PSYCHOLOGICAL ASPECTS AND STRESS-RELATED HORMONES IN MENIÈRE'S DISEASE

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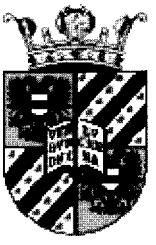

Psychological aspects and stress-related hormones in Menière's disease

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Introduction to Menière's disease

Historical background and pathogenesis

Menière's disease was first described by Prosper Menière (1799-1862) who reported a clinical picture of patients with hearing loss, tinnitus and episodic vertigo accompanied by nausea, vomiting and syncope in the Gazette Médicale de Paris (1). Menière's new concept that this mainly triadic symptomatology originated in the labyrinth instead of being a vascular cerebral dysfunction brought him fame in the last year of his life.

In 1938, Yamakawa and also Hallpike and Cairns independently found hydrops of the endolymphatic system (inner ear fluid system) in the temporal bones of deceased Menière patients (2;3). Endolymphatic hydrops has been the established histopathological origin of Menière's disease since these findings. Lawrence and McCabe (1959) proposed the most accepted theory for endolymphatic hydrops generating episodic vertigo and fluctuating hearing loss (4). They suggested that distension of the endolymphatic compartment would lead to displacement and possibly rupture of Reissner's membrane. Consequently, an excess of potassium-rich endolymphatic fluid leaks into sodium-rich perilymphatic fluid (the other inner ear fluid), which has neurotoxic effects on the sensorineural tissues.

The hydrops is thought to be caused by a disturbance of the endolymphatic homeostasis through reduced absorption and temporary overproduction of endolymph (5). It remains unclear how the exact mechanism for episodic increases in endolymphatic volume and the pathophysiology of the symptom complex works. Nevertheless, many mechanisms for the reduced absorption of endolymph have been proposed in a congenital or acquired dysfunction of the endolymphatic sac. It has been shown that the endolymphatic sac and duct of Menière patients were small compared to healthy controls (6). The acquired dysfunction could be caused by a variety of factors as infections (bacterial or viral), immune-mediated aetiologies and vascular disorders (7). It seems more logical to conclude that Menière's disease includes the classical triad and additional symptoms, which may be caused by multiple aetiological factors (Figure 1 (8)). No convincing scientific evidence is present to support any of these hypothetical mechanisms (9).

Although the endolymphatic hydrops is the most commonly used pathophysiologic model, not every patient with endolymphatic hydrops experiences the clinical triad of Menière's disease (10). Endolymphatic hydrops is more a histological indicator for Menière's disease than being directly responsible for its symptoms. Kiang mentioned in 1988 that endolymphatic hydrops could be an epiphenomenon in Menière's disease (8). Creating acute endolymphatic hydrops in guinea pigs resulted in minimal effect on cochlear function (11). Nevertheless, repetitive endolymphatic hydrops may lead to biochemical disturbance of inner ear homeostasis. Hopefully, new imaging techniques (high-resolution functional magnetic resonance imaging) can bring us more insight to the pathophysiology of this disease.

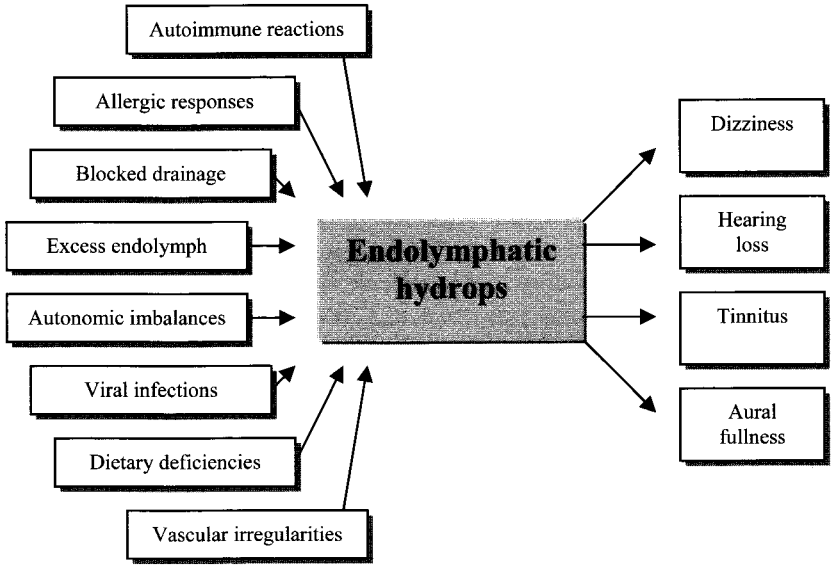


Figure 1. Aetiological factors in Menière's disease by Kiang (8).

Definitions

Menière's disease has known many different definitions through the years. In 1972, the Committee on Hearing and Equilibrium of the American Academy of Ophthalmology and Otolaryngology defined Menière's disease as being "a disease of the membranous inner ear with characteristic symptoms and with a pathological correlate of endolymphatic hydrops". The American Academy of Otolaryngology-Head and Neck Surgery (AAO-HNS) revised these definitions in 1985 and 1995 (12;13), see Table 1.

Parallel to this definition, in our clinic it was considered that the definition must include the clinical symptoms as the direct consequence of the idiopathic endolymphatic hydrops. After profound studies the "Definition Menière Groningen" was established by Mateijsen in 2001, see Table 2 (14). The diagnosis of Menière's disease is by exclusion of other pathology, and makes thorough history examination very important for the correct diagnosis. The "Definition Menière Groningen" is used in this thesis for diagnosing patients with Menière's disease.

Table 1. AAO-HNS-criteria for the diagnosis of Menière's disease (1995)

1. Recurrent, spontaneous episodic vertigo lasting at least 20 minutes (commonly several hours), often prostrating, accompanied by disequilibrium that may last several days; usually nausea, commonly vomiting or retching, no loss of consciousness. Horizontal or horizontal rotatory nystagmus is always present
2. Sensorineural hearing loss (not necessarily fluctuating)
3. Either aural fullness or tinnitus (or both)

Table 2. Definition Menière Groningen (2001)

1. History of at least two spontaneous vertigo attacks lasting longer than 20 minutes
2. Sensorineural hearing loss of at least 60 dB added up from the three worst octaves in the same ear, present or past
3. Tinnitus ipsi- or bilateral, present or past

Symptoms and epidemiology

Menière's disease is characterised by the classical triadic symptomatology of fluctuating, progressive hearing loss, periodic episodes of rotatory vertigo and tinnitus. Sometimes this is accompanied by a sensation of fullness or pressure in the ear (9). The symptoms do not necessarily portray themselves all at the same time. It can take months or years before all three or four symptoms are present and we can diagnose the patient with Menière's disease. In general, the sensorineural hearing loss starts of as fluctuating in the lower frequencies and progresses to a permanent, flat audiometric pattern on all frequencies with loss of speech discrimination. Tinnitus is either intermittently or constantly present. The vertigo appears suddenly and gives the sensation of a false movement. It seems as if the surroundings are constantly spinning and moving around. Due to the perception of rotating the patients often suffer from nausea and vomiting. During vertigo attacks the hearing loss usually increases and tinnitus intensifies. The unpredictability of the vertigo attacks and the chronic character of the hearing loss and tinnitus make it a stressful and disabling disease.

There are two variations on the typical triad of Menière's disease. Drop attacks occur in about 7% of the Menière patients next to their usual vertigo attacks (15). They occur out of the blue and last less than a second. Patients perceive that they are firmly pushed or drawn to the ground without loss of consciousness. These

drop attacks are thought to originate in the otolithic organs and are named the "otolithic crises of Tumarkin" named after the British otologist Tumarkin in 1936 (16). They occur more common in patients with long-term Menière's disease and during periods when the vertigo attacks are more frequent en intense. Lermoyez' syndrome distinguishes from the classical Menière's disease in hearing improvement around a vertigo attack (17). Its incidence is estimated about 1% of the patients with Menière's disease.

The natural course of Menière's disease is variable. The end-stage Menière's disease is generally characterised by irreversible sensorineural hearing loss, continuous tinnitus with intermittent or chronic disequilibrium (18). It has been shown that up to 50% of the patients will eventually develop symptoms in the opposite ear (19;20). Shea Jr and Filipo have both suggested a classification for the different stages of Menière's disease (21;22). These are mostly used in studies concerning natural course and investigating treatment modalities.

The incidence and prevalence of Menière's disease differs widely for continents and countries. The prevalence of Menière's disease has been estimated to range from 4 to 157 per 100,000, although this depends upon a number of factors, such as the diagnostic criteria used to define the disease (23). Based on these numbers it is estimated that there would be over 10,000 Menière patients in the Netherlands. Menière's disease most commonly affects people in their 40's and 50's, although individuals from 20 onwards may be affected (24). It is rarely, though occasionally reported in children (25).

Treatment

There is no curative treatment available for Menière's disease. Since the exact pathophysiologic mechanism remains unclear, every treatment remains symptomatic. The treatment options are medical and surgical. Many studies have been performed to test different medical treatment modalities, e.g. diuretics, antihistamines, sedatives, steroids and overpressure treatment. Betahistine and diuretics seem to be the only effective treatment options for long-term treatment of vertigo (26). According to a Cochrane study in 2001, there was not sufficient evidence to state whether betahistine has any effect on Menière's disease (27). Surgical procedures are executed in certain clinics when medical treatment fails. These invasive treatment modalities as endolymphatic sac surgery, vestibular neurectomy or labyrinthectomy are performed with different results (9). The less invasive intratympanic application of steroids does not seem to alter symptomatology (28), although intratympanic aminoglycosides (gentamycin) do have an effect in reducing vertigo (29). It is acknowledged that the placebo-effect of any treatment is large, namely 70-80% (30).

Nevertheless, Menière patients are not helped with the statement that no exact cause or curative treatment is available for their disease. So, every Menière patient needs individual treatment, wherein psychosocial help or even temporary sedative medication should be included.

Summary

Menière's disease is a disabling disease with stressful symptoms: progressive hearing loss, tinnitus and sudden vertigo attacks. Idiopathic endolymphatic hydrops is thought to be the cause of Menière's disease, although compelling scientific evidence has never been given. It is estimated that there are over 10,000 Menière patients in the Netherlands. Since no Menière patient has similar exposition to or presentation of symptoms, or perception of disease, individual treatment is required. Psychological problems have to be taken into account and psychosocial help should be provided where needed.

Psychological aspects are often mentioned in the chronic and disabling Menière's disease. In the following chapters a review of this subject and of general aspects of stress are presented. Thereafter, the aims of this thesis are introduced in chapter 4.

Psychological aspects in Menière's disease: a review

Van Cruijsen N, Wit HP, Albers FWJ. Psychological aspects of Menière's disease. Acta Otolaryngologica 2003; 123(3), 340-347.

Introduction

Menière's disease is amongst the conditions in which psychological factors are often emphasised. Many physicians have reported accompanying emotional disturbances in Menière disease. Others have suggested that Menière patients have specific personality traits. These observations seem to have led to the conclusion that psychological factors could play a role in the development and continuation of Menière's disease. Therefore Menière's disease has received a lot of attention from a psychological point of view.

The early literature on psychological considerations in Menière's disease focussed on the psychosomatic causes and somatopsychic results of the disease. A psychosomatic illness is defined as "a disease where the symptoms have an organic basis but the causes of the illness are to be sought in psychosocial stressors and the inability of the patient to cope with stress". This is in contrast with the somatopsychic theory, where psychological disturbances are due to physical complaints. The concept of an interaction of both psychological and somatic factors in Menière's disease has lead to more research in this field. The latest subject of interest is the impact of the disease on the daily life of Menière patients, the quality of life. Since the latest literature reviews on psychological aspects in Menière's disease were written in the 70s, a synopsis of the studies with this subject until now seems appropriate (31;32).

A chronological summary of studies on the psychosomatic, the somatopsychic and both combined hypotheses in Menière's disease is shown and reviewed in separate paragraphs. In an additional paragraph the studies concerning the impact of Menière's disease and their quality of life are presented and discussed. At last, some suggestions for further research in this field are made.

Psychosomatic theory in Menière's disease

In many reports psychological factors have been mentioned as aetiological or covariant factors in Menière's disease by different researchers.

Fowler and his associates were the first to apply personality measures to patients with Menière's disease and proposed a psychosomatic aetiology for the condition. Fowler and Zeckel (1953) have done psychiatric interviews and a series of psychological tests in 23 patients with Menière's disease (33). They concluded in this non-controlled study that the patients had different types of life stress and that they lacked an ability to cope with excessive tension. They stated that the emotional tension might precipitate the attacks. Their physiological explanation was that by sympathetic stimulation and release of adrenaline through the emotional stress, blood vessels in the labyrinth sludge (clotting of cells and slowed blood flow), which subsequently causes the vertigo attacks.

In another study, Fowler and Appell (1956) compared the personality, physiques (somatotype) and otological diagnosis of patients with Menière's disease and patients with otosclerosis (34). They concluded that the body type of Menière's

patients as a group were more mesomorphic (athletic) and less ectomorphic (fragile) in the direction of the perfectionist type, compared to the otosclerosis patient.

In a sequence of papers, Hinchcliffe (1967) examined the psychosomatic hypothesis in Menière's disease from several perspectives (35-37). In the first study on emotion as a precipitating factor to disease, Menière patients (28/44) related their disease significantly more to emotional factors than otosclerosis patients (2/20) did. Next, he tested the personality profile of Menière's patients using the Minnesota Multiphasic Personality Inventory (MMPI). In this study was shown that 11 out of 44 Menière patients had a psychosomatic type of personality compared with none of the 20 otosclerosis patients. This difference was significant. In the last study of this series, he used the same groups of people as mentioned above and their blood relatives, and added an unselected group of hospital employees. He asked them all whether they had psychosomatic disorders (e.g. arthritis, migraine and peptic ulcer). The patients with Menière's disease and their families reported more psychosomatic conditions than the otosclerosis patients and their relatives, and the employees. All the patients with Menière's disease reported a history of migraine and 11 (25%) reported cyclical vomiting of childhood. Hinchcliffe concluded that his findings enhanced a psychosomatic origin in Menière's disease.

Siirala and Gelhar (1970) submitted Menière's patients to a psychological interview and the Rorschach Inkblot Test (38). They found that these patients were overambitious, lacked insight and spontaneous affective responses to other people. They summarised their observations as evidence for a predisposing psychosomatic constitution for somatic complaints.

In 1975 Stephens published a paper titled "Personality tests in Menière's disorder" (39). Stephens carried out this study using the Middlesex Hospital Questionnaire (MHQ) and the Eysenck Personality Inventory (EPI). The personality characteristics of 104 Menière patients were compared with the personality characteristics of 62 patients suffering from idiopathic peripheral vertigo, of 170 randomly selected ENT outpatients and with the mean values for the separate scales of the tests. The Menière patients had higher scores on anxiety, phobic anxiety, obsessionality, somatic preoccupations, depression and hysteria scales when compared to the normal controls. When these patients were compared to the vertiginous patients they showed significantly higher obsessionality scores and depression scores. The scores for most scales decreased with increasing severity of the disorder, although the obsessionality scores did not follow this tendency. Stephens concluded that his results supported the earlier findings of Fowler (33;34).

In a study by Czublaski et al. (1976) 30 randomly chosen Menière patients were compared to 30 non-Menière ENT patients by means of a psychiatric interview, the Maudsley Personality Inventory (MPI) and a 25-question Neuroticism Scale (40). In Menière's disease various psychic stresses experienced in childhood were found to be more common. In 76.6% of the cases the onset coincided with psychic conflicts and psychic stresses were found to intensify the symptoms in a high percentage of patients (60%). They felt that these results support the hypothesis of a psychosomatic aetiology of Menière's disease.

Groen and Schmidt (1983) presented a study wherein 21 Menière patients were submitted to a biographical interview and a systemic psychosomatic follow-up (41). The group had a more or less specific personality structure; they had a high intelligence, great diligence and a great sense of duty and they were to a great extent rigid and conscientious. Despite the absence of a control group or a systematic data collection, the authors considered that these results confirmed previous indications of the psychosomatic hypothesis of Menière's disease.

In summary, it seems clear that Menière's disease is often associated with anxiety or other emotional problems. Most of the studies that favour the psychosomatic theory are based upon clinicians' opinions and subjective reports of the patients. Many researchers used psychological tests without standardised psychometric properties. One of the problems with the reporting of (psychological) stress as precipitating factor is the retrospective reporting bias. This means that patients may selectively remember episodes of stress and anxiety and wrongly perceive and describe themselves as having been abnormally anxious prior to developing vertigo. Another problem with most of these investigations is that the symptom of vertigo is not controlled for. Thus the emotional disturbance could be caused by vertigo rather than is the cause of the vertigo. Stephens (1975) has performed a well-constructed study in this field using vertiginous patients and other ENT patients as controls (39). His conclusion that Menière patients do have more obsessionality traits and are more depressed than the controls, justifies more research in this field. Nevertheless, the conclusion that Menière's disease has a psychosomatic origin is dubious and needs at least more justification.

Somatopsychic theory in Menière's disease

Researchers favouring the somatopsychic theory in Menière's disease concluded that the psychological problems would be secondary to the inner ear disease.

Watson et al. (1967) were the first in line to support the somatopsychic theory more than the psychosomatic hypothesis (42). They compared the MMPI profiles of 40 Menière patients and 38 non-psychogenic vertiginous controls. The only significant between-group scale difference appeared on the hypochondriasis scale. Individual analysis provided only weak support for the psychosomatic hypothesis. They concluded that this could be attributed to the physical symptomatology of the disorder and gives minimal evidence for the general psychosomatic hypothesis.

In a neuropsychological study by Löchen (1970), 30 Menière patients were compared with a group of 50 patients with verified severe cerebral atrophy (43). Among other things, they were individually examined with a set of psychological tests and underwent neurological examinations. He showed that the more serious the intellectual impairment was, the higher was the incidence of organic lesions judged from neurological signs, otological, EEG and pneumo-encephalographic examinations. Therefore, he supported the hypothesis that the psychological disturbances in Menière's disease are secondary to an organic disorder.

Pulec (1972) presented the results of a two and one-half year study of aetiology, natural course and results of treatment (44). He performed a psychological investigation using the MMPI, an anxiety scale, a self-esteem scale, a psychosomatic checklist, a personal stress questionnaire and an interview by a psychologist. The results lacked evidence regarding involvement of emotional factors in the aetiology of this disease. But, continued evaluation suggested that patients already suffering from a vertiginous problem would sometimes have an exaggeration of symptoms during periods of stress. They explained this observation by two causative factors. Firstly, stress and fatigue are thought to reduce the effectiveness of the vestibular efferent system and its suppressing effect upon a malfunctioning inner ear. When suppression is reduced, the existing abnormal labyrinthine stimulation becomes evident. Secondly, Menière patients are on the border of control and have inadequate adrenocortical output during periods of stress with subsequent exaggeration of symptoms.

In the year 1975, Brightwell and Abramson tested 13 patients with Menière's disease, 18 non-Menière vertiginous patients, patients with otosclerosis (n=13) and patients with lymphoma (n=12), using the EPI and the Cornell Medical Index (CMI) (45). The groups did not differ from each other in their personality test mean scores. Numerous correlations were found between personality scores and symptom severity within the Menière group. The authors suggested a subgroup of Menière patients who may have significant emotional factors involved in their illness and that psychological vulnerability might be a useful concept.

Crary and Wexler (1977) constituted a new approach to the question whether the data used to support the psychosomatic hypothesis is actually evidence of a somatopsychic process (31). In their study four groups were compared: 63 Menière patients, 15 Menière patients (cross-validation group), 33 non-Menière vertiginous patients and 17 non-vertiginous ENT patients. They conducted a comprehensive investigation to examine the development, onset, course and outcome in Menière's disease. The patients were followed for 2 years with many questionnaires regarding severity of the disorder, stress preceding the disorder and personality. A random subsample of 20 Menière patients recorded the presence or absence of life stress, tinnitus and vertigo on a daily diary sheet. No clear-cut differences were found when Menière patients were compared to vertiginous patients on psychological variables concerning development, onset, course or outcome of the disease. Parallel to the clinical study on the psychosomatic hypothesis, they analysed the literature relating psychological aspects to Menière's disease, vertigo and tinnitus. According to them, most of the clinical studies revealed a variety of methodological flaws: simple case reports, no use of objective measurement techniques, no appropriate statistical tests or no control groups. They concluded that it could not be ruled out that psychological stress may play a developmental and/ or precipitating role, but that on the basis of current available research designs and instruments, the best evidence indicates that the effects are somatopsychic. In 1980 House, Crary and Wexler presented the same results and

conclusions of their 1977 study at a Symposium on Menière's disease and subsequently in another paper (16).

