treated with gentamicin had significantly less vertigo than the ELS patients or the surgically untreated patients. Nevertheless, the majority of the patients in all three treatment groups rated their general opinion of quality of life as very good or good. There was no significant difference in the patients' ratings of general quality of life in between the three groups.

Of the patients with vertigo, 55% rated their quality of life in general as very much/much influenced by the condition. The impact of hearing loss on quality of life in general was rated very much/very much by 28% and the impact of tinnitus by 35% of the patients. When separating patients with or without present vertigo there were no significant differences were found between their rated general quality of life or their quality of life related to hearing loss or tinnitus.

According to the AAO/HNS guidelines, 88% of the gentamicin treated patients had total or substantial control of vertigo (Classes A or B). The corresponding number for the ELS-patients was 79%.

Neither age, nor treatment nor duration of illness had any impact on vertigo, hearing loss or tinnitus. The male patients perceived more problems than the females according to the Somatic Anxiety Scale. According to the Non-Speech Sound Scale, a subscale of the HDHS, the females reported more problems.

All dependent variables in all analyses were statistically correlated to the SOC Scale scores. Thus, the stronger the SOC, the less severe were the vertigo symptoms, the tinnitus and the hearing disability, as well as less of tinnitus and hearing disability. The mean SOC score did neither differ from a healthy reference group nor from the score obtained in a group of patients with peripheral vestibular disorders.

*Paper III*  
*Factors influencing quality of life in Meniere's disease,*  
*identified by a multidimensional approach*

Both the mental (MCS-12) and physical (PCS-12) summary scores from the Short Form 12 were significantly lower than the scores obtained from a Swedish reference material, indicating a lower quality of life regarding both the mental and the physical dimensions.

According to the Sickness Impact Profile the patients with Meniere's disease rated their functional status in all areas, except eating, as significantly worse than the healthy reference group. When compared with a group of patients with peripheral vestibular diseases [130], the Meniere patients rated their functional status significantly better regarding the psychosocial dimension.

According to the Hospital Anxiety and Depression Scale 18 patients (17%) were classified as suffering from anxiety and a further 35 patients (34%) as possibly cases having anxiety. The corresponding numbers for the depression subscale were 3 (3%) and 14 patients (13%) patients respectively. The HAD results from the Meniere patients did not differ from Mendel's results from patients with peripheral vestibular disease.

As can be seen in Table 6 the SOC correlated with the HAD, the MCS-12 and the psychosocial dimension of the SIP, but not with the physical dimension of the SIP or the PCS-12.

The surgically treated patients answered the questions in the FLS according to AAO/HNS' criteria. Of these patients, 38 (48%) reported that dizziness did not limit their daily life activities. Thirty-three (41%) patients reported slight limitations, 2 (3%) serious limitations and 6 (8%) were unable to work or perform their regular daily activities because of dizziness.

Age significantly affected physical health i.e. the older the patient, the poorer the physical health. Gender, duration of disease or treatment modality did not affect the results of any of the generic instruments.

Vertigo severity (as measured by the Vertigo Symptom Severity subscale) had negative impact on the results of the recreation, the physical and the psychosocial dimensions of the SIP as well as PCS-12.

Tinnitus severity (as measured by the new subscale of the TSQ) had negative impact on the results of the anxiety subscale of the HAD.

Impaired speech perception (according to the subscale of the HDHS) had negative impact on the results of the MCS-12.

Thus, the higher the scoring on the symptom scales, indicating more severe problems, the worse rated the answers on the generic instruments.

The results of the VSS, as the single instrument, had significant negative effect on the FLS.

Table 6. Variance analysis of patients with Meniere's disease. Weak, moderate and strong sense of coherence (SOC) are independent variables. The scores on the SF-12, HAD and SIP including the subscales are the dependent variables. Means and p-values are given

	SOC Weak	SOC Moderate	SOC Strong	
n (%) total 112	26 (23)	59 (53)	27 (24)	
<b>SF-12</b>				
PCS-12	42,9	44,1	47,8	ns
MCS-12	37,3	51,0	54,8	p<0,001
<b>HAD</b>				
Total	18,0	9,6	5,7	p<0,001
Depression	7,3	3,9	2,4	p<0,001
Anxiety	10,7	5,7	3,3	p<0,001
<b>SIP</b>				
Overall SIP	10,7	5,3	4,0	p<0,05
Psychosocial dimension	15,6	4,8	3,9	p<0,001
Emotional behavior	19,6	5,4	4,7	p<0,01
Social interaction	17,7	5,9	2,8	p<0,001
Alertness behavior	19,7	3,8	7,1	p<0,05
Communication	8,1	1,3	1,7	p<0,05
Physical dimension	4,5	2,9	2,5	ns
Mobility	6,6	4,2	2,3	ns
Body care	3,9	2,0	2,6	ns
Ambulation	4,1	3,2	2,8	ns
Sleep	18,7	11,8	6,5	p<0,05
Work	11,9	10,5	7,6	ns
Eating	1,1	0,6	0,7	ns
Home management	7,5	5,4	3,5	ns
Recreation and pastimes	17,9	14,8	9,2	ns