Hereupon, Hinchcliffe (1983) argued from a variety of measures that the classical Menière patients and the patients with primary vertigo are merely on different parts of the same continuum, making comparison between these groups somewhat questionable (46). In 1986, Wexler and Crary reiterated their standpoint as made in the paper of 1977 and emphasised the question of what constitutes a psychosomatic disorder (47). They stated that any research on psychological factors in Menière's disease should also address this question. The conclusion of Crary and Wexler (1977) was also challenged by Jakes (1987), who pointed out that several aspects of the data were not considered, e.g. the occurrence of stress without vertigo attacks (48). Jakes also stated that the patients' discomfort from the disease might also cause stress and fatigue.

In neuro-psychological studies by Sorensen et al. (1977) and Zilstorff et al. (1979) Menière patients were subjected to a battery of neuro-psychological tests (20, 21). They demonstrated that patients with longstanding Menière's disease had psychological disturbances, presumably localised in the non-dominant hemisphere. In short-duration Menière's disease these results could not be replicated. It is concluded that the central changes in the non-dominant hemisphere function develop over a longer period of time.

In 1984 Rigatelli et al. examined 60 patients with vertigo by means of a biographic interview and of three self-rating scales (MHQ, Zung's Self-rating Depression Scale and Anxiety Scale) (49). The patients were divided into groups: Menière's disease (n=8), neuronitis (n=14), vertebrobasilar insufficiency (n=16), sensorineural deafness (n=8) and nucleoreticular syndrome of Ararslan (n=12). The other two patients had respectively inner ear lithiasis and damage of the labyrinth after stapedectomy. The control group was composed of 60 ENT patients with non-vertiginous and non-surgical pathology. The comparison between the vertiginous patients and the control subjects showed significant differences in depressive state, anxiety, somatisation and total neuroticism. The patients affected by Menière's disease showed no significant differences regarding depressive symptomatology and anxiety, when compared with the other vertigo sufferers. On the other hand, Menière patients had statistically lower indices on obsessional traits and higher levels of somatisation compared to the sum of the other disease groups. They concluded that vertigo syndromes need a strict collaboration between psychiatrist and the otorhinolaryngologist.

Grigsby and Johnston (1989) presented two cases of women with Menière's disease who also experienced concurrent feelings of depersonalization and derealization (23). They argued that emotional disturbances previously identified as predisposing causes of Menière's disease are more likely effects of the disease.

In summary could be said that the researchers favouring the somatopsychic theory did perform better constructed studies than the ones who supported the psychosomatic hypothesis by using vertiginous controls. Although the evidence for the somatopsychic theory is stronger than the psychosomatic hypothesis, it is not

waterproof. Emotional factors do seem to play more of a role in subgroup of Menière patients. Nonetheless, a correlation between emotional factors and a vertigo attack could never be scientifically proven for every Menière patient. This difference in psychological problems in Menière patients could be explained by individual differences in psychological vulnerability and coping. The psychological disturbances can not exclusively be explained by physical factors. There seems to be no straight answer to the question whether the psychological problems are psychosomatic or somatopsychic. Both theories could not be proven solidly. It suggests reciprocity of psychological and somatic factors in the continuation of Menière's disease.

Reciprocity of psychological and somatic factors in Menière's disease

After three decades of studies based upon the psychosomatic and somatopsychic theories in Menière's disease, it was concluded that once the disease has appeared, psychological and somatic factors interact. This is parallel to the general consideration of psychosomatic diseases developed through the years.

Coker et al. (1989) examined the psychological profiles of 21 patients with active Menière's disease and 27 patients with inactive Menière's disease using the MMPI and the Diagnostic Inventory of Personality and Symptoms (DIPS) (50). The differentiating factor for active versus inactive disease was the presence of vertigo or disequilibrium in the past 3 months. In this study, depression was clearly the significant diagnosis seen in individuals with active Menière's disease, compared to the normal values of the separate tests. The MMPI classified 80% of the active (n=20) and 32% of the inactive group (n=25) as depressed and the DIPS classified 70% of the active (n=20) and 39% of the inactive Menière patients (n=23) as depressed. The authors concluded that psychological assistance and possibly anti-depressant medication may be beneficial to the patient as an adjunctive treatment for Menière's disease.

In 1991 Martin et al. assessed 45 Menière patients with the Symptoms Checklist (SCL-90) and 37 Menière patients with the French "Questionnaire Depression" (QD2) (51). It appeared that Menière patients have significantly more psychopathological disorders than "normals", namely anxiety, depressive tendency and phobia.

A study titled "Illness behaviour, personality traits, anxiety, and depression in patients with Menière's disease" was presented by Savastano et al. in 1996 (52). 50 Menière patients were psychologically tested with the Illness Behaviour Questionnaire (IBQ), EPI, State Trait Anxiety Inventory (STAI), and the Zung's Self-Rating Depression Scale. They found higher neuroticism scores, more markedly psychological perception of the disease and a lower level of affective inhibition than normal. Anxiety and depression scores were not significantly higher than normal. Cluster analysis of the IBQ scores identified subgroups of Menière patients with normal scores and with severe psychological distress. Patients from the latter group were older and had a longer history of Menière's disease and more

hospital stays. Savastano et al. concluded that their results indicate the possibility of distinguishing those patients whose personality traits could facilitate the development of abnormal illness behaviour and psychological symptoms in relation to Menière's disease.

Erlandsson et al. (1996) did a "focus group interview" with four Menière patients and a semi-structured interview with another four patients with Menière's disease (53). It was reported that attacks were triggered by distressing thoughts and by sensory sensations.

Sawada et al. (1997) studied the psychosomatic profile of Menière patients in relation to their plasma anti-diuretic hormone (p-ADH) concentration (54). Psychological aspects were tested using the Cornell Medical Index (CMI) and the Yatabe-Guiltford personality test in 34 patients. The CMI showed significantly more subneurosis and neurosis types than "normals", but this was not related to p-ADH levels. The personality test classified the patients with Menière's disease in the normal range. In a self-constructed stress questionnaire another 46 patients were asked if they have had stress before vertigo and what kind of stress it was. 78% of the 46 patients were conscious about stress before an attack and they had a significantly higher p-ADH level than the patients without stress.

Andersson et al. (1997) presented a time-series analysis of stress and symptoms of Menière's disease (55). Twenty Menière patients reported daily on four visual analogue scales from "none at all" to "the maximum possible" about discomfort of dizziness, tinnitus, hearing problems and experienced stress. Concurrent associations between stress and symptoms of Menière's disease were found, particularly in relation to vertigo. However, this study did not support the role of stress as a precursor of symptoms in Menière's disease.

In another study Hagnebö et al. (1998) investigated the premonitory sensations of Menière attacks in 514 patients (56). They developed three scales for measurement of somatic (SOM) and psychological (PSYCHOL) sensations and of situational (SIT) characteristics, surrounding an attack of Menière's disease. Principal components factor analyses showed that the SOM scale could be divided into two subscales: dizziness/vertigo/anxiety and sensations in the ear. The PSYCHOL scale showed an energy/awareness factor and a negative emotional state factor. The SIT scale showed the two factors environmental disturbances and stressful conditions. The authors concluded that knowledge of somatic, psychological and situational premonitory characteristics of attacks in Menière's disease could lead to improved therapy and counselling.

Takahashi et al. (2001) devised a questionnaire to analyse lifestyle and behavioural characteristics in Menière patients (57). The Menière patients (n=60) compared to 936 healthy controls had a significant more stress-causative tendency in behavioural characteristics, felt stronger anxiety and showed more severe symptoms owing to this anxiety.

Handicaps and quality of life in Menière's disease

Recently there has been a strong push toward outcome-based research in medicine to assess the results of treatments. Important elements in the outcome-based research are the issues of handicap and quality of life. This trend is also seen in studies concerning Menière's disease.

The International Classification of Impairments, Disabilities and Handicaps (ICIDH) was first published by the World Health Organisation (WHO) in 1980. The original goal of the ICIDH was to provide a framework to organise information about the consequences of diseases in terms of resulting impairments, disabilities and handicaps. Impairment refers to the loss of physiologic function, such as hearing loss. Disability refers to the loss of function caused by the impairment, such as the inability to use verbal language because of the hearing loss. Handicap refers to the social effects of disability, such as the inability to converse with co-workers owing to hearing loss. In 1995 the WHO Quality of Life group defined the concept "Quality of Life" as the individuals' perception of their position in life in the context of culture and value system in which they live and in relation to their goals (32). The quality of life is divided in three separate domains: physical, psychological and environmental. The physical component of quality of life refers to physical effects of the disease: pain, fatigue or vertigo. The psychological domain is related to an individual's mood in a global sense, e.g. fear or depression. The environmental component of quality of life has two important elements: social participation and role activities. The interaction between the disabling process and quality of life is presented in Figure 1 (32, 33).

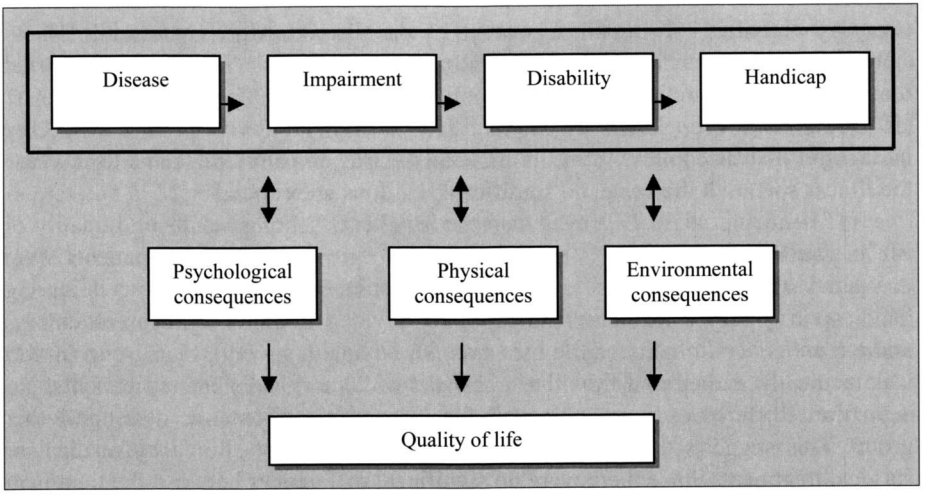


Figure 1. Disabling process and quality of life.

The studies mentioned in this paragraph were more concerned with the seriousness of the psychological disturbances. Anxiety and depression are common problems in Menière's disease. It seems clear that the possible consequences of vertigo might be frightening. The acute vertigo attacks are infrequent, unpredictable and violent. The patients try to avoid the attacks and tend to impose restrictions on their activities and lifestyle, which may generate further feelings of helplessness and depression. In many retrospective studies psychological stress was a precipitating factor in aggravating the disease. But a correlation of stress and the development of a vertigo attack could not be shown in the only prospective study presented by Andersson et al. (1997) (55). On the basis of the most recent research, it cannot be ruled out that psychological stress might play a precipitating role in Menière's disease, but its more likely that the psychological picture is a result of, and not specific to this illness. It may rather express an individual's generalised vulnerability.

As a result of a chronic condition, like Menière's disease, life will change considerably. Just a few studies have dealt with disability factors, influences on the daily life of patients and their experience of the quality of life.

The first published study on Menière's disease and quality of life came from Cohen et al. in 1995 (58). Data concerning disability in Menière's disease were analysed from 51 Menière patients who filled in a self-administered questionnaire. They found that vertigo is the most bothersome symptom influencing a subject's performance at work, followed by hearing loss. Their results also pointed out individual differences in coping with the symptoms.

Hagnebö et al. (1997) devised a questionnaire to investigate the influence of vertigo, hearing impairment and tinnitus on the daily life of 514 Menière patients (59). The results indicated that the three key symptoms had a strong negative effect on the daily life of Menière patients. 75 percent of the subjects avoided certain everyday activities or situations because of the disease. More than half of them stated that they never felt free of discomfort from the illness. The subjects reported most discomfort from the tinnitus; this is in contrast with the findings of Cohen et al. (58). This may be explained by the fact that vertigo is a symptom of a temporary nature and that discomfort from tinnitus and hearing impairment seems to increase the illness span. All the same, no significant relations were found.

Kinney et al. (1997) evaluated the long-term hearing results and quality of life in patients with Menière's disease (60). Two groups of Menière patients were compared using audiometric tests, disease-specific quality of life tests (Hearing handicap inventory, Dizziness handicap inventory and Tinnitus handicap inventory) and a more general quality of life measure (SF-36 health survey). One group (n=31) was medically treated and the other consisted of 20 surgically treated patients. No significant differences were observed for long-term audiometric data for either group. This suggests that long-term hearing results are not altered by medical or surgical treatment. Since there were no significant differences between the treatment groups in the disease-specific handicap scales and in the global health scale, data were analysed as one group (n=51). More than three-quarter of the patients reported

that hearing loss, dizziness and/or tinnitus affected their quality of life to some degree. Patients with Menière's disease functioned more like patients with minor medical conditions on the physical function, role limitations due to physical problems, bodily pain and general health perceptions. In contrast, Menière patients functioned more like patients with major medical conditions for the vitality, social function, and role limitations due to emotional problems. These findings suggest that the underlying emotional component of Menière's disease is more handicapping than the physical components are.

Murphy and Gates (1999, 2000) reported the development of two clinically useful methods to quantify the morbidity of Menière's disease: the Menière's Disease Patient-Oriented Severity Index (MD POSI) and the daily vertigo diary card (37, 38). The MD POSI could be a useful disease-specific outcome instrument, but will be revised and further evaluated and validated.

In 2001 Söderman et al. presented a study with subjective evaluations of quality of life related to disease specific symptoms, sense of coherence and treatment in Menière' disease (61). 112 patients with Menière's disease were split up in three groups: endolymphatic sac surgery (n=59), intra-tympanic gentamycin injections (n=26) or surgically untreated (n=27). All patients were measured with the Vertigo symptom scale, Hearing disability handicap scale, Tinnitus severity questionnaire, the AAO-HNS criteria for reporting results of treatment of Menière's disease and the Sense of Coherence scale. There was no difference in general quality of life, present hearing loss or tinnitus between the three treatment groups, but the gentamycin-treated patients had less vertigo than did the other groups. Sense of coherence showed a strong correlation to reported quality of life in all measurements.

Anderson and Harris (2001) studied the impact of Menière's disease on the quality of life using several general health measures (Quality of Well-being Scale, SF-12 physical and mental scores and a Depression scale) (62). 19 Menière patients who requested for further treatment got pre-treatment interviews to establish baseline quality of life characteristics before medical intervention. The results indicated a loss of well being compared to people with no symptoms and full functional status. Furthermore, the Depression scale indicated a clinically significant depression in Menière patients.

In general, disability in Menière's disease is difficult to quantify. Three of the four symptoms are subjective, with hearing being the most quantifiable of the symptom complex. Another factor, which makes the disability difficult to determine, is the fluctuating, unpredictable nature of the Menière's disease process. This complicates giving the employers and insurance companies of the Menière patients exact data how much the Menière patient is disabled. Nevertheless, it seems clear that Menière's disease is an intensely handicapping disease and needs individual psychosocial support.

Future of psychosocial research in Menière's disease

The psychosomatic theory is not adequate enough to be the exclusive aetiological cause for Menière's disease. Although a somatopsychic factor seems evident, it is not the sole explanation. The best way to interpret this complex process seems to be a continuous interaction of psychological, somatic and environmental factors. It is opted and very likely, that the process is becoming a vicious cycle: symptoms of the disease could worsen the emotional state, which in turn could worsen the (perception of) symptoms.

Nevertheless, the question "Which came first, the hen or the egg?" remains unsolved. Since it is not feasible to have the personality profile or other psychological measures before the disease has developed, we'll presumably never know the answer. But that is probably irrelevant: more important is to know how the emotional and physical factors interact exactly and why one person develops more frequent and more severe chronic problems after getting Menière's disease than the other. However, of the utmost importance is the question how we can interfere in this suggested vicious cycle of physical symptoms and emotional or environmental disturbances and help these patients.

To get these answers, the suggested reciprocal process has to be studied in a prospective design. Firstly, the process has to be put in a general model of stress with stressors (physical symptoms and psychological disturbances), appraisal (coping and personality) and stress responses (psychological, physical and behavioural). In this multifactor model, the separate psychological, somatic and behavioural aspects of Menière's disease all have their specific place in the model and interrelate. Of course, the impact of the disease, the quality of life, plays an important role in this model. Not only as an endpoint measurement of general impact of the disease, but also as a possible stressor in the process. All together, these factors interact in a vicious cycle. Every single factor in the model has to be qualified and quantified by means of validated, standardised measures containing the appropriate psychometric properties. Information about this process and its factors might give us better insight in which Menière patient and in what way psychosocial support has to be intensified.

Aspects of stress

Introduction

As suggested in the preceding chapter, Menière's disease may develop into a vicious cycle of physical and psychological factors that can be put in a universal model of stress with stressors and stress responses.

In this chapter aspects of stress in general and their relation to disease are presented. Firstly, it is used to present the background and aims of this thesis. Secondly, it allows us to expose the definitions as used in this dissertation. It includes old and new facts about stress, as well as the effects of stress and stress hormones upon bodily systems and organs, healthy ears and Menière ears.

General aspects of stress

Stress has been a subject of interest among many researchers who are studying environmental and psychosocial influence on health for a long period of time. Historically, the first description of stress was by Cannon in 1932, who defined it as the systemic stress that causes disturbances of the tissue system (63). He observed that a pattern of physiological mobilisation was elicited during times of arousal, which he described as the "fight and flight response".

In 1956 Selye defined the General Adaptation Syndrome as "the sum of all non-specific, systemic responses to the body that ensues upon sustained exposure to stress" (64). This syndrome generally develops through three stages of pathological and biochemical changes: the alarm reaction, the stage of resistance and the phase of exhaustion. Selye's model has been very influential, but it has also been critiqued for underestimating the role of psychological factors in stress, such as a person's emotional state or the way a person thinks about stressors.

This led to the development of a psychobiological model, the transactional model, by Lazarus and Folkman (65). In this model the stress response depends on the evaluation of the stressor, called appraisal. They proposed that a stress response is elicited if an individual appraised a potentially stressful event as stressful. Appraisal depends on the received characteristics of the stimulus and the psychological structure of the individual (primary appraisal) or on the individual's coping style (secondary appraisal).

Still, the definition of the term "stress" lacks conformity and it is not used very consistently. Researchers in this field use the term "stress" variably as the event (stressor) or the reaction (stress response). Cohen et al. properly summarised the stress process in the following way: "environmental demands tax or exceed the adaptive capacity of an organism, resulting in psychological and biological changes that may place people at risk of disease" (66). The stress response is a reaction to a stressor and its evaluation is split up into three separate reactions, namely psychological, physiological and behavioural.

The *psychological stress response* is defined as the effect on the emotional state. In the acute situation this could be fear and anger. If stressors persist for a longer period of time or occur in rapid succession, people do not have time to

recover from this situation. This situation may lead to a state of tension, irritation or depression.

The *physiological stress response* is the effect of the stressor on the physiological balance of the body, the homeostasis. The physiological stress response results in more glucocorticosteroid and catecholamine secretion. The physiological response and the stress hormones are discussed in detail in paragraph "Stress and stress hormones".

Stress reactions become clear in the way people look, act or talk in the acute situation. Strained facial expressions, tremors or a trembling voice are common *behavioural stress responses*. In the long run, people develop ways to avoid the stressors, for instance giving up jobs or education, abusing alcohol or even attempting suicide.

In this work, the stress process has been divided into specific components as Cohen et al. did namely *stressors* (potentially threatening events or situations), *appraisal* (perception of stress) and the *stress response* (instinctive, behavioural and biological responses on stressors or appraisals). Whereas the term "*stress*" is used exclusively for situations that the individual interprets as threatening and causes some physiological, affective and behavioural responses.

New terms: allostasis and allostatic load

Due to problems defining the concept of "stress" and of quantifying it psychologically and physiologically, two new terms have been formulated: allostasis and allostatic load. Allostasis means literally stability through change. In 1988 this term was introduced by Sterling and Eyer to describe the adjustment of the cardiovascular system to the bodily state, in rest or in strain (67). This regulation can be ascribed to physiological mediators such as cortisol and catecholamines.

McEwen defined allostasis as "the ability of the body to increase or decrease vital functions to a new level within that range upon challenge, particularly in anticipation of a challenge" (68). Whenever the brain considers an event as threatening (stressful), physiological and behavioural responses are generated. These responses lead to allostasis and adjustment. In this process the stressor is everything which brings the body out of balance and the stress response is the physical reaction to restore the balance by secretion of hormones.

The term "allostatic load" refers to an overload of the body. It is the price the body has to pay for constant allostatic reactions to psychosocial or physical situations. It involves damaging effects of continuously increased secretion of catecholamines and glucocorticosteroids. This allostatic load may lead to wear and tear of organs and tissues, and make individuals more susceptible to illness.

In the cardiovascular system the catecholamines are needed for adjustment of the pulse rate and blood pressure during different situations such as sleeping, awakening and physical exertions. Frequent increases in blood pressure during stress or a failure to stop this increase of pressure accelerates arteriosclerosis. Adrenal hormones cause allostasis by the extra intake of food and the use of the energy

reserves. Recurrent stress brings on insulin resistance and accelerated progression to diabetes mellitus type 2, including obesity. While acute stress activates the immune function, chronic stress suppresses the immune system. Subsequently, suppression of the immune system makes an individual more susceptible to infection and inflammation. In the brain catecholamines and glucocorticosteroids are related to the preservation of both positive and negative emotional memories. During frequent and chronic increases of glucocorticosteroid levels, the memory function of the brain declines through hippocampal atrophy (see paragraph "Glucocorticosteroids and hippocampus").

Stress and stress hormones

In this paragraph the current view on the physiological response during stress is presented. The physiological stress response elapses through two systems, namely the hypothalamic-pituitary-adrenal (HPA) axis and the autonomic nervous system (ANS). During stress the hypothalamus releases more corticotrophin releasing hormone (CRH) and antidiuretic hormone (ADH). The CRH activates the pituitary gland into producing more adrenocorticotropic hormone (ACTH), which stimulates the adrenal cortices to secrete more glucocorticosteroids (cortisol) and mineralcorticosteroids (aldosterone). Secondly, stressors activate the sympathetic branch of the ANS, which stimulates the medullae of the adrenal glands to secrete more catecholamines, namely adrenaline and noradrenaline.

Cortisol

Cortisol is a potent glucocorticosteroid (GC) that affects the metabolism of carbohydrates, proteins and fats. It has a profound effect on glucose serum levels. Cortisol tends to increase glucose by stimulating gluconeogenesis from glucose stores and inhibits glucose transport into cells. There are three mechanisms of neuro-endocrine control for cortisol secretion (69). The first is the circadian rhythm and episodic secretion of ACTH. Cortisol secretion is at its highest level in the early morning, approximately one hour before waking up, which declines again as wakefulness occurs. Cortisol levels then gradually diminish during the day and night, but cortisol secretion increases in response to eating and exercise. Although this pattern is consistent, there is considerable intra- and inter-individual variability, and the circadian rhythm may be altered by changes in sleep pattern, light/ dark exposure and eating times. Another neuro-endocrine control for cortisol secretion is the stress responsiveness to physical stress (illness, starvation) and psychological stress (anxiety, depression). Stress responses originate in the central nervous system and increase hypothalamic CRH and thus pituitary ACTH secretion. The third mechanism is the negative feedback of cortisol on the hypothalamus and pituitary. With continued cortisol secretion, ACTH levels continue to decrease and become unresponsive to stimulation with CRH.

Cortisol circulates bound to plasma proteins. The plasma half-life of cortisol is around 80 minutes and is determined by the extent of plasma binding and

by the rate of metabolic inactivation. In basal conditions approximately 75% of the cortisol is bound to corticosteroid-binding globulin (CBG), around 10% is unbound (free) and the remainder is bound to albumin. Synthetic glucocorticosteroids such as prednisolon are bound to albumin.

Analysis of plasma cortisol is predominantly done with radioimmunoassay (RAI), which measures the total, bound and free cortisol (70). Cross-reactivity with some synthetic glucocorticosteroids is variable. Normal values of plasma cortisol concentration demonstrate a circadian rhythm. The highest concentrations range from 200-800 nmol/l and are seen in the early morning. Urinary free cortisol is measured from a 24-hour urine collection by RAI. Less than 1% of the secreted cortisol is excreted unchanged in the urine. This method is particularly useful in differentiating obesity from Cushing's disease. The normal range of urinary free cortisol is 20-270 nmol/24h.

Dexamethasone is a potent glucocorticosteroid and normally suppresses pituitary ACTH release with a fall in plasma and urine cortisol as a result. This fact is used in the dexamethasone suppression test (DST), where 1 mg dexamethasone is administrated as a single dose at 11:00 PM and the following morning a plasma sample is obtained for cortisol measurement. The inhibition feedback is abnormal when the cortisol level is above 50 nmol/l, which is mostly present in patients with Cushing's disease. False negative results are rare, but may occur in patients whose dexamethasone metabolism is slow. On the other hand, false positive results occur in 15% of patients with obesity and 25% of hospitalised and chronically ill patients. Acute illness, depression, anxiety, alcoholism, high-oestrogen states and uraemia may cause false-positive results (70).

A relatively new development is the measurement of cortisol in saliva. Its foremost advantage over plasma cortisol is obtaining material without stressful or invasive procedures such as venipunctures. Saliva is obtained using a Salivette cotton swab (Sarstedt, Nümbrecht, Germany) under the tongue for a few minutes. Normal values with the competitive protein-binding assay at 8:00 AM are 16 ± 1.7 nmol/l for men with a range of 6.4 to 32 nmol/l, and 9.8 ± 3.1 nmol/l for women with a range of 4.8 to 18 nmol/l (70).

Catecholamines

The adrenal medullae are ordinarily activated during ANS arousal, and subsequently they release adrenaline and noradrenaline into the circulating system. The effects of catecholamines are seen in the cardiovascular system, such as an increase of frequency and force of the contraction of the myocardium and the contraction of the vascular smooth muscle. Overall, this leads to an increase of blood pressure. Catecholamines also have effects on relaxation and/ or contraction of some extravascular smooth muscles, e.g. uterus, intestine, bladder, sphincters, trachea and pupils. Furthermore, catecholamines increase oxygen consumption and heat production. They also regulate glucose and fat mobilisation from storage depots.

Circulating levels of catecholamines can be measured by assaying blood samples, but the half-lives of adrenaline and noradrenaline are very short (1-3

minutes), and the turnover or decay of the circulating levels can occur within two minutes. Adrenaline and noradrenaline blood levels fluctuate and vary intra-individually considerably, which is not particularly useful in studying chronic stress. Measurement of urinary adrenaline and noradrenaline or their metabolites provide longer, more stable indices of ANS activity than do blood measures. For studies of ambient or chronic stress, 24-hour urine samples are traditionally used. Normal values for urine adrenaline range from 0.1 to 10 μm/mcrea and noradrenaline between 0.1-30 μm/mcrea.

Glucocorticosteroids and hippocampus

The hippocampus (Greek for seahorse) is a compact structure in the brain lying posterior from the amygdala. It consists of gray matter (Ammon's horn and dentate gyrus) and white matter (alveus and fimbriae). The term hippocampus has to be distinguished from the hippocampal formation, which includes the Ammon's horn, dentate gyrus, subicular complex and entorhinal cortex. The two hippocampi are located in the temporal lobes and lie on the medial floor of the temporal horn of the lateral ventricle (Figure 1).

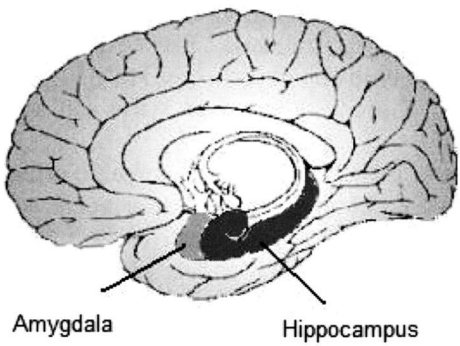


Figure 1. Sagital view of the brain

The role of the hippocampus in memory has long been appreciated. More recent reports have suggested that a functional hippocampus is needed for a specific cognition process termed declarative, explicit or relational memory. Another function of the hippocampus is to provide a negative feedback to the HPA axis (71). The hippocampus is a primary central nervous system target for glucocorticosteroids and it is a highly plastic and vulnerable region of the brain. In the short term a stress-induced increase in catecholamines and glucocorticosteroids facilitates saving emotional events. Though, repeated stress with high glucocorticosteroid levels and an overactive release of excitatory neurotransmitters cause shortening and debranching of the dendrites in the Ammon's horn and suppresses neurogenesis of the dentate gyrus neurons (72). Damage of hippocampal tissue may lead to impaired

information processing and memory loss, as well as elevated plasma levels of CRH, ACTH and cortisol.

Signs of hippocampal damage including HPA axis dysregulation and memory impairment are found in affective disorders (73;74), Cushing's disease (75;76), human aging (77), Alzheimer's disease (78) and in posttraumatic stress disorder (79). The reduced hippocampal volume in these conditions was shown on magnetic resonance imaging scans (Figure 2).

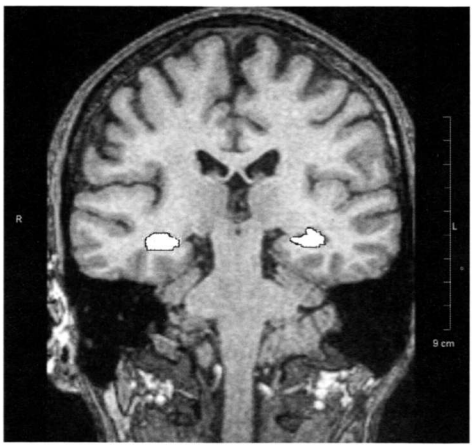


Figure 2. Hippocampus (in white) on MRI scan

Effect of stress and stress hormones on the ear

During stress many changes in cognitive and sensory skills appear. According to Sapolsky, certain aspects of memory improve and the detection of sensations is better during stress (80). Some obscure mechanisms are supposed to make the sensory receptors more sensitive. The cochlear cells of the human ear need less stimulation under moderate stress in order to be stimulated and to process the information to the brain. Sapolsky's statement seems to have no scientific foundation and has never been underlined by others. Studies concerned with the effects of stress and its hormones in both animal and human ears will be presented in this paragraph.

Effect of stress and stress hormones on the animal ear

Several animal studies have been performed on auditory functioning, stress and certain stress hormones (catecholamines, mineralcorticosteroids (MCs) and glucocorticosteroids (GCs)).

Muchnick et al. have mainly focused on the effects of stress and catecholamines on the hearing thresholds (81;82). Guinea pigs under stress had to be given a louder stimulus than to the ones without stress to get the same response. Furthermore, vasoconstriction of the labyrinthine blood vessels induced by adrenaline reduced the cochlear blood flow and increased the mean action potential

threshold with 11 dB. They gave two explanations for these findings. Firstly, the increased cochlear action potential threshold induced by a stressful situation creates a new level of responsiveness of the auditory receptors to a certain sound pressure level. The stressed guinea pigs probably have a higher receptor response level, which causes less threshold shifting compared to sedated guinea pigs. The second option is thought to be associated with changes in cochlear blood flow. The cochlear function may be partly determined by the difference in the magnitude of two forces: vasoconstriction of the cochlear vessels which tends to decrease the cochlear blood flow and increased systemic blood pressure which tends to overcome this difficulty.

In a study by Juhn et al. was shown that adrenaline infusion in chinchillas increased the osmolality in serum and perilymph and significantly elevated the compound action potentials for all frequencies (83). Continuous infusion with adrenaline (max. 4 weeks) lead to a transient 20 to 45 dB threshold shift that increased with time and was relatively constant across a certain frequency. The cochlear dysfunction could be caused by decreased blood flow to the cochlear tissues due to vasoconstriction.

Many studies have been published concerning the influence of corticosteroids on inner ear fluids in the 90s (84-89). Bilateral adrenalectomized rats showed a decline in Na^+K^+ ATPase activity and morphological changes in the stria vascularis, spiral ligament and dark cells. Suppletion with aldosterone gave restoration of dark cell tissue in these rats; suppletion with dexamethasone did not. The highest levels of GC receptors were observed in the spiral ligament and spiral ganglion cells, compared to significantly lower levels of GC receptors in the stria vascularis. Aldosterone binding sites in the inner ear have been demonstrated in ion-transporting tissues. The GC receptor protein level in the organ of Corti was significantly decreased by the stress of noise exposure with at the same time a rise in corticosterone serum levels. In that same field, Lohuis et al. (2000) demonstrated that the absence of adrenal hormones had no effect on most of the cochlear potentials in adrenalectomized guinea pigs (90). The absence of adrenal hormones caused a reduction in volume of the scala media (imdrops). Evidently, the cochlea seems capable of compensating for the absence of circulating adrenal hormones and of creating a situation whereby an accurate cochlear conduction is maintained. This research group attributes the effects of the missing adrenals and their hormones to aldosterone.

Ferrary et al. measured that the cellular transport systems involved in the endolymph secretion are altered by the replacement of ADH and/ or corticosteroid hormones in rats with genetic deprivation of ADH and in adrenalectomized rats (91). Administration of aldosterone resulted in (over) production of endolymph into an endolymphatic hydrops in guinea pigs, where the distal part of the endolymphatic sac was surgically damaged (5).

The data show that stress and its hormones change inner ear fluids composition and inner ear function. Stress seems to make the ear less sensitive to stimuli. Whether it is due to vasoconstriction or inner ear fluid changes remains uncertain.

Effect of stress and stress hormones on the healthy human ear

Higher hearing detection thresholds, increased amplitudes of auditory evoked cortical potentials and higher stapedial reflex thresholds were found in healthy individuals taking the synthetic glucocorticosteroid hydrocortisone (92;93). Also, ingestion of hydrocortisone gave significantly reduced latencies of auditory brainstem waves. It was also seen that after stress induction the contralateral ear needed significantly more (louder) noise to generate a stapedial reflex than at baseline or control measurements. Moreover, this effect on the stapedial reflex is only found in people who had a proven higher level of plasma cortisol (responders versus non-responders).

Furthermore, patients with untreated adrenal insufficiency had lower hearing detection and pain thresholds, respectively 11 and 20 dB (94;95). These auditory changes normalised after supplementing with exogenous corticosteroids (prednisolone).

It is concluded from these findings that GCs impair auditory acuity, whereas sensory processing and perceptual integration may be improved.

Stress and stress hormones in patients with Menière's disease

The psychological effect of stress has been discussed in the former chapter. Therefore, we only present a summary of studies concerning stress hormones in patients with Menière's disease. Powers was the first in the metabolic evaluation of patients with Menière's disease (96). He found that 30% had an abnormal glucose tolerance test, one third had a lowered adrenocortical reserve (ACTH stimulation test) and 27% were hypothyroid. Coletti et al. also performed a comprehensive endocrinologic evaluation of Menière patients, which showed no differences in plasma and urine renin-aldosterone, cortisol or ACTH levels compared to healthy individuals (97). Elevated plasma concentrations of noradrenaline and ADH have been reported in patients with inner ear disorders caused by endolymphatic hydrops, including Menière's disease (98). Others have found normal ADH levels in Menière patients (99). The plasma aldosterone levels were also found in the normal range in patients with Menière's disease (100). The levels of prolactin, growth hormone, cortisol and ACTH in Menière patients were not significantly different from patients with acoustic neurinoma and with facial spasm (101). Another group also confirmed that Menière patients have normal blood prolactin levels (102).

Recent facts on the role of glucocorticosteroids during stress

In recent years the role of the glucocorticosteroids (GCs) during stress situations has been reassessed. Munck et al. have proposed an alternative functional role for GCs in the primary stress responses (103). They suggested that the physiological function of stress-induced increases in GC levels is not to protect from the source of stress itself, but from the normal defence reactions. Furthermore, the GCs would accomplish this function by turning off those defence reactions, thus preventing them from overshooting and threatening homeostasis. In contrast to the traditional

view that GCs enhance the defence mechanisms, however, is the view that it has become increasingly clear that high levels of GCs generally suppress them. The use of high doses of GCs in organ transplantation to suppress the immune system is a good example of this fact. This paradox, which first emerged when GCs were discovered as anti-inflammatory agents, remains a major obstacle to a unified picture of GC function.

Sapolsky et al. considered certain criteria for determining whether a particular GC action permits, stimulates or suppresses an ongoing stress response or, as an additional category, is preparative for a subsequent stressor (104). The specific action of the GCs depends on the physiological endpoint. The actions are mediated through different receptors: the permissive actions through mineralcorticosteroid receptors and the suppressive actions through GC receptors.

In 2000 hypocortisolism was given a potential role in the pathophysiology of stress-related bodily disorders (105). Hypocortisolism has been found in posttraumatic stress disorder patients, healthy individuals living under chronic stress and patients with chronic bodily disorders, like fibromyalgia, chronic fatigue syndrome, rheumatoid arthritis and asthma. The manifestation of this neuro-endocrine abnormality may be determined by genetic vulnerability, previous stress experience, coping and personality styles. These are the same factors that are mentioned for stress responses in general. The nature of the underlying mechanism remains speculative. The paradox of the simultaneously presence of hippocampal atrophy next to hypocortisolism in chronic stress situations stays a mystery as well.

All put together, there seem to be new considerations in neuro-endocrine research in stress-related diseases. Although, the mechanisms explaining these facts are not quite clear.

Multifactor model in Menière's disease and aims of this thesis

Multifactor model in Menière's disease

Previous chapters make it clear that the Menière's disease is a complex phenomenon that cannot be understood in terms of a single cause and effect relation. Menière's disease comprehends more than vertigo, tinnitus and hearing loss. Moreover, regarding Menière's disease as (the result of) a psychological problem does not give the ultimate insight either. For a better understanding it has to be considered as a multifactor disease, in which somatic, psychological and environmental aspects have to be taken into account.

The model that is presented in Figure 1 is an attempt to illustrate the complex interrelations between the factors that are thought to play a role in the development and continuation of the Menière symptoms. The elements described in preceding chapters are included in the model.

Firstly, some definitions of the mentioned factors in the model will be given in short. *Stressors* are potentially threatening events or situations. Internal stressors arise from the person itself, e.g. fear or vertigo attacks. External stressors are defined as daily problems, catastrophic life events or chronic problems. Whether the individual perceives or evaluates the stressor as potentially stressful depends on a person's *appraisal*. Appraisal depends of the received characteristics of the stimulus, psychological structure of the individual (primary appraisal) or on the individual's coping style (secondary appraisal). The reaction to the stressor and its appraisal is divided in three sub-reactions: *psychological, somatic and behavioural responses*. This is discussed in detail in **chapter 3**.

As mentioned before, the histopathological substrate for *Menière's disease* is thought to be the *endolymphatic hydrops*. In earlier studies, this increase of endolymph is related to two processes (5). The first is reduced resorption of endolymph due to anatomical abnormalities in the drainage system of endolymph. In studies is shown that Menière patients have a significant smaller saccus endolymphaticus (6) and/or a hypoplastic aquaductus vestibularis (106). The other process is related to a temporary increased production of endolymph. In animal models is shown that stress hormones could increase the endolymph production (83). Possibly, this may account for the human situation as well. Glucocorticosteroid receptors have been found in the human ear (107).

The term "allostatic load" as discussed in the former chapter, may be applied to the suggested model. Patients with Menière's disease are thought to have a longstanding increased stress load (allostatic load), because of their obsessive-compulsive and introvert personality structure (39;41;52). Next to this allostatic load, the Menière patient experiences more fear or stress through the unpredictable character of the disease. This may lead the patient into a vicious cycle of chronic stress (see Figure 1).

A combination of both factors either causal or conditional, seems to be the most eligible theory based upon indicative research and clinical experience. The question that arises immediately is why one patient recovers after a few attacks, while another patient develops a chronic disease.