ns=non significant

SIP results in different patient groups

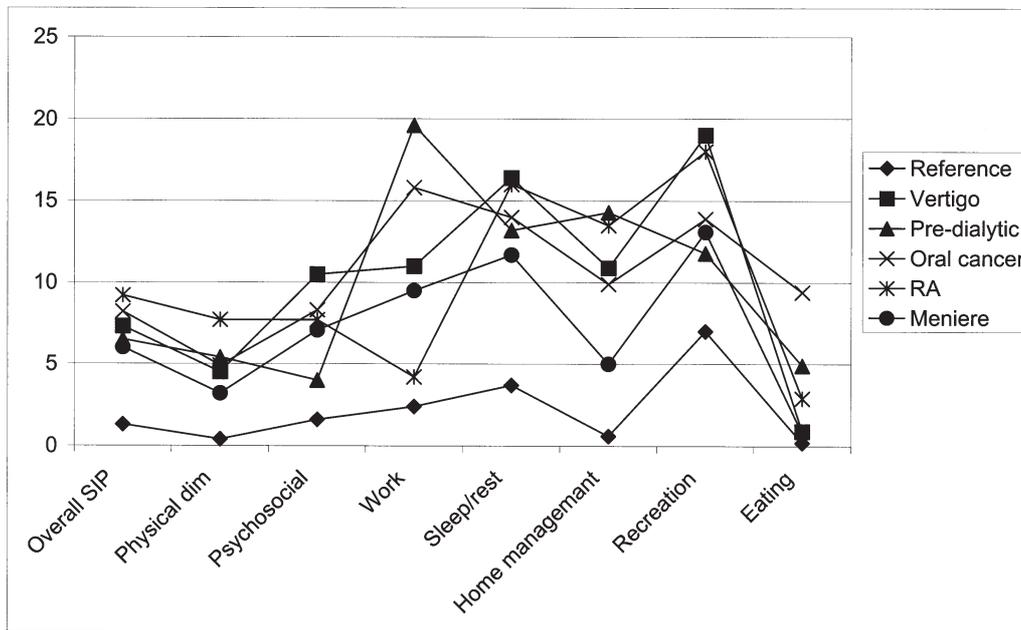


Fig. 3. The SIP scores, expressed as percentages of the total score of the possible dysfunction, ranging from 0 to 100. The lower the score, the less the perceived dysfunction. The cut-off level of dysfunction of clinical relevance is 10 points.

The Meniere patients reported a higher level of anxiety but the same level of depression, than had been the case in a previously published Swedish population sample, according to the HAD instrument. Compared with a group of patients who had survived Hodgkin's lymphoma for more than 5 years, the Meniere patients had the same level of anxiety but experienced more depression. This was also the case when comparing the Meniere patients with a group obtained from a healthy Swedish population. We also compared the results of the SF-12 in our study with those of the Hodgkin lymphoma survivors, and found that the Meniere patients reported significantly worse quality of life in both the physical and mental dimensions. Results of the SIP instrument obtained from Meniere patients and other patient groups (peripheral vestibular disorder, uremic patients in the predialysis stage, patients with oral cancer 12 months after surgery and a group of women with rheumatic disorders) are presented in Figure 3. With regard to general health as measured by the SF-12, results available show mental health for a group of patients with spinal cord injuries at the same level as the Meniere patients' but the physical health is scored lower. A group of patients studied after myocardial infarction reported lower mental and physical health than the Meniere patients' scores.

*Paper IV*  
*Stress as a trigger of Meniere's disease attacks.*  
*A case-crossover study*

During the study period 24 of the 46 patients (52%) reported attacks. 153 attacks were registered in all. The mean number of attacks per patient was 4.3 (range 1-29). The total number of control questionnaires, collected from the patients having at least one attack, was 259 (mean 10.8 questionnaires per patient, and range 4-29).