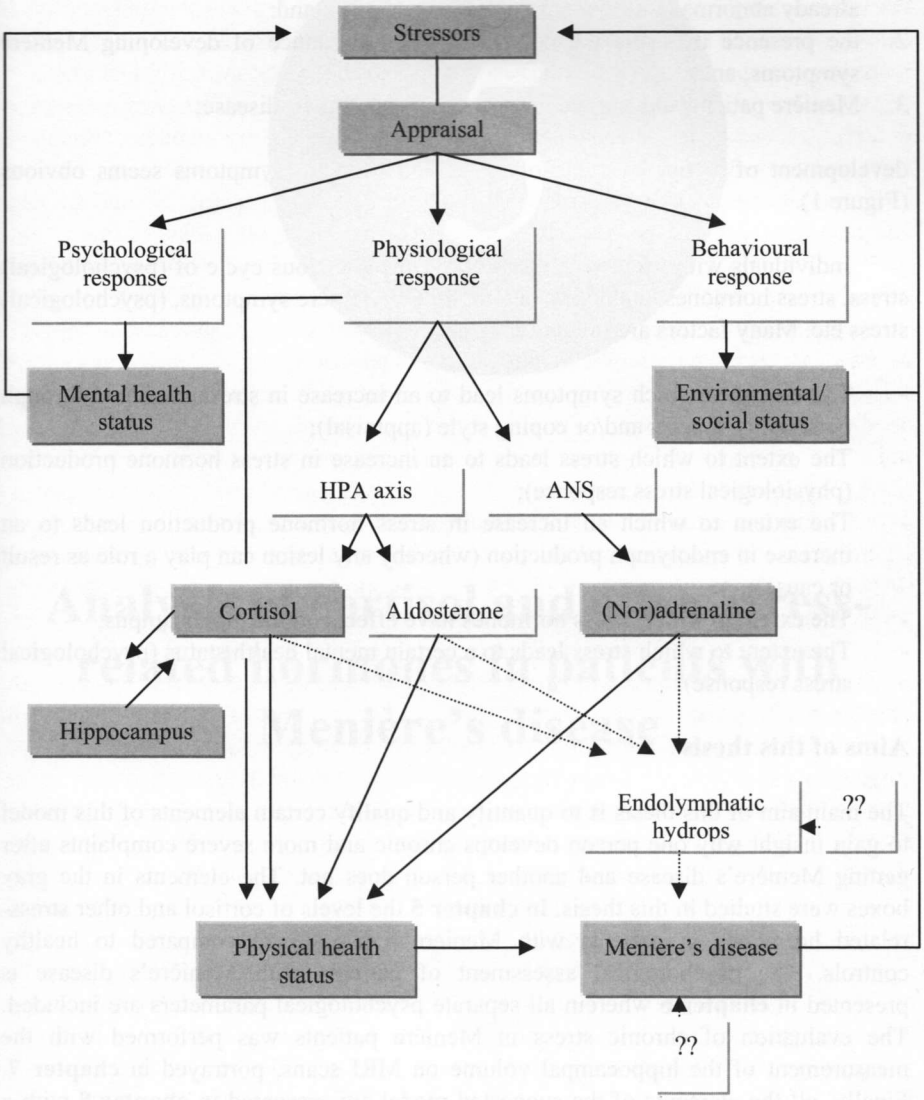


Figure 1. Multifactor model in Menière's disease.
HPA axis = Hypothalamus-Pituitary-Adrenal axis; ANS = Autonomic Nervous System

If we assume that:

1. certain people are more susceptible to develop Menière's disease through an already abnormal endolymphatic drainage system; and:
2. the presence of stress hormones adds to the chance of developing Menière symptoms; and
3. Menière patients experience more stress through their disease;

development of a vicious cycle of stress and Menière symptoms seems obvious (Figure 1).

Individuals with Menière's disease fall into a vicious cycle of (psychological) stress, stress hormones, endolymphatic hydrops, Menière symptoms, (psychological) stress etc. Many factors are involved, namely:

- The extent to which symptoms lead to an increase in stress mediated through personality aspects and/or coping style (appraisal);
- The extent to which stress leads to an increase in stress hormone production (physiological stress response);
- The extent to which an increase in stress hormone production leads to an increase in endolymph production (whereby any lesion can play a role as result or cause);
- The extent to which stress hormones have effects on the hippocampus;
- The extent to which stress leads to a certain mental health status (psychological stress response).

Aims of this thesis

The main aim of this thesis is to quantify and qualify certain elements of this model to gain insight why one person develops chronic and more severe complaints after getting Menière's disease and another person does not. The elements in the gray boxes were studied in this thesis. In **chapter 5** the levels of cortisol and other stress-related hormones in patients with Menière's disease are compared to healthy controls. The psychological assessment of patients with Menière's disease is presented in **chapter 6** wherein all separate psychological parameters are included. The evaluation of chronic stress in Menière patients was performed with the measurement of the hippocampal volume on MRI scans, portrayed in **chapter 7**. Finally, all the elements of the suggested model are presented in **chapter 8** with a summary in **chapter 9**.

Analysis of cortisol and other stress-related hormones in patients with Menière's disease

Van Cruijsen N, Dullaart RP, Wit HP, Albers FW. Analysis of cortisol and other stress-related hormones in patients with Menière's disease. Otol Neurotol 2005; 26(6):1214-1219.

Introduction

Menière's disease is a chronic, stressful disease with handicapping symptoms as fluctuating hearing loss, tinnitus and vertigo attacks. Its exact pathogenesis is complex and remains unresolved. Two-phase endolymphatic hydrops is the most commonly used aetiological model. This is based on dysregulation of the endolymph homeostasis, where the endolymph absorption is chronically malfunctioning, complicated by an intermittent overproduction of endolymph (5). Earlier, it was found that the endolymphatic sac was undersized in Menière patients compared with healthy controls (6). Many aetiological explanations have been given for the irregular endolymph overproduction.

The psychological aspects in Menière's disease have frequently been studied as cofactors in the pathogenesis of or contributors to Menière's disease (108). Because stress seems to influence Menière symptoms in specific patients, it is postulated that stress (hormones) affects endolymph homeostasis. Receptors for several stress hormones have been located in the human inner ear, including those for glucocorticosteroids (107). In animal and human studies, it has been shown that stress (hormones) could change inner ear fluid composition and inner ear function (83;87;93).

Stress is linked to changes in the hypothalamic-pituitary-adrenocortical (HPA) axis. During stress, the hypothalamus releases more corticotrophin-releasing hormone and antidiuretic hormone (ADH), which activate the pituitary gland to produce more adrenocorticotropic hormone, followed by glucocorticoid (cortisol) and mineralcorticoid (aldosterone) secretion. Cortisol is produced in a circadian rhythm, and increased levels cortisol are usually found during acute stress and also in chronic depressive patients (109). Stressors also activate the sympathetic branch of the autonomic nervous system, which stimulates the medulla of the adrenal gland to secrete more catecholamines, especially adrenaline and noradrenaline. Some authors have found increased plasma levels of noradrenaline, ADH or prolactin in Menière patients (54;98;110). In a study by Mateijsen et al., no anomalous plasma aldosterone values were measured in patients with Menière's disease (100).

To our knowledge, the stress hormone cortisol has never been studied in a controlled setting in Menière patients. We hypothesise that Menière patients have an overproducing neuro-endocrine stress system, which is expressed in higher cortisol levels in Menière patients compared with healthy controls. In this study we evaluated the serum, saliva and urine cortisol and the urine noradrenaline and adrenaline in a controlled, standardised setting.

Subjects and methods

Study population

Every week, one patient suspected of having Menière's disease is admitted at our otorhinolaryngology department for 3 consecutive days to confirm the diagnosis Menière's disease and to exclude other audiovestibular diseases by means of various

tests. This includes standard ear, nose and throat examination, several audiometric and vestibular tests; magnetic resonance imaging of the cerebellopontine angle; laboratory tests and evaluation of symptoms using standardised questionnaires. Two weeks before admission, patients discontinued their antivertiginous medication, including anxiolytics. Patients were considered having Menière's disease when they had a history of at least two vertigo attacks lasting longer than 20 minutes, tinnitus and sensorineural hearing loss of at least 60 dB added up from the three worst octaves in the same ear, and other pathology had been excluded.

The persons for the control group were voluntarily recruited from hospital personnel and through advertisements in a local newspaper. All persons in the control group were healthy and were not financially compensated for participation in this study.

The exclusion criteria for the study are listed in Table 1. The local medical ethics committee approved the study and all participants gave written informed consent.

Table 1. Exclusion criteria for the study.

Cushing's disease, hypoglycaemia or diabetes mellitus
Hypo- or hyperthyroidism
Liver or renal failure
Medication: corticosteroids (systemic/local), estrogens, oral contraceptives, androgens, amphetamines, barbiturates, benzodiazepines, betahistine, riphampicin, spironolactone, aminogluthethimides, danazol, lithium, levodopa, metyrapone, chloordiazepoxide, hydroxyzine, mebrobamate, phenothiazines, quinine en phenytoin.
Examination with radioisotopes
Anorexia nervosa or pregnancy

Methods

The healthy controls stayed 2 consecutive nights at our department in the same condition as the Menière patients. At 8:00 AM, blood was drawn from an intravenous catheter, with all the individuals in a supine position and after an overnight fast. The intravenous catheter was placed 30 minutes before obtaining the blood to minimise the stress reaction of inserting the needle. The venous blood was analysed for cortisol and glucose levels.

The first cortisol measurement was obtained without administration of dexamethasone. The night previous to the second cortisol evaluation the participant took 1 mg of dexamethasone at 11:00 PM, conformable to the dexamethasone suppression test (DST). The serum cortisol analysis was performed with an in-house radioimmunoassay method. The blood glucose level was measured using the APEC glucose analyser (APEC Inc., Danvers, MA, U.S.A.).

A 24-hour urine sample was analysed for sodium, potassium, creatinine, free cortisol, adrenaline and noradrenaline. The free cortisol was measured by

radioimmunoassay after extraction with organic solvents and affinity chromatography. The catecholamines were evaluated with the high-performance liquid chromatography with fluorescence detection. To validate a new cortisol evaluation method, we also measured free cortisol in the saliva. The Salivette cotton swab (Sarstedt, Nümbrecht, Germany) was placed under the tongue for 2 minutes at the same time (8:00 AM) that the venous blood withdrawal took place.

Duration and subjective severity of symptoms were scored using a standardised questionnaire. The duration time of the Menière symptoms (hearing loss, tinnitus and vertigo) was defined as the time between the first appearance of the symptoms and the admission date. We defined the total disease time as the duration time of the symptom that occurred first. The duration of disease in bilateral patients is confined to the first affected ear. The subjective severity of the symptoms was assessed as perceived in the last 3 months. Hearing loss could be characterised as "unchanged", "improved", "worse" or "fluctuating"; tinnitus and vertigo could be characterised as "none", "mild", "moderate" or "severe". The hearing loss was defined as the average hearing thresholds over five pure-tone audiogram frequencies (0.25-4 kHz).

Statistics

Power analysis was based on the difference between the mean serum cortisol levels of Menière's disease patients and healthy controls. If we hypothesised that the mean serum cortisol level in Menière's disease patients would not be 25% higher than in healthy controls using a power of 0.80 and a two-sided value of $p<0.05$, 20 individuals for both groups had to be included. In this power analysis we substituted a mean serum cortisol level of 250 ± 46 nmol/l (n=8) from a study by Kerstens et al. (111). Data are given in mean ± standard deviation. Statistical analyses were performed using the independent sample t-test and the Chi-square test after excluding the extremes of the groups ($z < -3$ and >3). Values of $p \leq 0.05$ were considered to be statistically significant.

Results

Study population

From January 2002 to August 2003, we included 66 patients with audiovestibular symptoms in the protocol. We concluded after evaluation of all the test results, that 54 patients had Menière's disease using the criteria mentioned above. Twelve individuals (18%) had other disease (e.g. epilepsy, congenital or hereditary deafness, vascular problem, neuronitis vestibularis [n=2] or otosclerosis). Others had vertigo without hearing loss (n=2), idiopathic sudden sensorineural hearing loss, or cisplatinum toxicity. One had endolymphatic sac dysfunction after ear surgery.

Thirty of the 54 patients with Menière's disease met the cortisol study criteria. The exclusion motives were use of oral contraceptives or estrogens (n=5), use of systemic or local corticosteroids (n=6), use of anxiolytics or betahistine (n=4), hypo- or hyperthyroidism (n=6) and diabetes mellitus (n=3).

Noteworthy is the fact that 6 of the 54 Menière affected patients (11%) had preexisting thyroid dysfunction. One of the patients had undergone endolymphatic sac surgery in another hospital. In the included Menière affected group (Menière group, n=30) were 21 unilateral (70%) and 9 bilateral (30%) affected individuals. The Menière group consisted of 7 women (23%) and 23 men (77%) with a mean age of 48 and 53 years, respectively. The overall mean age of the Menière group was 52 ± 9 years.

Nine of the 12 patients with other disease (non-Menière group) were also included in the study; 5 men (56%) and 4 women (44%). Their mean age was 50 ± 14 years. Three of the twelve patients were excluded because of hypothyroidism (n=1), diabetes mellitus (n=1) or use of benzodiazepines (n=1).

The original control group consisted of 20 healthy persons (control group). However, 2 men were excluded from analysis because they had taken topical corticosteroids. So, the control group contained 18 persons: 8 men (44%) and 10 women (56%), with a mean age of 41 and 49 year, respectively. The overall mean age of this group was 45 ± 11 years.

The gender and age match between the Menière and the control group was not perfect. The Menière group had significantly more male individuals (77% versus 44%) and was older (mean age, 52 versus 45 years). This difference was significant for both variables ($p<0.05$). The general characteristics of both groups are listed in Table 2.

	Menière group (n=30)	Control group (n=18)
Age (years)	52 ± 9	45 ± 11 *
Gender (male/ female) (%)	77 / 23	56 / 44 *
Body Mass Index (kg/m2)	25 ± 2.3	24 ± 2.6
Mean arterial pressure (mmHg)	104 ± 13	108 ± 10
Pulse (beats/min)	64 ± 9	66 ± 8
Creatinine clearance (ml/min)	107 ± 18	128 ± 31 *
Duration slept night before blood sample (min)	417 ± 65	378 ± 51 *
Duration awake before blood sample (min)	103 ± 59	78 ± 48
Other chronic disease (yes/ no) (%)	30 / 70	6 / 94 *

Table 2. General characteristics of Menière and control group.
* $p<0.05$, results are presented as mean ± standard deviation.

None of the individuals exceeded the ranges of the reference values as used in our hospital. The reference values are as follows: serum cortisol (200-800 nmol/l), DST value (<100 nmol/l), urine free cortisol production (20-270 nmol/24h), urine noradrenaline (0.1-30 µm/mcrea) and adrenaline (0.1-10.0 µm/mcrea).

Cortisol data

1. Menière versus control group

The results are presented in Table 3. Two of the 30 blood samples of the Menière group were not correctly analysed for cortisol measurement. The mean serum cortisol levels were 440 ± 127 nmol/l (median 465; n=28) and 366 ± 90 nmol/l (median 348; n=18) for the Menière and control group, respectively. This was a significant difference ($p<0.05$). These results are also presented in Figure 1.

	Standard reference	Menière group (n)	Non-Menière group (n)	Healthy controls (n)
Serum cortisol (nmol/l)	200-800	440 ± 127 (28)	450 ± 84 (9)	366 ± 90 (18) *
Saliva cortisol (nmol/l)	not available	17.2 ± 6.1 (18)	13.3 ± 0.9 (3)	11.6 ± 4.6 (9) *
Serum cortisol after DST (nmol/l)	<100	27 ± 13 (25)	32 ± 14 (6)	21 ± 12 (18)
Urine free cortisol (nmol/24h)	20-270	102 ± 51 (27)	120 ± 65 (9)	98 ± 58 (18)
Urine noradrenaline (µm/mcrea)	0.1-30	19 ± 7.1 (27)	19 ± 6.8 (9)	22 ± 6.7 (18)
Urine adrenaline (µm/mcrea)	0.1-10	3.3 ± 1.5 (28)	3.9 ± 2.2 (9)	5.4 ± 2.0 (18)

Table 3. Cortisol and catecholamine values for the three subgroups.
* $p<0.05$ between Menière group and healthy controls. Reference values are presented in minimum to maximum and the results for the three subgroups as mean ± standard deviation. DST= dexamethasone suppression test

The saliva cortisol value was significantly higher in the Menière group than in the controls: 17.2 ± 6.1 (n=18) and 11.6 ± 4.6 nmol/l (n=9), respectively ($p<0.05$). The DST values showed no significant difference: 27 ± 13 nmol/l (Menière group; n=25) and 21 ± 12 nmol/l (control group; n=18). The 24-hour free cortisol production in the urine was 102 ± 51 nmol/24h (n=27) and 98 ± 58 nmol/24h (n=18), respectively. The adrenaline and noradrenaline levels were comparable for the Menière and control group. The controls had a significantly better creatinine clearance than de Menière group, namely 128 ± 31 versus 107 ± 18 ml/min ($p<0.05$).

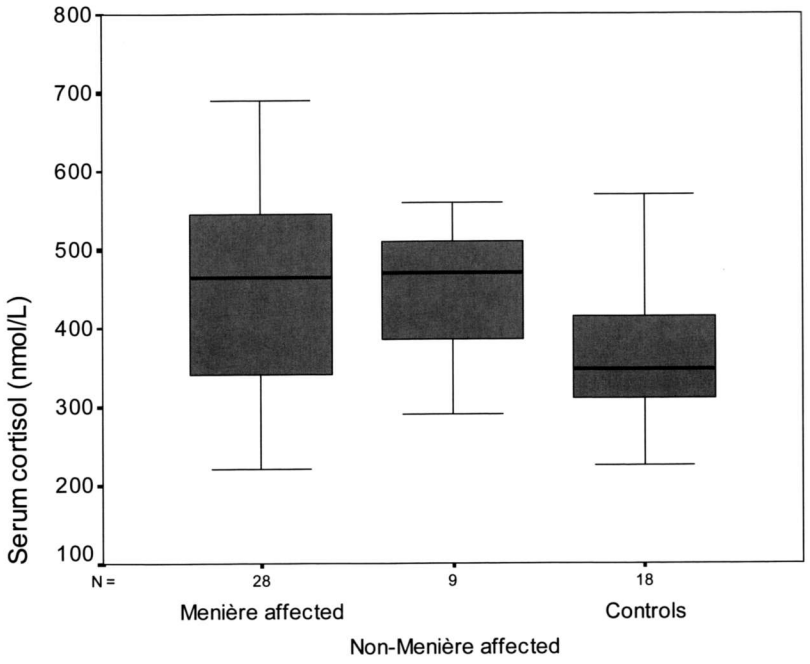


Figure 1.Serum cortisol for the 3 subgroups.

2. Menière versus non-Menière group

The mean serum cortisol level was 440 ± 127 nmol/l in the Menière group (n=28) versus 450 ± 84 nmol/l in the non-Menière group (n=9). There were also no significant differences in DST (27 ± 13 and 32 ± 14 nmol/l) and urine free cortisol values (102 ± 51 and 120 ± 65 nmol/24h) (Table 3).

3. The Menière group

We also examined the Menière affected group (n=28) for inter-individual variations in cortisol levels by dividing this group into high-cortisol (HC) and low-cortisol (LC) groups, taking the median serum cortisol value of 465 nmol/l as the cutoff point. The two groups were matched for age and gender and were equally affected unilaterally or bilaterally. The mean DST and urine free cortisol values were not significantly different. In one patient of the LC group two venipunctures failed before the blood could actually be taken; the other 27 patients had only one venipuncture. Thus, the higher cortisol levels could not be explained by a difference in the number of venipunctures. The mean arterial pressure and pulse of the HC and LC groups were 102 ± 12 mmHg versus 108 ± 14 mmHg and 63 ± 9 versus 64 ± 10 beats/min, respectively; this was not significant. The HC group did not have more

other chronic diseases than the LC group. Individuals in both groups slept the same amount of time during the night and woke up approximately at the same time, so there was no difference in circadian rhythm. The hearing loss was equivalent in both groups, 56 ± 23 dB (HC group) and 49 ± 18 dB (LC group).

The total Menière disease time and the duration of tinnitus tended to be longer in the HC group (p=0.07, two-tailed). The total Menière disease time was 13.5 ± 9.9 (n=14) versus 7.1 ± 7.4 (n=14) years in the HC versus LC group. The duration time of tinnitus was 11.9 ± 9.7 (n=14) and 5.8 ± 7.1 years (n=14), respectively (p=0.07, two-tailed). The duration of hearing loss and vertigo attacks was 10.1 ± 7.6 versus 5.7 ± 6.7 years and 7.6 ± 6.7 versus 5.6 ± 6.0 years, respectively. The subjective evaluation of Menière symptoms as vertigo, tinnitus and hearing loss was the same in both groups. These results are presented in Table 4.