The length of the hazard period after an episode of stress was investigated in separate analyses of each of the six hours before the attacks. The increased risk from emotional stress reached a peak value after one hour after stress, but it seemed to remain elevated for three hours. Twelve of the 153 attacks (8%) were preceded by emotional stress 0-3 hours earlier. These 12 attacks were distributed between 7 patients (29% of all patients with attacks).

The hazard period for mental stress was just one hour and mental stress was reported to have preceded five of the attacks (3%) by less than an hour. All these five attacks were in different patients. Two of the five attacks occurred after exposure to both mental and emotional stress.

Physical stress had preceded only one of the attacks. This patient had also been attack had also been exposed to emotional stress before the attack.

In the analysis using information from two control windows, before and after the attack, the relative risk of having an attack of Meniere's disease was 7.1 (95% C.I. 2.0-25.3) during a period of 3 hours after being exposed to emotional stress. The relative risk of having a Meniere attack was 10.0 (95% C.I. 1.2-85.5) during the first hour after being exposed to mental stress. Physical stress was not found to trigger Meniere attacks.

## DISCUSSION

Patients with Meniere's disease suffer from a chronic disease with a well-known natural course. During two decades the patient is exposed to often frequent attacks of intense vertigo, increasing hearing loss, tinnitus and eventually drop attacks. In the final stage of the disease the patient is free from attacks, but has a profound hearing loss and tinnitus.

Except for symptomatic treatment of the acute attack, according to evidence-based evaluation [43], medical treatments are probably no more effective than placebo. Surgical treatments aim on reducing the vertigo symptoms, but have no proven effect on hearing or tinnitus. Furthermore, both labyrinthectomy and (at least high-dose) gentamicin injections are destructive procedures, which must be considered in the presence of an ongoing or later appearing bilateral disease. From our clinical experience however, psycho-social care may reduce the severity of the disease. Therefore we wanted to gather more information about and try to increase our knowledge about the HRQL experienced by Meniere's disease patients. We selected the HRQL in order to see if this could provide a better assessment of the psycho-social measures which can be undertaken in order to get an optimal treatment policy for patients with Meniere's disease.

We also wanted to identify triggers to the attacks in order to be able to find a way to prevent attacks in the future. Based on our clinical experience, stress was the first and most important trigger factor to study.

When studying HRQL, one important finding was that vertigo mainly had influence on the physical dimension of quality of life. On the other hand, hearing loss and tinnitus had negative impact on the emotional/psycho-social dimension. The fact that Meniere's disease affects both the physical and psychosocial/emotional dimensions of quality of life has clinical impact. Vertigo, which is the only treatable symptom of the triad, affects mainly the physical dimension of quality of life. The psychosocial/emotional aspects of quality of life are therefore less affected by the treatment. This could explain treatment failures, when patients report dissatisfaction even though the numbers of vertigo attacks have decreased.

Regarding the impact on HRQL by the presence of symptoms, vertigo did not dominate over hearing loss and tinnitus. This result is in agreement with other studies [87, 88], where alternatively vertigo and tinnitus have been reported to be the most handicapping symptom.

As demonstrated in Papers II and III, the capacity to cope with stressful situations has profound impact on the experienced HRQL, while no significant correlation was found between the treatment modality and the HRQL or functional status. There are however limitations to this study. It was not a randomised trial, and another limitation is that the untreated patients had probably had a milder form of the disease. Therefore conclusions must be made with these reservations in mind. Still it may be concluded that the patients with a strong sense of coherence rate their functional status and HRQL better than those

with a weaker one. Thus it is proposed that the Sense Of Coherence Scale can serve as a tool to understand a patient's perception of his or her well being after surgery and thereby may be a predictor of treatment results [108].

According to the AAO/HNS classification only the definite vertigo attacks are counted [3]. No information is given about unsteadiness or other balance problems. As we could demonstrate in Paper I, unsteadiness was a common problem postoperatively, which will not be detected by using the AAO/HNS classification. The treatment results in Paper I would have been reported as more successful, if the degree of unsteadiness had been evaluated. As shown in Paper II, inclusion of the FLS gives more information, but is not as sensitive as the quality of life instruments. To give a fair picture of treatment results regarding the vestibular function, it seems reasonable to supply the AAO/HNS classification and FLS with quality of life instruments, disease specific as well as generic.

New information in this study point out the profound impact of stress, and especially emotional stress, on the manifestations of the disease. Being subjected to emotional stress increases the risk for having an attack of Meniere's disease within 3 hours after exposure. Almost one third of the patients that experienced attacks during the study reported that at least one of the attacks had been preceded by stress. The ability to cope with stressful situations, as reflected in the degree of SOC, was also the strongest predictor of the experienced HRQL.

It can be hypothesized that hypothalamus constitutes a link between stress and attacks in Meniere's disease. Stress leads to an increased secretion of the adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland, followed by an increased adrenocortical production of gluco-corticoids (cortisol and corticosterone) and mineral-corticoids (aldosterone) [104]. Endolymphatic hydrops may arise as a result of the destabilization of the natural regulation through overproduction and/or reduced absorption of the liquid. The production of endolymph is thought to be regulated by the enzyme Na/K-ATP-ase in the marginal cells of the stria vascularis of the cochlea as well as in the dark cells of the utricle and the cristae ampullares of the semicircular canals. In animal experiments, a relationship between circulating adrenal steroids and Na/K-ATP-ase activity in the inner ear has been observed [33]. Stress might lead to activation of the neuroendocrine effector systems, resulting in the increase of endolymphatic production. It is suggested that aldosterone might be a possible triggering substance to Meniere attacks. In a recent Dutch study aldosterone levels in Meniere patients were measured [40]. Compared with normal subjects, the Meniere patients' plasma levels of aldosterone were however not elevated. The reason for this might have been that the samples were collected during hospital admission, and none of the patients had an attack during that period.

Further studies on the aldosterone levels within 24 hours after a Meniere attack might contribute to better understanding of the endocrine mechanisms behind attacks of Meniere's disease.

The fact that patients that experienced more attacks during the study time reported a higher frequency of attacks triggered by stress might depend on the dose-response curves between the potency of a stressor and the activity of the stress system in normally reactive individuals versus hyper-reactive (hypersensitive) ones. Thus, the patients might have heightened responses of the stress system to certain stressors [137].

### *Methodological aspects*

Desirable criteria for questionnaires to be efficient are that they should be short and easy to interpret. The short version of the SOC was chosen instead of the longer, as well as the SF-12 instead of the SF-36 partly because of the length. The SF-12 has been criticized for being less valid than the SF-36, especially in smaller samples. The summary scores MCS and PCS have also been discussed and it has been argued that PCS and MCS scores are not independent and may in part be measuring the same constructs [138], but this is denied by the constructors of the scale [139]. Still, the summary scores offer the advantage of simplifying data analyses and interpretation. The SF-12, the SIP, the HAD and the SOC all have scores published from a healthy Swedish population.

Since Maclure published the case-crossover design, it has mainly been used for studying triggers to myocardial infarction, such as physical exertion [140, 141], anger [142] and sexual activity [134]. Epidemiologists have used the method to study injuries and adverse drug events [143]. The design received widest recognition for a study showing that car telephone calls increased the risk of collisions [144]. The case-crossover design has previously been used mostly in a retrospective way to identify triggers to events that has already occurred. To have a population of identified patients and collect control data *before* the event has occurred is a new application of the method, and might decrease the risk of recall bias. Recall bias is a potential limitation in case-crossover studies due to the different ways of obtaining the case and the control information [143]. To avoid differential memory problems we used control information from separate days and the questions were identical, asking for information 48 hours back. The fact that a patient could contribute with an unlimited number of attacks could be identified as a potential problem concerning generalization of the results, if the exposed attacks had been collected from a single patient. In the present study, however, nearly one third of the patients with attacks reported that at least one attack had been preceded by stress. The similarity of the results from analyses using different ways of sampling the control information is also reassuring. A nice feature of the design is that it automatically controls for confounding from ordinary long-term risk factors as the analysis is individually matched. Confounding from other triggers is difficult to judge as few risk factors triggering spells of Meniere's disease are identified. Fifteen attacks were exposed to some kind of stress. The fact that three of these 15 attacks were preceded by more than one of the three stress dimensions we asked for should probably not be understood as potential confounding but as conceptual and methodological ambiguity regarding the stress perception. However, it seems fair to conclude that the emotional aspect of the stressors was the most important issue. The study did not have control over the selection of patients from the clinics but those in charge of the selection process did not have any information of the hypotheses in the study. Therefore we consider bias from exposure-dependent selection should not to be a problem. The questionnaires contained questions on a number of potential triggers and we don't have any indication that non-participation of the patients should depend on earlier stress exposure and its association with attacks. Another form of self-selection is possible in that patients susceptible to the triggering effects of stress try to avoid stress and therefore experience no attacks. However, this form of selection does not bias the results; it only decreases the power of the study. The unit of analysis is the attack, but they are not totally independent as they cluster in patients. The exposed attacks are, as shown earlier, broadly distributed among the patients and not confined to just a few special cases. This hierarchical nature of the data implies a slight underestimation of the variance

when using ordinary logistic regression methods, but as the lower bounds of the confidence intervals are well above unity this should not be problem.