	Low serum cortisol group (n=14)	High serum cortisol group (n=14)
Total disease time (years)	7.1 ± 7.4	13.5 ± 9.9 *
Duration hearing loss (years)	5.7 ± 6.7	10.1 ± 7.6
Duration tinnitus (years)	5.8 ± 7.1	11.9 ± 9.7 *
Duration vertigo (years)	5.6 ± 6.0	7.6 ± 6.7
Severity hearing loss (unchanged/better/worse/fluctuating) (%)	57 / 0/ 14 / 29	71 / 0/ 14 / 14
Severity tinnitus (none/mild/moderate/severe) (%)	0 / 7 / 57 / 36	0 / 14 / 43 / 43
Severity vertigo (none/mild/moderate/severe) (%)	36 / 21 / 14 / 29	15 / 23 / 15 / 46
Vertigo attacks last 3 months (yes/no) (%)	50 / 50	71 / 29

Table 4. Disease characteristics of the high- and low-serum cortisol groups.
* p=0.07, results are presented as mean ± standard deviation.

Discussion

In this study we confirmed our hypothesis that the serum cortisol and saliva cortisol levels were significantly higher in Menière patients compared with controls. This was not caused by higher ectopic cortisol production, confirmed by the normal serum cortisol levels after the dexamethasone suppression test and the normal urine free cortisol production. Earlier studies by Powers and Colletti did not show any cortisol variances in patients with Menière's disease (96;97). In this study, the catecholamine production was not elevated in patients with Menière's disease.

How can these findings be explained and interpreted? It has been shown that depressive patients and people having chronic stress have higher levels of serum cortisol (112). This was explained by the allostatic load theory. Allostasis is the adaptation to stress, creating a new bodily homeostasis after stress. The term "allostatic load" refers to an overload of the body. It is the price the body has to pay for constant allostatic reactions to psychosocial or physical stressful situations. It has damaging effects through the continuous secretion of catecholamines by the

autonomic nervous system and glucocorticosteroids by the HPA axis. This allostatic load may lead to wear and tear of organs and tissues, and make individuals more susceptible to illness. This could be the explanation of coronary disease and diabetes mellitus, which appear predominantly in people in their 50s. Frequent and chronic elevated levels of glucocorticosteroids could cause atrophy of the hippocampus. In turn, the negative feedback function of the hippocampus declines and results in even more cortisol secretion in stressful situations. An identical defect in the central regulation of stress hormones could be the case in Menière's disease. Because the DST levels in all participants were normal, it seems that the hippocampus is (not yet) depressed in its feedback function. In 1962, Goldman proposed that exhaustion of the adrenocortical reserves because of continuous stress may play a role in certain cases of Menière's disease (113).

This study also showed that patients with higher serum cortisol levels tended to be longer affected by the Menière symptoms. Patients affected longer by the Menière symptoms, are consequently more exposed to physical and psychological stress. This suggests that the higher cortisol levels are rather the result than the cause of Menière's disease. The high cortisol levels in non-Menière group seem to confirm this suggestion. It is recommended that other effects of allostatic load in Menière patients (e.g. hippocampal atrophy) are looked for.

Other stress-related factors (e.g. previous stress experience, coping strategies and personality characteristics) also affect cortisol levels. This was not analysed in this setting, although what we do know is that the subjective experience of the vertigo, tinnitus and hearing loss did not differ between the LC and HC groups. The difference in serum cortisol levels could also be accounted for by the mismatch in gender and age. Male gender and older age in the Menière group are both factors for a higher cortisol level.

Many clinical studies reported abnormal hormonal levels in Menière patients (e.g. noradrenaline, vasopressin (ADH) and prolactin [(54;98;110)). Others measured normal levels of aldosterone and ADH in patients with Menière's disease (100;114). Thyroid dysfunction has also been associated with Menière's disease (96;115). Our results showed that 11% of the Menière patients had hypothyroidism or hyperthyroidism. Because these are subjective, retrospective data, we recommend studying thyroid function in a prospective setting.

The question remains of how stress could generate an exacerbation in Menière symptoms in specific patients. Maybe the higher cortisol levels affect the inner ear and especially the endolymph homeostasis. Several experiments on glucocorticosteroids and their receptors in the inner ear have been performed by others. They showed that glucocorticosteroid receptors are present in inner ear tissues within varying levels and that they are responsive to stress (87;89). It seems that glucocorticosteroids could directly affect glucocorticosteroid receptors protein within the inner ear and not only suppress the systemic release of corticosterone (84). Furthermore, adrenal corticoids appear to cause changes in auditory thresholds (93). Although much work has been done, the answer is still unknown.

Conclusion

The higher cortisol levels in patients with Menière's disease imply an overproducing HPA axis. It is suggested that these higher cortisol levels are rather the result than the cause of this chronic disease, because patients longer affected by the disease seem to have higher cortisol levels. What the exact impact of these higher cortisol levels on the inner ear and endolymph homeostasis could be is yet unknown. It remains difficult to measure hormonal levels properly and reproducibly, because so many factors have an effect on the stress hormone production.

Psychological assessment of patients with Menière's disease

Van Cruijsen N, Jaspers JPC, Van de Wiel HBM, Wit HP and Albers FWJ. Psychological assessment of patients with Menière's disease. Int J Audiology. Accepted.

Introduction

Menière's disease is a chronic, stressful disease with disabling symptoms such as (fluctuating) hearing loss, tinnitus and spontaneous vertigo attacks. The exact pathogenesis remains unknown, but the endolymphatic hydrops is the most commonly used pathophysiologic substrate (9). Hydrops is supposed to be caused by a congenital or acquired reduction in endolymph absorption and a temporarily increased production of endolymph (5). Its unpredictable character makes it a stressful disease.

Menière's disease is amongst the conditions in which psychological factors are often emphasised. The early literature on psychological considerations in Menière's disease focussed on the psychosomatic causes and somatopsychic effects of the disease (31;35). Neither the psychosomatic or somatopsychic theory does seem to be the sole clarification for the development of Menière's disease. Most of the studies are methodologically weak and provide no definitive support for the claims made (108).

Earlier studies have shown that Menière patients experience more anxiety, depression and phobia (50;51;57), while others did not (52). It was also shown that Menière patients experience the same level of anxiety, depression and somatic complaints compared to patients with only vertigo (116). In the field of personality characteristics, previous studies have described Menière patients as obsessive-compulsive persons, perfectionists and neurotics, who are supposed to be more vulnerable and have more stress exposure (39;41;52). On the other hand, other researchers classified the personality of Menière patients in the normal range (54). A time-series analysis of stress and vertigo expression did not support the role of stress as a precursor of symptoms in Menière's disease (55). On the contrary, Söderman et al. did find that emotional stress increased the risk of getting a vertigo attack (117).

The former studies evaluated specific aspects of the psychological process. More likely, the disease is characterised by a continuous interaction of many psychological, physical and environmental factors: symptoms of the disease worsen the emotional state, which in turn impairs the (perception of) symptoms. To our knowledge, all these factors have never been evaluated simultaneously in one study. To outline the psychological process in Menière's disease, a general model of stress with stressors (physical and psychological disturbances), appraisal (coping and personality) and stress responses (psychological, physical and behavioural) is presented (Figure 1). All elements have their specific place and interrelate in this model. Whether the disease or the psychological condition presents first, remains unresolved and is probably irrelevant. More important is to know how the emotional and physical factors interact and why one patient develops more frequent and severe problems after getting Menière's disease than others.

Information about this psychological process and its factors might give us better insight into which Menière patients are most at risk and in what way psychological support needs to be intensified. In this study, each factor in the model

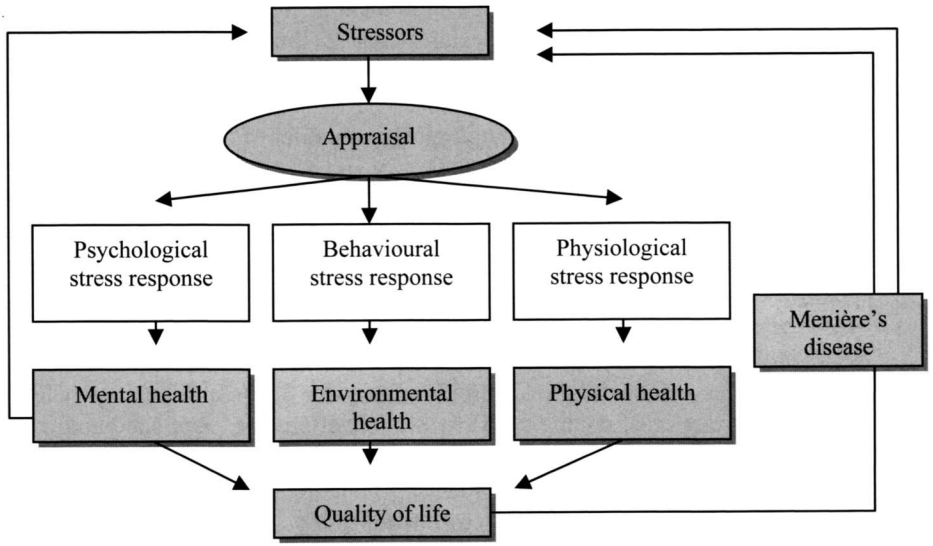


Figure 1. Multifactor model of Menière's disease.

is qualified and quantified by means of validated, standardised measures containing the appropriate psychometric properties. Several self-report questionnaires were selected to assess daily stressors, coping, personality, physical and mental health and quality of life.

We hypothesized that Menière patients have more daily stressors, cope with stressors less adequately, report more psychological symptoms, and have a worse quality of life than healthy reference groups. Moreover, we explore personality traits that make Menière patients more vulnerable for stressors.

Patients and methods

Study population

Every week one patient suspected of Menière's disease is admitted to our otorhinolaryngology department for 3 consecutive days to confirm the diagnosis of Menière's disease and to exclude other audiovestibular diseases, by means of various tests. The diagnostic work-up includes standard ear, nose and throat-examination, several audiometric and vestibular tests, MRI-scanning of the cerebellopontine angle, laboratory tests and evaluation of symptoms using standardised questionnaires. Two weeks prior to admission all patients discontinued their antivertiginous medication, including anxiolytics. Patients were considered having Menière's disease when they had a history of at least two vertigo attacks lasting longer than 20 minutes, tinnitus and sensorineural hearing loss of at least 60 dB summed from the three worst octaves in the same ear, while other pathology had

been excluded. Aural fullness was not a requirement of the diagnosis, but could be present as well.

Psychological assessment

During the clinical admission the psychological evaluation of Menière patients was performed using the following questionnaires:

1. The Daily Hassles List (APL) quantifies the frequency and intensity of problems in different circumstances (118). 112 situations are given and have to be answered as to whether they had occurred in the past two months. If a positive reaction was given, it also had to be scored as to whether it was "not a problem at all (0)", "not so bad (1)", "bad (2)" or "very bad (3)". A higher score implies more daily hassles.
2. Coping was assessed with the Coping Inventory for Stressful Situations (CISS) (119). 48 strategies of coping with stressful situations are mentioned and have to be answered from "not at all (1)" to "very strongly (5)". The CISS has three dimensions: task, emotion and avoidance oriented coping. The CISS has been translated and validated for the Dutch situation (120).
3. The NEO Five Factor Inventory (NEO-FFI) measures five personality domains: neuroticism, extraversion, openness to experience, altruism and conscientiousness (121). 60 statements have to be answered on a 5-point scale ranging from "strongly disagree" to "strongly agree". Higher scores indicate that the specific trait is more pronounced. The NEO-FFI has been translated into Dutch and validated for the Dutch cultural situation (122).
4. The Symptoms Checklist (SCL-90) is a multidimensional self-report questionnaire measuring physical and psychological complaints on a scale from 1 to 5 (123;124). It encompasses 90 items containing 8 dimensions: anxiety, agoraphobia, depression, somatic complaints, obsessive-compulsive behaviour, interpersonal sensitivity (personal inadequacy and inferiority), hostility and insomnia. The total score is called psychoneuroticism, which is a measure for general level of psychological and physical dysfunction. Higher scores indicate more psychological or physical problems.
5. The General Health Questionnaire (GHQ-12) is designed to screen for minor psychiatric disorders in the general population (125). 12 items are scored as to whether the situation was "better (0)", "the same (0)", "worse (1)" or "much worse (1)" as usual, with higher scores corresponding with a worse mental health (126).
6. The 36-item Medical Outcome Short Form Health Survey (SF-36) evaluates well-being and functional status (quality of life). It contains the following dimensions: physical, mental and social functioning, role limitations due to physical or emotional problems, general health perception, bodily pain and vitality. Each dimension has several items with different scales; a lower score represents worse functioning in that specific dimension (127).

The Daily Hassles List is a free translation of the APL (Alledaagse Problemen Lijst), which is a standardised and validated Dutch questionnaire. The other five tests are internationally standardised and validated tests, which have been translated into Dutch and validated for the Dutch cultural situation. The normative values of all tests match the Menière cohort for age and are given for gender.

Duration and subjective severity of symptoms were scored using a self-report questionnaire. The duration time of Menière symptoms (hearing loss, tinnitus and vertigo) was defined as the time between the first appearance of the symptom and the admission date. We defined the total disease time as the duration of the first presenting symptom. The duration of disease in those with bilateral disease was confined to the first affected ear. The subjective severity of the symptoms was assessed as perceived in the last 3 months. Hearing loss could be characterised as "unchanged", "improved", "worse" or "fluctuating"; tinnitus, aural fullness and vertigo as "none", "mild", "moderate" or "severe". The patients also had to score whether they had experienced vertigo attacks lasting more than 20 minutes in the past three months.

Furthermore, the symptoms of hearing loss, tinnitus, aural pressure and vertigo had to be rated by the patients as "none", "mild", "moderate" and "severe" (1-4) as experienced in the past week. The total severity symptom score is a summation of these four separate scores (variance 4-16). The median total severity symptom score for the 110 patients was 10 and served as the cut-off point for creating the low (LSG) and high severity symptom group (HSG).

The presence of another chronic disease besides Menière's disease, alcohol and nicotine usage, and education level had to be noted as well. The hearing loss was defined as the extended Fletcher index over 5 pure-tone audiogram frequencies (0.25 - 4 kHz). Informed consent was obtained from all participants and the study was approved by the medical ethics committee of our hospital.

Statistics

Data are given in mean ± standard deviation (SD). Statistical analyses were performed using the Student's t-test, Chi-square and Mann-Whitney-test. Two-tailed p-values were used for all tests. Pearson product-moment correlation coefficients were used to examine relationships between variables. If appropriate, we made Bonferroni corrections for multiple comparisons. For each test we set the alpha level at 0.05 divided by the number of comparisons. For instance, for 10 comparisons $p = 0.05 / 10 = 0.005$.

Results

Study population

From January 2002 to January 2005 132 consecutive patients with audiovestibular symptoms were admitted for clinical assessment. We diagnosed 111 patients with Menière's disease and 21 individuals (16%) with other pathology after evaluation of all the test results. This other pathology included acoustic neurinoma, otosclerosis, neuritis vestibularis, ototoxicity, benign paroxysmal positional dysfunction, migraine, hereditary hearing loss and partial epilepsy. Those patients with other audiovestibular diseases were considered as a control group. One Menière patient could not participate in the psychological assessment because of language problems. Of the 110 Menière patients were 81 patients unilaterally (74%) and 29 bilaterally (26%) affected.

The study population consisted of 67 male (61%) and 43 female (39%) patients with a mean age of 52 ± 12.1 and 52 ± 10.3 years, respectively. The male Menière patients had a total disease time of 8.3 ± 7.0 years compared to the female group 8.0 ± 6.0 years. In this matching two outliers of the male group were excluded. They had a disease time of 36 and 56 years due to other ear problems. When they were included, the male total disease time was 9.4 ± 9.6 years. The total disease time was not significantly different for gender with or without the outliers.

A similar proportion of men (31/67; 46%) and women (23/43; 54%) had another chronic disease. The extended Fletcher index for the male and female group was respectively 53 ± 20.3 dB and 49 ± 19.9 dB. Male and female patients rated their hearing loss, tinnitus and vertigo of the past three months and the last week comparable and had a similar frequency of vertigo attacks lasting longer than 20 minutes in the past three months. The female patients had a significantly lower alcohol intake ($p<0.001$, Chi square test). The education level was equal for both genders.

Psychometric results

Published normative data for all the questionnaires are derived from their respective manuals or papers (see methods section) and are given for gender. The results of the six questionnaires are presented in Table 1 and 2. Some questionnaire test results had too many missing values and were therefore not used in the analysis. The main results are outlined below.

The Menière patients, male and female, experienced more daily hassles compared to the normative values (Table 1). Also, they were less task oriented in their way of coping with stressful situations. Moreover, the male patients were also less emotion and avoidant oriented in their coping (Table 1). The personality test (NEO-FFI) showed that the Menière patients had no abnormal personality traits compared to the reference values (Table 1).

	Menière patients		Reference values	
	Male (n)	Female (n)	Male (n)	Female (n)
APL Frequency [a]	28.2 ± 13.3 (63)*	22.8 ± 15.9 (39)*	18.5 ± 13.0 (504)	15.8 ± 12.4 (602)
APL Intensity [a]	1.17 ± 0.45	1.27 ± 0.64	1.23 ± 0.51	1.24 ± 0.32
CISS Task oriented [b]	53.5 ± 11.5 (65)*	46.3 ± 12.4 (41)*	59.8 ± 8.4 (374)	60.9 ± 8.9 (309)
CISS Emotion oriented [b]	33.5 ± 9.2*	38.0 ± 13.2	36.7 ± 10.1	40.2 ± 10.7
CISS Avoidant oriented [b]	36.8 ± 10.5*	44.2 ± 11.3	46.6 ± 9.8	48.2 ± 9.7
NEO-FFI Neuroticism [c]	29.6 ± 8.6 (67)	33.8 ± 7.8 (42)	29.6 ± 7.8 (958)	32.2 ± 8.2 (1390)
NEO-FFI Extraversion [c]	37.4 ± 6.9	37.4 ± 6.6	39.8 ± 6.5	40.3 ± 6.6
NEO-FFI Openness [c]	36.3 ± 7.4	36.5 ± 5.9	35.4 ± 6.6	36.3 ± 6.3
NEO-FFI Altruism [c]	43.8 ± 5.0	47.2 ± 5.1	42.5 ± 5.1	45.1 ± 5.0
NEO-FFI Conscientiousness [c]	45.3 ± 6.0	45.9 ± 5.7	45.3 ± 5.7	45.3 ± 5.6

Table 1. APL, CISS and NEO-FFI results of Menière patients and reference values.
Values in mean ± standard deviation; * $p<0.05$, t-test, Bonferroni correction applied; reference values from [a] Vingerhoets & Van Tilburg 1994; [b] De Ridder et al. 2004; [c] Hoekstra et al. 1996.

	Menière patients		Reference values	
	Male (n)	Female (n)	Male (n)	Female (n)
SCL-90 Psychoneuroticsm [a]	133.3 ± 34.4 (67)*	147.8 ± 38.5 (43)*	117.2 ± 27.3 (432)	128.9 ± 36.4 (577)
GHQ-12 [b]	2.24 ± 2.94 (66)	3.29 ± 3.39 (41)	< 1	< 1
SF-36 Physical [c]	79.3 ± 20.0 (67)	73.0 ± 20.7 (43)	85.4 ± 21.0 (976)	80.4 ± 24.2 (766)
SF-36 Role-physical [c]	59.9 ± 40.9*	43.7 ± 43.7*	78.7 ± 34.1	73.8 ± 38.5
SF-36 Bodily pain [c]	79.1 ± 23.2	71.0 ± 24.5	77.3 ± 22.7	71.9± 23.8
SF-36 General health [c]	59.3 ± 17.9*	58.7 ± 20.1*	71.6 ± 20.6	69.9 ± 20.6
SF-36 Vitality [c]	60.4 ± 20.1*	55.1 ± 21.6	71.9 ± 18.3	64.3 ± 19.7
SF-36 Social functioning [c]	70.8 ± 24.1*	66.8 ± 31.0*	86.0 ± 21.1	82.0 ± 23.5
SF-36 Role-emotional [c]	79.8 ± 34.6	74.4 ± 39.1	85.5 ± 29.9	78.5 ± 35.7
SF-36 Emotional health [c]	73.4 ± 17.2	70.7 ± 18.7	79.3 ± 16.4	73.7 ± 18.2

Table 2. SCL-90, GHQ-12 and SF-36 results of Menière patients and reference values.
Values in mean ± standard deviation, * $p<0.05$, t-test, Bonferroni correction applied; reference values from [a] Arindell & Ettema 1986; [b] Koeter & Ormel 1989; [c] Aaronson et al. 1998.

The SCL-90 results illustrated that the Menière patients experienced more psychological and physical problems (Table 2). A GHQ-12 score of more than one indicates psychopathology (Table 2). In that case, 63% of the Menière patients showed psychopathology; 71% of the female and 58% of the male Menière patients. According to the SF-36 scores (quality of life), the Menière patients had more limitations due to their restricted physical functioning. They had a worse general health perception and poorer social functioning with less vitality (Table 2). The SF-36 results are also shown in a bar graph to illustrate the differences from the control group and patients with migraine and rheumatoid arthritis (Figure 2). The mean values from the last two groups are from studies by Aaronson et al. and Kvien et al. and the exact values are presented in Table 3.

For further comparison the study population was divided into two subgroups; one with a short duration of disease ($\leq$ 3 years, n=33) and one with a long duration of disease (> 3 years, n=77). The patients who were longer affected by the disease (> 3 years) had significantly more daily stressors (APL), worse physical and social functioning, and more bodily pain (SF-36). They were also less vital (SF-36). Both groups did not differ in their psychometric results for coping strategies (CISS), personality traits (NEO-FFI), mental health (GHQ-12) and psychoneuroticism (SCL-90).

	Menière patients (n=110)	Control group (n=20)	Migraine patients (n=423)[a]	Rheumatoid arthritis (n=1030)[b]
Physical	76.9 ± 20.4	76.3 ± 27.0	82.4 ± 21.3*	47.3*
Role-physical	54.1 ± 42.4	62.5 ± 46.2	62.2 ± 40.8	27.0*
Bodily pain	75.9 ± 23.9	71.3 ± 23.3	64.9 ± 22.4*	41.0*
General health	59.1 ± 18.7	56.8 ± 15.3	67.5 ± 20.5*	42.0*
Vitality	58.3 ± 20.8	55.3 ± 21.6	61.1 ± 18.6	39.4*
Social functioning	69.2 ± 26.9	70.6 ± 32.0	76.2 ± 20.9	63.7
Role-emotional	77.7 ± 36.3	72.0 ± 42.0	74.5 ± 37.8	52.0*
Emotional health	72.4 ± 17.8	66.6 ± 20.0	72.0 ± 18.7	68.1

Table 3. SF-36 results of Menière, control, migraine and rheumatoid arthritis patients.
Values in mean ± standard deviation, * $p<0.05$, t-test between Menière patients vs. control and Menière patients vs. migraine patients and Menière patients vs. rheumatoid arthritis patients, Bonferroni correction applied; [a] Aaronson et al. 1998; [b] Kvien et al. 1998.

The psychometric results of the 110 Menière patients and the results of the patients with other audiovestibular diseases (control group, n=21) were compared. This showed no significant difference in any of the psychological test results (Mann-Whitney-test). The statistical comparison between these two groups is underpowered to detect differences in the psychological tests, because of the small size of the control group.

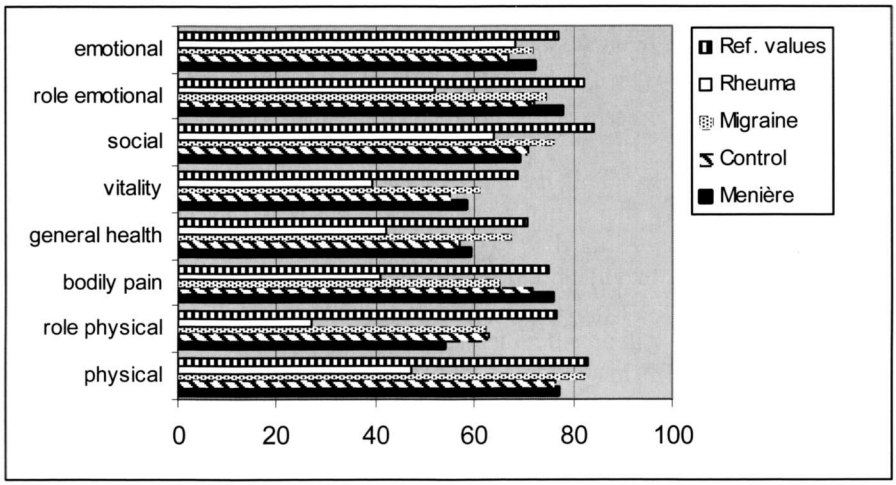


Figure 2. SF-36 results for Menière patients, control group, migraineurs, patients with rheumatoid arthritis and reference values (see also Table 3).

Both groups of patients with low and high severity symptom scores (LSG and HSG) were equally affected by the presence of other chronic diseases and had the same total disease time. The HSG experienced significantly more psychological and physical problems (SCL-90) and a worse quality of life (SF-36) (Table 4). No differences in daily stressors, coping or personality were found between the patients with mild and severe symptoms.

This study also showed some correlations between different psychological parameters, using Pearson product-moment correlation coefficients. Emotion oriented coping strategy use was positively correlated with neuroticism (r=0.68) and negatively correlated with conscientiousness (r=-0.21). Also, emotion focused coping was correlated with psychoneuroticism (r=0.49, SCL-90), general health (r=-0.30, SF-36) and mental health (r=0.35, GHQ-12). Task oriented coping was positively correlated with extraversion (r=0.32). The total severity symptom score was significantly correlated to neuroticism (r=0.27, NEO-FFI), psychoneuroticism (r=0.39, SCL-90), general health (r=-0.29, SF-36) and mental health (r=0.31, GHQ-12).

	LSG (n)	HSG (n)
APL Frequency	27.2 ± 14.3 (52)	24.9 ± 14.8 (50)
APL Intensity	1.15 ± 0.50	1.27 ± 0.56
CISS Task oriented	52.3 ± 11.4 (54)	49.1 ± 13.2 (52)
CISS Emotion oriented	34.3 ± 10.5	36.2 ± 11.7
CISS Avoidant oriented	38.7 ± 10.8	40.6 ± 11.9
NEO-FFI Neuroticism	29.5 ± 8.7 (55)	32.9 ± 8.1 (53)
NEO-FFI Extraversion	37.8 ± 7.3	37.0 ± 6.2
NEO-FFI Openness	36.4 ± 6.5	36.3 ± 7.3
NEO-FFI Altruism	44.6 ± 5.3	45.6 ± 5.3
NEO-FFI Conscientiousness	46.3 ± 5.8	44.7 ± 6.0
SCL-90 Psychoneuroticsm	129.0 ± 31.4 (55)	149.4 ± 39.1 (54)*
GHQ-12	2.11 ± 2.85 (54)	3.19 ± 3.40 (52)
SF-36 Physical	82.5 ± 17.7 (55)	71.2 ± 21.7 (54)*
SF-36 Role-physical	69.6 ± 39.0	37.7 ± 40.3*
SF-36 Bodily pain	82.1 ± 20.6	69.2 ± 25.5*
SF-36 General health	64.4 ± 18.2	52.9 ± 16.9*
SF-36 Vitality	65.5 ± 17.6	50.3 ± 20.6*
SF-36 Social functioning	79.2 ± 21.3	58.8 ± 28.4*
SF-36 Role-emotional	81.2 ± 32.6	74.1 ± 39.8
SF-36 Emotional health	77.8 ± 13.3	66.5 ± 20.0*

Table 4. Psychological results for the low (LSG) and high severity symptom group (HSG) of Menière patients.Values in mean ± standard deviation, * $p<0.05$, t-test, Bonferroni correction applied.

Discussion

This study showed that Menière patients had a deviant psychological profile compared to published normed values. Menière patients experienced more daily stressors and used certain coping strategies less often. There was also more psychopathology and a worse quality of life in Menière patients. No abnormalities in personality were found.

To our knowledge no analysis has been carried out which evaluated all these separate factors in one study. The psychological test results seem comparable to other studies. The psychopathology (e.g. anxiety and depression) in Menière patients was also found by other researchers (50;51;57). The obsessive-compulsive and neurotic personality found by others, could not be confirmed in our study (39;52). Sawade et al. also classified the personality structure in the normal range (54). It remains difficult to compare these studies due to the use of different types of tests.

It has also been shown that Menière patients experience a bad quality of life and vertigo seems to be the most influencing factor in the major implications of this disease on their daily lives (58;59;128). A strong sense of coherence (ability to cope with stressful situations) appears to be an important predictor of Menière patients' perception of symptoms and quality of life according to Söderman et al. (61). They suggested that the quality of life or perception of the disease is also a result of the patient's ability to cope with difficult life situations. This is also seen in our study with the positive correlation between emotion oriented coping and psychoneuroticism (SCL-90) and a negative correlation with general health (SF-36). However, coping strategies and the frequency of daily stressors were the same in the low and high severity symptom group, while the quality of life was significantly worse in patients with more severe symptoms. This suggests that the severity of the symptoms in Menière's disease has more effect on the quality of life than coping or daily stressors. Kinney et al. also evaluated the quality of life of Menière patients with the SF-36 questionnaire (60). In contrast to our findings, they found that patients with Menière's disease have a greater emotional than physical disability. It is difficult to compare both studies since Kinney included patients with surgical treatment and only unilaterally affected patients.

How do these results fit in our theoretical model? Firstly, it needs to be mentioned that causal relations are not justified because of the cross-sectional character of this study. It is not defendable to consider this model as causative. Therefore, the psychological aspects are presented as a descriptive study.

It seems obvious that patients with this unpredictable and disabling disease have more stressors. Nevertheless, patients with more severe symptoms did not experience more stressors than the patients with mild symptoms according to the APL scores. This could be explained by the fact that the general stressors which are mentioned in the questionnaire are not disease-related. The presence of more daily stressors next to disease-related stressors implies some overload of the stress system.

Menière patients recruited fewer task oriented strategies for coping with stressful situations. This implies that they coped with stressors less adequately. There is much debate on which coping strategies are most adequate in which situations; task oriented coping is generally more effective. People's ability to modify their coping according to the situational demands is sometimes referred to as coping flexibility, which involves the systematic use of a variety of strategies across different situations rather than the more rigid application of a few coping strategies (129). So, less use of coping strategies overall may be a sign for inadequate coping. Our results suggest that coping was a stable factor with prolonging disease time, but due to the cross-sectional design of this study we can not draw conclusions in this respect.

The fact that the psychological outcomes did not differ between Menière patients and patients with other audiovestibular disease, emphasises the notion that the psychopathology seems to be the result of having a chronic disease. The psychological profile of Menière patients seems more or less comparable to those of patients with other chronic diseases. Patients with migraine and asthma also show

more depression and anxiety disorders than normals (130;131). Data show that migraineurs and patients with chronic fatigue syndrome are more neurotic, and that the latter group also has lower self-esteem and are more introvert (131;132). It is suggested that the neurosis is related to anxiety and depression; and it is a reaction to the chronic illness. Asthmatics do not seem to have specific personality traits (133). As shown in Figure 2 and Table 3, the quality of life in Menière patients appears to be more equivalent to migraine patients than rheumatoid arthritis patients (127;134). The Menière patients had worse physical functioning, general health and social functioning, but less bodily pain than migraineurs. This could be explained by the continuously present tinnitus and hearing loss in Menière patients, which could give more physical problems and no real painful moments as a result of the disease. Rheumatoid arthritis has more impact on all the eight dimensions of the quality of life.

The knowledge of the specific psychological problems and the quality of life in patients with Menière's disease, gives us insight as to where, when and how we should give psychological support. It was seen that Menière patients with longer disease duration had more daily stressors and worse quality of life in certain dimensions. Statements on changes in the psychological profile occurring over time can not be made due the cross-sectional character of the study. Furthermore, patients with more severe subjective complaints from their disease had more psychopathology, were more emotionally unstable and had a worse quality of life. Patients with severe symptomatology did not differ in personality or coping from the ones with mild symptomatology. Therefore, the question why some Menière patients develop more intense symptoms than others, could not be answered from this study.

Conclusion and recommendations

Menière patients have a deviant psychological profile compared to published normed values, but comparable to patients with other chronic diseases. Many psychological factors and the symptoms of the disease seem to interact. To interfere in this psychological process, we need to break in by reducing the severity of symptoms with hearing aids and medication. Next to that, the psychological support needs to be intensified where needed. The coping and psychopathology (e.g. anxiety and depression) should be approached by a psychologist or a psychiatrist. The impact of the disease on the daily functioning (mental, physical and social) should also be a point of attention. When Menière patients are helped with these issues, they function and feel better and consequently handle their stressful disease more effectively

Hippocampal volume measurement in patients with Menière's disease; a pilot study

Van Cruijsen N, Hiemstra WM, Meiners LC, Wit HP and Albers FWJ. Hippocampal volume measurement in patients with Menière's disease; a pilot study. Submitted.

Introduction

Menière's disease is a chronic inner ear disease with disabling symptoms: spontaneous vertigo attacks, hearing loss, tinnitus and aural fullness. Endolymphatic hydrops is the most commonly used pathophysiologic model, but the exact pathogenesis remains unclear (8). It is a common observation in clinical practice and seen from earlier studies that Menière patients experience more stressful events, have more psychopathology and a poor general health perception (135). Stress could play a role in the development or precipitation of the symptoms (117).

In general, stress leads to higher levels of stress hormones, e.g. glucocorticosteroids (cortisol) and catecholamines, through activation of the hypothalamic-pituitary-adrenal axis (HPA axis) and the autonomic nervous system respectively. Animal studies have shown that stress and chronically elevated cortisol levels generate selective hippocampal atrophy (136). Human hippocampal atrophy with HPA axis dysregulation and memory impairment has been found in affective disorders (73;74), Cushing's disease (75), human aging (77), Alzheimer's disease (78) and in posttraumatic stress disorder (79). Some researchers did not find differences between hippocampal volumes of depressed patients and control subjects (109;137). All these studies used magnetic resonance imaging (MRI) for hippocampal volume measurement. It is thought that the individuals with hippocampal atrophy are subjected to enduring stress and high levels of cortisol. The wear and tear of the body due to chronic stress, including the hippocampus, is called allostatic load (68).

The hippocampus is located in both temporal lobes and involved in memory, learning and emotion. It also plays a role in the negative feedback of the HPA axis (71). Therefore, hippocampal atrophy may not only be a result of higher glucocorticosteroid levels, but may also lead to increased levels of circulating glucocorticosteroids.

It is hypothesised that Menière's disease with its unpredictable and handicapping nature leads to a vicious cycle of chronic stress, allostatic load and consequently hippocampal atrophy. The aim of this study was to evaluate the hippocampal volumes in patients with Menière's disease. Two blinded raters measured the hippocampal volumes of 10 patients with Menière's disease and 10 healthy controls using MRI scans. Saliva cortisol and the frequency of daily stressors were also evaluated in both groups to obtain objective stress parameters.

Subjects and methods

Subjects

Patients were considered having Menière's disease when they had a history of at least two vertigo attacks lasting longer than 20 minutes, tinnitus and sensorineural hearing loss of at least 60 dB added up from the three worst octaves in the same ear, and other pathology had been excluded. The diagnostic work-up included standard ear, nose and throat examination, several audiometric and vestibular tests; magnetic resonance imaging (MRI) of the cerebellopontine angle; laboratory tests and evaluation of symptoms using standardised questionnaires. Two weeks before scanning, patients discontinued their antivertiginous medication, including anxiolytics. We defined the total disease time as the duration time of the first presenting symptom until the day of MRI scanning. The total disease time in patients with bilateral complaints was calculated from the time the first ear was affected. The presence or absence of another chronic disease besides Menière's disease was also noted. The hearing loss was defined as the extended Fletcher Index over five pure-tone audiogram frequencies (0.25-4 kHz). MRI scanning of the cerebellopontine angle was part of the diagnostic work-up to exclude intratemporal or retrocochlear pathology. During the same session, we scanned the total brain including the hippocampal region using a 3D-scan.

The control group included healthy volunteers without any signs of Menière's disease. In this group only a 3D-scan of the whole brain was made. All participants of this study had no neurological conditions, history of myocardial infarction or head trauma, hypertension, diabetes, Cushing's disease, alcohol or drugs abuse and did not use corticosteroids. We started with a pilot study with 10 persons in each group. The local medical ethics committee approved the study and all participants gave written informed consent.

Methods

MRI parameters, processing of the images and segmentation

T_1-weighted MR images were obtained on a 1.0 Tesla scanner (Vision, Siemens, Erlangen, Germany). The 3D-volume was acquired using a magnetisation prepared rapid gradient echo (MPRAGE) technique (TR 30 msec, TE 5 msec and flip angle 30^0). The pixel size was 0.977 x 0.977 mm with a slice thickness of 1.2 mm, matrix size of 256 x 256 and FOV of 256.

The segmentation of the right and left hippocampus was done with a manual tracing method using a mouse-driven cursor and light pen system on a display console. The tracing was performed on a workstation using Imod software (University of Colorado, Boulder, Colorado, U.S.A.), which is originally designed for 3D-reconstructions of electron microscopy cells. The greyscale threshold was judged visually. The volumes were digitally calculated using the given voxel size. The segmentation was performed by two raters (NvC and WMH), who were blinded to subject identity.

Anatomical borders of the hippocampus

The hippocampus is a sea-horse-like structure in the medial temporal lobe of both hemispheres. The anatomical borders of the hippocampus for segmenting were chosen according to the protocol of Watson et al. (138). The anterior border of the hippocampus was marked in the coronal slice in which the mamillary bodies were seen, which served as delineation between amygdala and hippocampus. The posterior demarcation was defined at the slice where the fornix was visible as a continuous tract. The borders of the hippocampus were defined as grey matter, whereby the superior border included the inferior horn of the lateral ventricle. The collateral white matter in the parahippocampal gyrus served as the inferior border. The subiculum and the uncal sulcus were included in the segmentation (Figure 1). The anterior and posterior borders of the hippocampus were defined by the first rater.

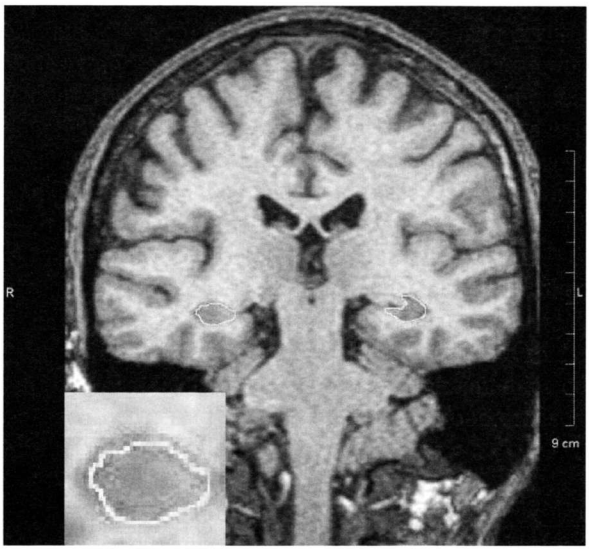


Figure 1. Segmentation of the hippocampus on MRI scan with 3 times enlargement.

Correction for head size

The total brain and intracranial surface was segmented on those slices where the hippocampus was present on. The brain surface was defined as all the brain tissue of both hemispheres (gray and white matter) excluding the cerebellum and brainstem. Intracranial volume was defined as all the contents directly under the skull with the inferior border of the both hemispheres as the caudal margin. Both volumes were calculated using traced surface, voxel size and length of the hippocampus. This was different for the right and left hippocampus. Knowledge of these volumes was obligatory to correct for variation in brain size (139). Herewith, the relative hippocampal volume was determined as a ratio: hippocampal volume to partial brain volume and hippocampal volume to partial intracranial volume.

Cortisol and stressors analysis

Saliva cortisol measurement was performed at 8:00 AM with a Salivette cotton swab (Sarstedt, Nümbrecht, Germany). The saliva was evaluated for cortisol with an in-house radioimmune assay method. Normal values at 8:00 AM are 16 ± 1.7 nmol/l for men with a range of 6.4 to 32 nmol/l, and 9.8 ± 3.1 nmol/l for women with a range of 4.8 to 18 nmol/l (70).