One of the main problems issues in measuring the degree of stress was to find a suitable questionnaire. Several stress-measuring questionnaires have been published, but the majority deals with personality types. Somewhat surprisingly, the most appropriate questionnaire found had been developed for a study on vertigo patients [132]. In the literature of stress there is a general agreement that no specific stress-stimuli exist. It is the individual, that based on earlier experiences decides if a situation is dangerous, threatening or tempting [135]. In our case-crossover questionnaire we gave examples of emotional, mental and physical stress and left it to the patients to decide which kind of stress they had experienced.

### *Clinical applications*

The treatment policy according to Paper I was published a couple of years ago, and since then changes in the clinical routine in the Karolinska Hospital have occurred. Of the three treatments, only ELS still is used on the same indications as earlier: patients with persisting attacks after medical treatment, serviceable hearing and no contraindications against surgery in general anaesthesia. Vestibular neurectomy is nowadays almost never performed, partly as a result of the findings in Paper I. On the other hand, gentamicin treatment is more frequently used. The present gentamicin dosage is much lower than the doses given to the earlier patients, accounted for in Paper I, who reported a high frequency of hearing loss. The rationale for giving lower doses is that the risk for hearing impairment has been shown being, at least to some degree, depending on the amount of gentamicin given. According to the results in Paper II, the more recently gentamicin treated patients, who had received lower gentamicin doses, do not consider their post-treatment hearing impairment as a severe problem, causing only a moderate impact on the hearing-related quality of life. The conclusion is that low dose gentamicin injections are a good treatment alternative to offer to the patients, when active treatment beyond diuretics and betahistine is needed and if ELS has failed. According to Paper II, gentamicin treatment resulted in fewer patients with present vertigo compared with ELS treated patients.

The AAO/HNS classification as well as the FLS is not as exact as the quality of life questionnaires in discriminating results of surgical treatment. The AAO/HNS classification cannot detect anything but the definite attacks, while the patients' unsteadiness or positional vertigo not will be registered. Neither is the single question FLS sensitive enough to detect subtle changes in the patients' quality of life. For evaluating treatment results, symptom specific questionnaires, regarding vertigo as well as hearing loss and tinnitus should be added. The questionnaires used in this study have served well, being simple and easy for the patients to fill in. There have been no difficulties in the interpretation, and the questionnaires could provide useful information in a preoperative consultation.

Stress seems to be a key issue concerning the morbidity in Meniere's disease. The capacity to cope with stressful situations, as measured by the degree of SOC, has profound influence on the HRQL in Meniere patients, and stress has been demonstrated to be an important triggering factor to attacks of Meniere's disease. It is obvious that Meniere patients have to be informed of the impact of stress on the disease, and be encouraged to make life-style changes in order to be able to prevent attacks. A future field of interest could be to study if stress management techniques could decrease the number of attacks.

## CONCLUSIONS

1. Being subjected to emotional stress increases the risk for an attack of Meniere's disease to occur one to three hours later. Mental stress has less impact on the risk for having a Meniere attack and physical stress does not trigger attacks of Meniere's disease.
2. Meniere patients rate their quality of life as being significantly worse poorer than reference groups of healthy subjects, in both the physical and the psychosocial dimensions.
3. Vertigo impairs the physical dimension of quality of life, while tinnitus and hearing loss have influence on the psychosocial dimension.
4. Strong sense of coherence seems to be an important predictor of the patient's evaluation of disease-specific quality of life, but the impact of SOC is stronger on emotional/psychosocial than physical aspects.
5. Generic and symptom-specific instruments on quality of life aspects can give complementary information to the AAO/HNS classification and FLS and should encouraged to be used when evaluating treatment results in patients with Meniere's disease.
6. When medical treatment has failed, ELS may be a useful treatment modality in patients with serviceable hearing. Recent treatment regime with low dose gentamicin can be used if ELS has failed or if for some reason surgery in general anaesthesia not is advisable. Vestibular neurectomy should be performed in a limited number of patients.
7. Considering the role of stress as a trigger of attacks it might be fruitful to test whether different kinds of stress management techniques could be taught to patients with the effect of reducing the number of attacks.

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