All participants were screened for daily stressors using "Daily Hassles List", which quantifies the frequency and intensity of problems in different circumstances (118). 112 situations are given and have to be answered, whether they had occurred in the past two months. If a positive reaction is given, it also had to be scored whether it was "not a problem at all (0)", "not so bad (1)", "bad (2)" or "very bad (3)". A higher score implies more daily hassles. "Daily Hassles List" is a free translation of "Alledaagse Problemen Lijst", which is a standardised and validated Dutch questionnaire.

Statistics

Data are presented as means ± standard deviations. Chi-square, Mann-Whitney and Wilcoxon signed ranks test were used to evaluate differences between groups. Significance is reached at a level of $p<0.05$. The intra- and inter-rater reliability will be presented as intraclass correlation coefficients (140). The intra-rater reliability could be calculated by segmenting 10 hippocampi twice with a certain time interval by the two raters. The one-way ANOVA is used in this calculation. Intraclass correlation coefficients (ICC) above 0.7 are considered reliable.

Results

Study population

Ten Menière patients and 10 healthy control participants were matched for age, gender, height, weight and the presence of other chronic diseases. Six Menière patients were right and 3 left handed, one patient was ambidextrous. All participants of the control group were right handed. The saliva cortisol levels and presence of daily stressors were similar in both groups (Table 1).

In the Menière group 7 patients were unilaterally and 3 were bilaterally affected. The mean total disease time was 9.9 years with a minimum of 2.0 and maximum of 21 years. Mean hearing loss was 56.4 ± 13.1 dB. Three of the 10 Menière patients had another chronic disease: two patients had hyperthyroidism and one had persistent complaints following lumbar disc herniation.

	Menière group (n=10)	Control group (n=10)
Age (years)	50.6 ± 11.5	48.4 ± 8.9
Gender (male/female)	6/4	5/5
Height (cm)	178.3 ± 7.4	174.6 ± 8.6
Weight (kg)	79.8 ± 9.2	75.5 ± 13.2
Handedness (right/left/ambidextrous)	6/3/1	10/0/0*
Saliva cortisol (nmol/l)	16.4 ± 5.7	11.7 ± 4.4
APL score total score	39.3 ± 25.8	24.6 ± 18.3
Other chronic disease (yes/no)	3/7	0/10

Table 1. General characteristics of Menière and control group.
Results presented in mean ± standard deviation; * $p<0.05$ (Chi square test).

Hippocampal segmentation results

The results are presented as mean ± standard deviation in Table 2. For the Menière and control group the first rater measured mean hippocampal volumes of 2.80 ± 0.36 cm^3 vs. 3.15 ± 0.52 cm^3 (right) and 2.49 ± 0.32 cm^3 vs. 3.06 ± 0.46 cm^3 (left), respectively. The second rater measured 3.44 ± 0.35 cm^3 vs. 3.60 ± 0.52 cm^3 (right) and 3.00 ± 0.40 cm^3 vs. 3.42 ± 0.45 cm^3 (left), respectively. The raw data of both raters are presented in Figure 2.

The absolute volume of the left hippocampus was significantly smaller in Menière patients compared to the control group for both raters ($p<0.05$). The right hippocampal volume was similar in the two groups. Furthermore, the length of the right and left hippocampus was 28.6 ± 2.5 and 27.6 ± 3.1 mm in the Menière group and 28.8 ± 2.0 and 28.6 ± 2.7 mm in the control group, respectively (Table 2).

	Menière group (n=10)	Control group (n=10)
Right hippocampal volume rater 1 (HR1) (cm^3)	2.80 ± 0.36	3.15 ± 0.52
Left hippocampal volume rater 1 (HL1) (cm^3)	2.49 ± 0.32	3.06 ± 0.46*
Right hippocampal volume rater 2 (HR2) (cm^3)	3.44 ± 0.35	3.60 ± 0.52
Left hippocampal volume rater 2 (HL2) (cm^3)	3.00 ± 0.40	3.42 ± 0.45*
Right hippocampal length (mm)	28.6 ± 2.5	28.8 ± 2.0
Left hippocampal length (mm)	27.6 ± 3.1	28.6 ± 2.7

Table 2. Hippocampal volume and length results.
Results presented in mean ± standard deviation; * $p<0.05$ (Mann Whitney test).

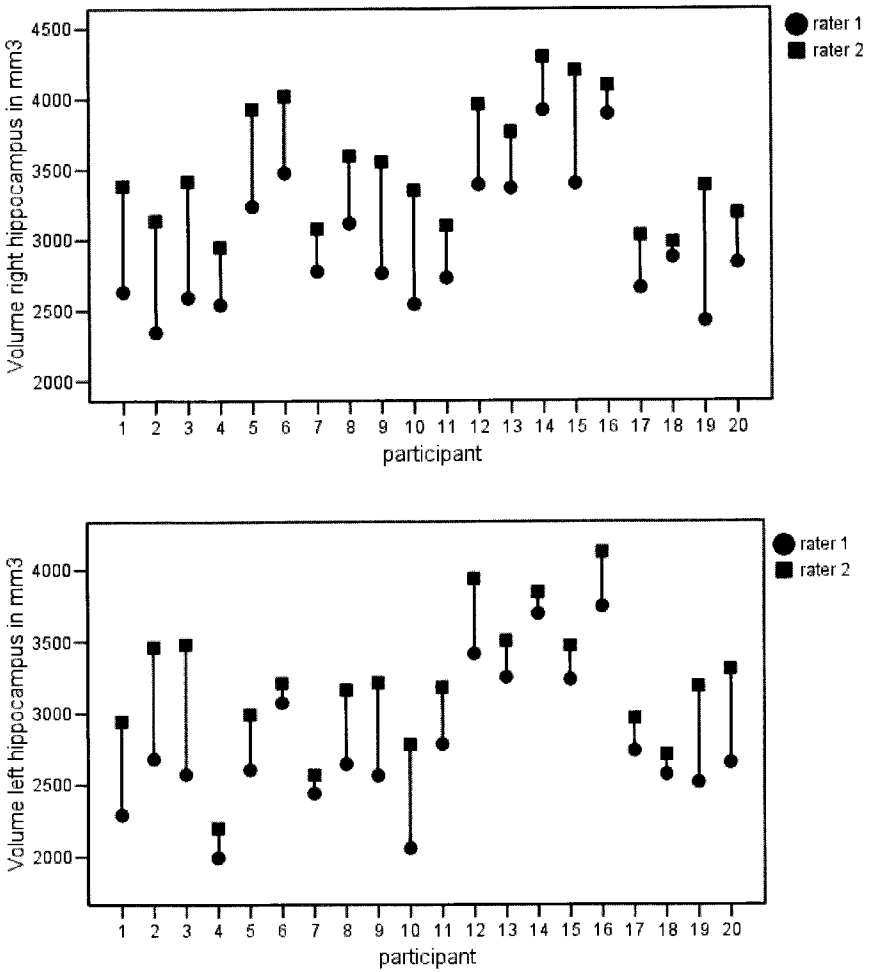


Figure 2. Absolute right and left hippocampal volume (mm^3) for both raters in all participants. Participant number 1-10 Menière patients and 11-20 controls.

The hippocampal volumes were corrected for variation in head size with the partial brain volume and partial intracranial volume. No significant differences in relative hippocampal volumes were observed between Menière patients and the control group (Table 3).

The Menière group could be divided into two subgroups of each five patients, a short-term disease and a long-term disease group. The mean total disease time for the respective groups was 2.5 ± 0.6 and 17.2 ± 2.4 years. Both small groups did not differ in absolute and relative hippocampal volume, saliva cortisol level or frequency of daily stressors. Furthermore, all right handed male Menière patients (n=5) were compared to right handed male controls (n=5). No differences were

observed in absolute and relative hippocampal volumes between these two subgroups.

	Menière group (n=10)	Control group (n=10)
Partial brain volume right (BR) (cm^3)	259 ± 26	277 ± 33
Partial brain volume left (BL) (cm^3)	252 ± 31	274 ± 35
Partial intracranial volume right (CR) (cm^3)	386 ± 36	395 ± 53
Partial intracranial volume left (CL) (cm^3)	378 ± 49	393 ± 58
Ratio rater 1 (HR1/BR) x 10^4	109 ± 16	115 ± 20
Ratio rater 1 (HL1/BL) x 10^4	100 ± 15	112 ± 16
Ratio rater 2 (HR2/BR) x 10^4	134 ± 16	131 ± 20
Ratio rater 2 (HL2/BL) x 10^4	120 ± 15	126 ± 17
Ratio rater 1 (HR1/CR) x 10^4	73 ± 11	81 ± 16
Ratio rater 1 (HL1/CL) x 10^4	67 ± 11	79 ± 13
Ratio rater 2 (HR2/CR) x 10^4	90 ± 11	92 ± 15
Ratio rater 2 (HL2/CL) x 10^4	80 ± 11	88 ± 15

Table 3. Hippocampal volume results in relation to brain and intracranial volume.
Results presented in mean ± standard deviation; Mann Whitney test.

Comparison of right and left hippocampal volumes of all participants showed that the left hippocampal volume was significantly smaller for both raters with and without correction for head size ($n=20$, $p<0.05$)

Correlations

The inter-rater correlation coefficient was 0.47 and the intra-rater correlation coefficient was 0.84 for rater 1 and 0.81 for rater 2. The partial brain volume and partial intracranial volume were significantly positively correlated ($r=0.788$ at the 0.001 level, Pearson product-moment correlation coefficient).

Discussion

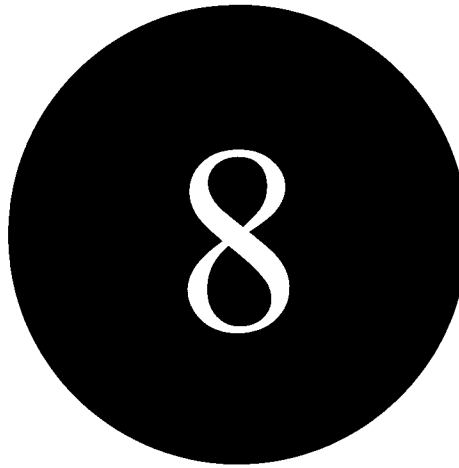
Hippocampal atrophy was not found in patients with Menière's disease compared to healthy controls. Correction for head size with partial brain and intracranial volume dissolved the smaller absolute left hippocampal volume in Menière patients. Furthermore, the Menière patients who were longer affected by the disease had similar hippocampal volumes as the patients with shorter disease time.

In general, results of hippocampal volumetry studies vary largely due to different data acquisition, software and definition of the anatomical borders (141). This makes it almost impossible to compare results of separate studies. Each study has its own normative data for hippocampal volume, which ranges from 2.8 to 5.3

cm^3 for the right and 2.4 to 4.9 cm^3 for the left hippocampus (138;142). The right hippocampus is generally larger than the left, which was confirmed in this study.

There were several study limitations. Firstly, the difference between hippocampal volumes of the two raters was significant. This difference occurred because the second rater drew the contours on the MRI slices systematically 0.5 pixel more to the outside than rater 1 (Figure 2). Nevertheless, the differences between the Menière and control group, and right vs. left hippocampal volumes, were comparable for both raters. In addition, the sample size was limited. Therefore, the results need to be interpreted cautiously and it is advised to study larger groups.

The hypothesis of hippocampal atrophy and HPA axis dysregulation as a possible consequence of chronic stress or allostatic load in Menière's disease could not be confirmed by this study. Another consequence of hippocampal atrophy, memory impairment was not studied in this setting. Earlier, we did find elevated cortisol levels and a higher frequency of not disease-related daily stressors in Menière patients compared to healthy people (135;143). This could be associated to the more short-term stress-related consequences of Menière's disease. The hippocampal atrophy found in patients with chronic depression and posttraumatic stress disorder probably leads to more frequently elevated glucocorticosteroid levels than in Menière patients, which results in measurable damage to the hippocampus (74;79).



Discussion

Multifactor model of Menière's disease: the answers?

The best way to interpret the complex process of the disabling Menière's disease seems to be a continuous interaction of psychological, somatic and environmental factors. It is opted, that the process is becoming a *vicious cycle*: symptoms of the disease could worsen the emotional, physical and social state, which in turn could worsen the (perception of) symptoms. This cycle is presented in the multifactor model of Menière's disease in **chapter 4**, where all factors of this process have been put forward (Figure 1). In this paragraph, all the separate elements of the model, either published by others or shown in our studies, are presented and discussed.

The first element of the process is *endolymphatic hydrops*. That endolymphatic hydrops causes Menière's disease, is taken as a fact in the model based upon other studies (7;144). However, not every patient with endolymphatic hydrops experiences the clinical triad of Menière's disease (10) and endolymphatic hydrops could be an epiphenomenon in Menière's disease (8). Patients are considered having *Menière's disease* when their audiovestibular complaints (vertigo, hearing loss and tinnitus) are conform the "Definition Menière Groningen 2001" (14).

The trias of Menière symptoms may be conceived as stressor next to other incoming *stressors*. *Stressors* are handled with certain coping strategies and personality features (*appraisal*) and may generate specific *psychological, physiological and behavioural responses*. Consequently, this results in a particular *emotional and behavioural state*. These last elements were evaluated in **chapter 6,** where a psychological assessment of Menière patients took place. It was found that Menière patients experience more daily hassles (*stressors*), use coping strategies less frequently (*appraisal*) and have more psychopathology (*emotional stress response*) and a worse quality of life compared to healthy people. The psychopathology consisted of depression, anxiety, agoraphobia and sleeping problems. No abnormal personality features were found. In previous studies was also shown that Menière patients experience more anxiety, depression and phobia (50;51;57). In the field of personality characteristics earlier studies have described Menière patients as obsessive-compulsive persons, perfectionists and neurotics, who are supposed to be more vulnerable and have more stress exposure (39;41;52), while others classified the personality of Menière patients in the normal range (54). A time-series analysis of stress and vertigo expression did not support the role of stress as a precursor of symptoms in Menière's disease (55). On the contrary, Söderman et al. did find that emotional stress increased the risk of getting a vertigo attack (117). Menière patients experience a bad quality of life and vertigo seems to be the most influencing factor on the major implications of this disease on their daily lives (58;59;128). A strong sense of coherence (ability to cope with stressful situations) appears to be an important predictor of Menière patients' perception of symptoms and quality of life according to Söderman et al. (61).

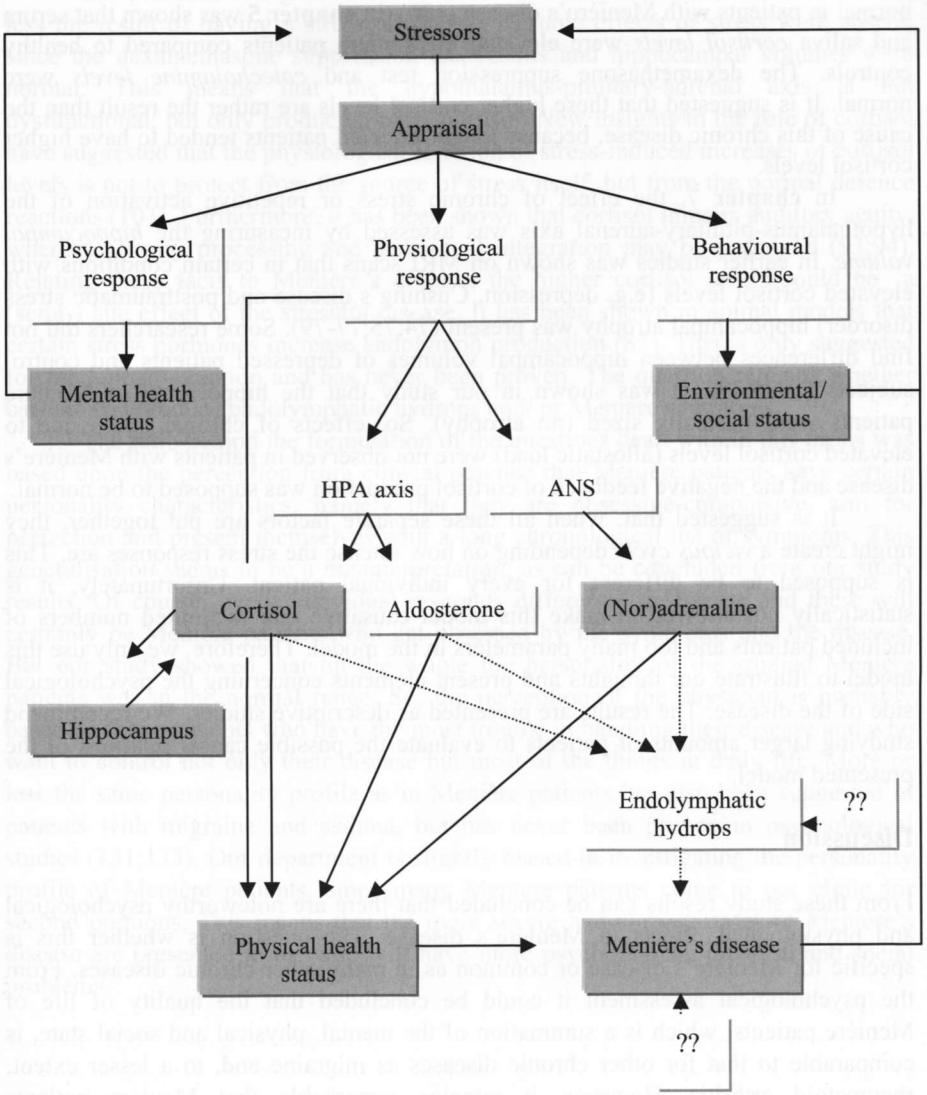


Figure 1. Multifactor model in Menière's disease.
HPA axis = Hypothalamus-Pituitary-Adrenal axis; ANS = Autonomic Nervous System

The *physiological stress response* is activated through two ways, resulting in corticosteroid (cortisol and aldosterone) and catecholamine secretion (noradrenaline and adrenaline). Mateijsen et al. have already shown that the *aldosterone levels* were normal in patients with Menière's disease (100). In **chapter 5** was shown that serum and saliva *cortisol levels* were elevated in Menière patients compared to healthy controls. The dexamethasone suppression test and *catecholamine levels* were normal. It is suggested that these higher cortisol levels are rather the result than the cause of this chronic disease, because longer affected patients tended to have higher cortisol levels.

In **chapter 7**, the effect of chronic stress or repetitive activation of the hypothalamus-pituitary-adrenal axis was assessed by measuring the *hippocampal volume*. In earlier studies was shown on MRI scans that in certain conditions with elevated cortisol levels (e.g. depression, Cushing's disease and posttraumatic stress disorder) hippocampal atrophy was present (74;75;77-79). Some researchers did not find differences between hippocampal volumes of depressed patients and control subjects (109;137). It was shown in our study that the hippocampi of Menière patients were normally sized (no atrophy). So, effects of chronic stress due to elevated cortisol levels (allostatic load) were not observed in patients with Menière's disease and the negative feedback of cortisol production was supposed to be normal.

It is suggested that, when all these separate factors are put together, they might create a *vicious cycle* depending on how intense the stress responses are. This is supposed to be different for every individual patient. Unfortunately, it is statistically not allowed to make this model causative due to limited numbers of included patients and too many parameters in the model. Therefore, we only use this model to illustrate our thoughts and present elements concerning the psychological side of the disease. The results are presented as descriptive studies. We recommend studying larger amounts of patients to evaluate the possible causal relations of the presented model.

Discussion

From these study results can be concluded that there are noteworthy psychological and physiological effects in Menière's disease. The question is whether this is specific for Menière's disease or common as in many other chronic diseases. From the psychological assessment it could be concluded that the quality of life of Menière patients, which is a summation of the mental, physical and social state, is comparable to that for other chronic diseases as migraine and, to a lesser extent, rheumatoid arthritis. However, it remains remarkable that Menière patients experience more daily hassles and use coping strategies less frequently than healthy controls. This could be an effect of a chronic disabling disease by getting a reduced mental state. But, it could also be present prior to disease and consequently create allostatic load. Whether this possible allostatic load initiates Menière symptoms or Menière's symptoms are the last piece to initiate the vicious cycle, remains unanswered. On the other hand, effects of allostatic load could not be confirmed,

because normal hippocampal volumes were measured in patients with Menière's disease.

The presence of higher levels of cortisol in Menière patients could be more or less the result of having a stressful disease. Chronic effects of stress were absent, since the dexamethasone suppression test results and hippocampal volumes were normal. This means that the hypothalamus-pituitary-adrenal axis is not dysfunctional, but only producing more cortisol. New insights to the role of cortisol have suggested that the physiological function of stress-induced increases of cortisol levels is not to protect from the source of stress itself, but from the normal defence reactions (103). Furthermore, it has been shown that cortisol impairs auditory acuity, whereas sensory processing and perceptual integration may be improved (93;94). Relating these facts to Menière's disease, the higher cortisol levels could be a (semi-) late effect of the stressful disease. It has been shown in animal models that certain stress hormones increase endolymph production (83). This is only suggested for the human situation and has never been proven. The question remains whether cortisol can produce endolymphatic hydrops and/ or Menière symptoms.

The ratio behind the formulation of the questions dealt with in this thesis was based upon the perception from clinical practice that Menière patients have certain personality characteristics, namely that they are obsessive-compulsive, aim for perfection and present themselves with a long chronological list of symptoms. This generalisation seems to be a misinterpretation, as can be concluded from our study results. Of course, every individual responds differently to disease and there will certainly be Menière patients who get obsessed by the symptoms and the disease. But our study showed that on the whole the personality of the studied Menière patients was in the normal range. So, the perception of the physician is probably based on those patients who have the most trouble in handling their disease and who want to control not only their disease but most of the things in daily life. More or less the same personality profile as in Menière patients has also been suggested in patients with migraine and asthma, but has never been proven in psychological studies (131;133). Our department is slightly biased in investigating the personality profile of Menière patients, since many Menière patients come to our clinic for second opinions. This means that the more severe and chronic cases of Menière's disease are presented to us, who will have more psychological, physical and social problems.

Summary and conclusions

Summary

Menière's disease is a chronic inner ear disease with handicapping symptoms as spontaneous vertigo attacks, progressive hearing loss and tinnitus. Endolymphatic hydrops is the most commonly used pathophysiologic model, but the exact pathogenesis remains unclear. There is no curative treatment available for Menière's disease, so any treatment remains symptomatic.

Menière's disease is amongst the conditions in which psychological factors are often emphasised. Many researchers have reported emotional disturbances in patients with Menière disease. Others have suggested that Menière patients have specific personality traits. These observations seem to have led to the conclusion that psychological factors could play a role in the development and continuation of Menière's disease. Therefore, Menière's disease has received a lot of attention from a psychological point of view. A review of psychological oriented studies in patients with Menière's disease is presented in **chapter 2.**

General aspects of stress and relations between stress (hormones) and bodily systems, especially inner ears and Menière patients, are exposed in **chapter 3.** It includes old and new facts about stress and presents clear definitions of most of the elements involved in the stress cascade.

In **chapter 4,** the suggested vicious cycle of psychological aspects and Menière's disease including other factors are shown. The presented multifactor model is used to explain certain aspects of Menière's disease other than the usual symptoms. Furthermore, the aims of this thesis are introduced.

In **chapter 5,** cortisol and catecholamine levels of patients with Menière's disease were evaluated in a controlled setting. The serum and saliva cortisol levels were higher in Menière patients compared to their control group, 440 ± 127 (n=28) versus 366 ± 90 nmol/l (n=18) and 17.2 ± 6.1 (n=18) versus 11.6 ± 4.6 nmol/l (n=9), respectively ($p<0.05$). There were no dissimilarities in urine cortisol and urine catecholamines for both groups. Menière patients (n=28) were divided into two subgroups, high (HC) and low cortisol group (LC) using a serum cortisol level cutoff point of 465 nmol/l (median). The total Menière disease time and the duration of tinnitus tended to be longer in the HC group ($p=0.07$, two-tailed). The total Menière disease time was 13.5 ± 9.9 versus 7.1 ± 7.4 years in the HC versus LC group (both n=14). The subgroups were matched for age, gender and uni- or bilaterally affected ears. It was concluded that patients with Menière's disease have higher serum cortisol levels. It was suggested that it was rather the result than the cause of this chronic disease, because patients who were longer affected by the disease, seemed to have higher cortisol levels.

In **chapter 6,** a psychological assessment of Menière patients took place. The objective of this study was to evaluate daily stressors, coping, personality, physical and mental health and quality of life in Menière patients. 110 consecutive patients with definite Menière's disease were assessed using the Dutch Daily Hassles List, Coping Inventory for Stressful Situations (CISS), Symptoms Checklist 90 (SCL-90), NEO Five Factor Inventory (NEO-FFI), General Health Questionnaire (GHQ-12)

and the Short Form Health Survey 36 (SF-36). Duration and subjective severity of symptoms were scored using a self-report questionnaire. It was shown that Menière patients had more daily stressors, used coping strategies less frequently, and had more psychopathology (e.g. anxiety and depression) and a worse quality of life compared to the general population. No abnormalities in personality structure were found. Patients with more severe symptoms had more psychopathology and a worse quality of life than patients with mild symptoms. Patients with either mild or severe symptomatology did not differ in personality or coping strategies. The deviant psychological profile of Menière patients seems comparable to patients with other chronic diseases. It is advised that psychosocial support should be intensified in certain patients with this disabling disease.

In **chapter 7,** the effect of chronic stress (allostatic load) was assessed by measuring hippocampal volume. Hippocampal atrophy is known to be caused by chronically or repetitive elevated levels of cortisol. The hippocampal volumes of 10 Menière patients and 10 matched healthy controls were measured on MRI scans. No differences in hippocampal volumes (corrected for head size) were found between the two groups. It was concluded from this pilot study that no signs of chronic stress (hippocampal atrophy) were present in Menière patients.

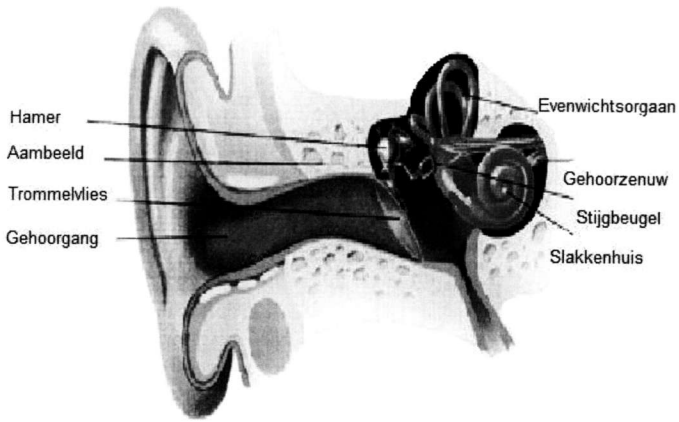
Conclusions

Menière patients have a deviant psychological profile compared to the general population, but more or less comparable to the profile of patients with other chronic diseases. The higher cortisol levels in Menière patients implied an overproducing HPA axis in some way. Nevertheless, effects of chronically elevated cortisol levels could not be found by measuring normal hippocampal volumes in patients with Menière's disease. What the exact impact of the deviant psychological profile and higher cortisol levels on Menière's disease, the inner ear and endolymph homeostasis could be, is yet unknown.

It is thought that the presented factors, symptoms and stress responses, seem to interact in a vicious cycle. What can we do to interrupt this suggested vicious cycle of symptoms, their effect on the state of mind and vice versa? First we have to keep in mind that every Menière patients needs individual treatment depending on the severity of symptoms and impact of the disease. Reducing the severity of symptoms can be achieved with hearing aids and medication. Furthermore, we need to intensify the psychosocial support. The coping strategies and psychopathology (e.g. anxiety and depression) should be approached by a psychologist or psychiatrist. The impact of the disease on daily functioning (mental, physical and social) should also be a point of attention. When Menière patients are helped with these issues, they function and feel better and consequently handle their stressful disease more effectively.

Nederlandse samenvatting

De ziekte van Menière is een chronische, invaliderende ziekte, waarbij de oorzaak in het binnenoor (slakkenhuis en evenwichtsorgaan) ligt (Figuur 1). De ziekte wordt gekenmerkt door progressief gehoorverlies, oorsuizen en aanvallen van draaiduizeligheid, gepaard gaande met misselijkheid en braken. In Nederland lijden ongeveer 10.000 mensen aan deze ziekte.



Figuur 1. Het oor.

Prosper Menière, een Franse arts, was de eerste die het ziektebeeld als zodanig beschreef in 1861 (Figuur 2). Een teveel aan binnenoorvloeistof (endolymfe), ook wel endolymfatische hydrops genaamd, lijkt de oorzaak. Het exacte mechanisme voor het ontstaan van de ziekte van Menière en endolymfatische hydrops is nog niet duidelijk. Tot op heden is er geen genezende behandeling voor de ziekte van Menière, waardoor de behandeling dan ook gericht is op vermindering van klachten.

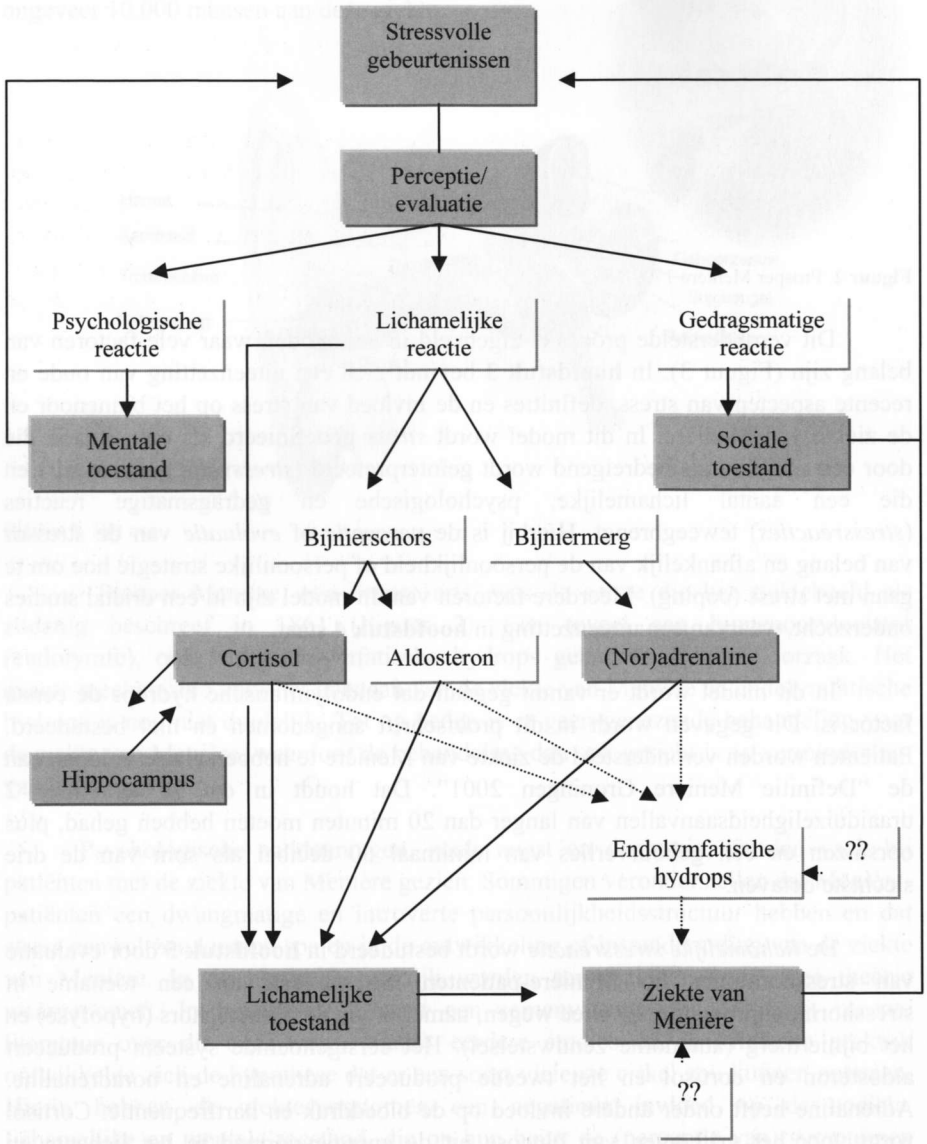
Psychologische aandoeningen, zoals angst en depressie, worden vaak bij patiënten met de ziekte van Menière gezien. Sommigen veronderstellen dat Menière-patiënten een dwangmatige en introverte persoonlijkheidsstructuur hebben en dat stress een rol zou kunnen spelen in de ontwikkeling of instandhouding van de ziekte van Menière. In de klinische praktijk worden aanwijzingen voor deze theorie waargenomen. In **hoofdstuk 2** staat een samenvatting van de meest recente literatuur over dit onderwerp. Vanuit eerdere studies en de klinische praktijk ontwikkelde zich de hypothese dat er een soort vicieuze cirkel zou kunnen ontstaan. Hierin hebben de ziektesymptomen een negatieve invloed op de sociale, lichamelijke en mentale toestand, die op hun beurt de (perceptie van) symptomen doen toenemen.

Figuur 2. Prosper Menière 1799-1862.

Dit veronderstelde proces is afgebeeld in een model, waar vele factoren van belang zijn (Figuur 3). In **hoofdstuk 3** bevindt zich een uiteenzetting van oude en recente aspecten van stress, definities en de invloed van stress op het binnenoor en de ziekte van Menière. In dit model wordt *stress* gedefinieerd als een situatie die door een individu als bedreigend wordt geïnterpreteerd (*stressvolle gebeurtenis*) en die een aantal lichamelijke, psychologische en gedragsmatige reacties (*stressreacties*) teweegbrengt. Hierbij is de *perceptie* of *evaluatie* van de stressor van belang en afhankelijk van de persoonlijkheid of persoonlijke strategie hoe om te gaan met stress (coping). Meerdere factoren van dit model zijn in een drietal studies onderzocht, waarvan een uiteenzetting in **hoofdstuk 4** staat.

In dit model wordt er vanuit gegaan dat endolymfatische hydrops de eerste factor is. Dit gegeven wordt in dit proefschrift aangenomen en niet bestudeerd. Patiënten worden verondersteld de ziekte van Menière te hebben als ze voldoen aan de "Definitie Menière Groningen 2001". Dat houdt in dat ze tenminste 2 draaiduizeligheidsaanvallen van langer dan 20 minuten moeten hebben gehad, plus oorsuizen en een gehoorverlies van minimaal 60 decibel als som van de drie slechtste octaven.

De *lichamelijke stressreactie* wordt bestudeerd in **hoofdstuk 5** door evaluatie van stresshormonen bij Menière-patiënten. Stress leidt tot een toename in stresshormoonproductie via twee wegen, namelijk via de bijnierschors (hypofyse) en het bijniermerg (autonome zenuwstelsel). Het eerstgenoemde systeem produceert aldosteron en cortisol en het tweede produceert adrenaline en noradrenaline. Adrenaline heeft onder andere invloed op de bloeddruk en hartfrequentie. Cortisol zorgt voor het vrijkomen van glucose uit de energievoorraad in het lichaam en onderdrukt ontsteking. We toonden in onze studie aan dat de bloed- en speekselspiegels van cortisol hoger waren bij Menière-patiënten dan bij gezonde proefpersonen. Er was geen verschil in adrenaline- en noradrenaline-spiegels in de urine.



Figuur 3. Multifactor model bij de ziekte van Menière.

Er wordt gesuggereerd dat stress en vooral de lichamelijke stressreacties van invloed zijn op het binnenoor en tot ontwikkeling of instandhouding van de Menière-symptomen kunnen leiden. In diermodellen is aangetoond dat stresshormonen een toename in endolymfeproductie kunnen veroorzaken. Mogelijkerwijs geldt dit ook in de humane situatie. In het menselijke binnenoor zijn receptoren voor bepaalde stress hormonen aangetoond. Echt sluitend bewijs voor deze relatie is er niet.

Ten tweede is een studie opgezet om de psychologische factoren rondom de ziekte van Menière te verhelderen (**hoofdstuk 6**). Hierbij werden de gedragsmatige en psychologische stressreacties onderzocht. In de *gedragsmatige stressreactie* leiden chronische stressoren bijvoorbeeld tot het stoppen met werken of opleiding, overmatig alcoholgebruik of zelfs zelfdoding. De *psychologische stressreactie* geeft angst en woede in de acute situatie en gespannenheid of depressiviteit als de stressoren aanhouden. Met behulp van zelfbeoordelingvragenlijsten zijn dagelijkse problemen, persoonlijkheid, coping, psychopathologie en kwaliteit van leven onderzocht. Onder de kwaliteit van leven wordt verstaan de impact van de ziekte op het sociaal, fysiek en psychisch functioneren in het dagelijkse leven. Deze studie liet zien dat Menière-patiënten meer alledaagse problemen hadden, copingstrategieën minder vaak gebruikten, meer psychopathologie (o.a. angst en depressie) en een slechtere kwaliteit van leven hadden. Er werden geen afwijkende persoonlijkheidskenmerken geconstateerd. De kwaliteit van leven van Menière-patiënten is vergelijkbaar met die van patiënten met andere chronische ziekten, zoals migraine en reuma. De resultaten van de psychologische evaluatie kwamen overeen met andere psychologisch georiënteerde studies bij Menière-patiënten. Alleen werden in de andere studies een beperkt aantal factoren onderzocht en waren nog nooit eerder alle verschillende elementen in één studie geanalyseerd.

Uit de literatuur is bekend dat een langdurige blootstelling aan hoge cortisolspiegels een beschadiging van de hippocampus (hippocampusatrofie) kan geven. De hippocampus bevindt zich in de linker en rechter hersenhelft en is van belang is bij leren, geheugen en emotie. Ook heeft de hippocampus een remmende werking op de cortisolproductie. Bij hippocampusatrofie vindt er ten tijde van stress dus een beperkte remming op cortisolproductie plaats, waardoor hogere cortisolspiegels worden waargenomen. Hippocampusatrofie is aangetoond bij mensen met depressie en de ziekte van Cushing, en bij de oudere mens. Het gaat hierbij om situaties waarbij langdurige stress en verhoogde cortisolspiegels een rol spelen. Er werd verondersteld dat Menière patiënten een al langdurig bestaande verhoogde stressbelasting hebben, waarbij zij hippocampusatrofie zouden kunnen ontwikkelen. In **hoofdstuk 7** werd de grootte van de hippocampus van Menière patiënten vergeleken met die van gezonde proefpersonen van gelijk geslacht en gelijke leeftijd. Met behulp van MRI-scans kon de hippocampus worden afgetekend en de grootte worden berekend als maat voor de beschadiging c.q. atrofie van de

hippocampus. Het bleek dat de Menière-patiënten en gezonde proefpersonen een vergelijkbare grootte van de hippocampus hadden.

Concluderend kunnen we zeggen dat Menière-patiënten een afwijkend psychologisch profiel hebben ten opzichte van de algemene populatie, maar vergelijkbaar met het profiel van patiënten met andere chronische ziekten. De hogere cortisolspiegels bij Menière-patiënten impliceren een overstimulatie van het stresssysteem. Een effect van langdurige blootstelling aan hoge cortisolspiegels, te weten hippocampusatrofie, werd niet aangetoond. Hoe het afwijkende psychologische profiel en de hoge cortisolspiegels met de ziekte van Menière, het binnenoor en de binnenoorvloeistofhuishouding in relatie zouden kunnen staan, is nog onbekend.

Waar kan worden ingegrepen in de gesuggereerde vicieuze cirkel van klachten, hun effect op de mentale, lichamelijke en sociale toestand en vice versa? Allereerst, elke Menière-patiënt heeft individuele hulp nodig, afhankelijk van de ernst van de symptomen en de impact op het dagelijkse leven. Hoortoestellen en medicijnen kunnen hierbij de symptomen verlichten. Verder zou bij een groep patiënten psychosociale hulp van belang kunnen zijn. De copingstrategieën en psychopathologie (angst en depressie) kunnen door een psycholoog of psychiater worden behandeld. Uiteraard dient de impact van de ziekte op het dagelijkse leven (mentaal, lichamelijk en sociaal) te worden besproken en indien nodig behandeld. Menière-patiënten functioneren en voelen zich beter als ze met deze zaken worden geholpen, waardoor ze hun stressvolle ziekte beter aankunnen.

Dankwoord

Vanzelfsprekend was dit werk niet tot stand gekomen zonder de medewerking van anderen. Graag wil ik enkele personen in het bijzonder bedanken.

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