

Stress as a Trigger of Attacks in Menière's Disease. A Case-Crossover Study

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Background: Menière's disease is defined as the presence of recurrent, spontaneous episodic vertigo, hearing loss (HL), aural fullness, and tinnitus. The occurrence of attacks is unpredictable. The etiology is still unknown, but the disease has a pathologic correlate in hydropic distension of the endolymphatic system. Earlier studies have shown increased incidence of stress on the same day as vertigo attacks, but it has not been determined whether stress occurring on the day of the vertiginous episode came before or after the onset of the vertigo. **Methods:** A case-crossover study including 46 patients with active Menière's disease. **Main Outcome Measure:** Relative risks with 95% confidence intervals (CI). **Findings:** During the study period, 153 Menière's attacks were reported. Twenty-four (52%) of the 46 patients reported attacks. Twelve of the 153 (8%) attacks occurred within 3 hours after exposure to emotional stress. The relative risk of having an attack was 5.10 (95% CI 2.37–10.98) during 3 hours after being exposed to emotional stress. Twenty-nine percent of the patients with attacks had at least one attack after exposure to emotional stress. For mental stress, the relative risk was 4.16 (95% CI 1.46–11.83) and the hazard period 1 hour, but only five attacks were exposed. No excess risk was found after physical stress. **Interpretation:** Being exposed to emotional stress increases the risk of getting an attack of Menière's disease during the next hour, and the hazard period is possibly extended up to 3 hours. **Key Words:** Menière's disease, case-crossover, stress, triggers.

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INTRODUCTION

Menière's disease is a chronic non-life-threatening inner-ear disorder. It has been defined as the presence of

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recurrent, spontaneous episodic vertigo, hearing loss (HL), aural fullness, and tinnitus. It has a pathologic correlate in hydropic distension of the endolymphatic system, but the etiology is still unknown. The disease has a well-known natural course. In the early stage, symptoms occur episodically, followed by complete remission, but during the course of the disease, the hearing impairment progresses and becomes permanent, whereas the vertigo becomes less prominent after approximately 2 decades. The mean number of annual attacks has been reported to vary from 6 to 11. Recent studies¹ have shown that the disease may severely reduce the patients' quality of life, and one important factor is the unpredictability of the attacks.

The relationship between stress and Menière's disease attacks has been discussed in the literature.^{2,3} However, with the exception of case reports, only three studies of this association have been published.^{2,4,5} In all three studies, the temporal resolution in the information about stress exposure is too inexact to give information about whether stress on the day of the attack occurred before or after the onset of the attack. Although none of the studies actually conclude that stress precedes the attacks, this might well have been the case.

The case-crossover design is a new epidemiologic tool for studying the triggering of disease, offering more reliable evidence in relation to causal inference and also quantitative estimates of the increase in risk.⁶ The design was first used in studies of risk factors triggering myocardial infarction and has later been applied in studies of injuries and infectious diseases.⁷ The methodology can be used to study triggering factors of any event with acute onset (i.e., intermittent exposures with short induction times and transient effects). To our knowledge, no case-crossover study on Menière's disease has been published. The aims of this study were to determine whether emotional, mental, or physical stress might trigger attacks of Menière's disease.

MATERIALS AND METHODS

Meniere's disease patients

Patients with definite Menière's disease according to the guidelines for reporting results of treatment of Menière's disease by the American Academy of Otolaryngology/Head and Neck Surgery

(AAO/HNS)⁸ were recruited from the departments of otolaryngology and audiology in the Karolinska Hospital, Stockholm, Sweden. Patients who had had at least one attack during the last year were asked to participate. Sixty-three nonconsecutive patients were enrolled, and 46 (73%) of these participated throughout the study. Two patients discontinued because surgery was performed. One patient emigrated, 2 did not think the questions were relevant to their symptoms, and the remaining 12 patients discontinued for unspecified reasons. The 46 patients who completed the study participated for 7 to 21 months, with a mean time of 18.8 months.

Questionnaires

Three different questionnaires were constructed for the study and were distributed by mail. The "background questionnaire" concerned demographic and socioeconomic data and the Menière's disease history. The "control period questionnaire" explored the frequency of stress and other defined trigger factors during a period without relation to an attack. The "attack questionnaire" contained the same questions as the control period questionnaire but was filled in immediately after a Menière's disease attack. The time periods investigated were 48 hours before each point 0. The 0 points were defined as the minute the attack began in the attack questionnaire and the minute for starting writing the answers in the control period questionnaire. Stress was divided into emotional, mental, and physical stress, according to the definition used by Andersson and Yardley.⁹ The patients were asked to give the exact time of all episodes of stress during the 48 hours. A maximum of three different exposures for each kind of stress during each of the two 24 hour periods could be entered. The items concerning stress in the questionnaires are shown in Figure 1. The questionnaires also contained questions about other hypothetical triggers, but the results of this part of the study will be reported elsewhere.

Data Collection

After recruitment and informed consent, the patients received the background and control period questionnaires to answer at home. When these questionnaires were returned, the attack questionnaire was sent to the patient. The patients were instructed to answer the attack questionnaire and return it as fast as possible when an attack had occurred. Immediately after the research assistant had received an attack questionnaire, a new one was sent to the patient, so that the patient always had attack questionnaires ready at home to fill in and return after each attack. During the study period, it was left to the patients themselves to decide whether an attack had occurred or not. Only patients with definite Menière's disease were included, and we judged that the patients were properly informed of the disease and capable to recognize an attack. The patients also received control period questionnaires to fill in on a given date 22 days after every attack (if a new attack had not occurred within 72 hours before the given date). Further, control period questionnaires were distributed to all study patients on randomly chosen control days. At the closing of the study, a last control period questionnaire was distributed. An example of the data collection from an individual patient is illustrated in Figure 2.

If answers were ambiguous, the research assistant contacted the patients by telephone. The research protocol was approved by the Ethical Committee of the Karolinska Hospital.

Case-Crossover Design

The case-crossover design⁶ assesses the change in the risk of an acute event during a brief period after exposure to a hypothetical trigger. The design resembles a retrospective, nonrandomized crossover study. It is based on the assumption that most

Here are some questions regarding stress. We have tried to differ between different kinds of stress. If you find that more than one answer is relevant: answer more than one question! It might be particularly hard to differ between mental and emotional stress.

- Mental stress:** Something that makes you mentally exhausted or worn out. It might be a task at the limit of your capacity – as a math test at school.
- Emotional stress:** Something that makes you nervous, worried or anxiety-ridden. It might be a positive event – to be nervous before making a speech or applying for a new job.
- Physical stress:** Something that demands your physical exertion to be able to manage in time.

As an example we can choose a man being late for an important meeting. He is worried that he won't catch the bus (emotionally stressed). Then he runs to be able to catch the bus (physically stressed), and when he sits on the bus he tries to recapitulate the speech he is going to make at the meeting (mentally stressed).

If you at any time the two last days have experienced stress, then note the time the stress began as precisely as you can remember.

During the day of attack or the day before, did you feel mentally stressed?

- No, not at all
- Yes, at the following times:

During the day of attack

Time _____

Time _____

Time _____

During the day before attack

Time _____

Time _____

Time _____

Fig. 1. The first page of the part of the questionnaire that concerns stress. In the following pages (not shown here), items concerning emotional and physical stress are entered.

people in their daily life cross over between short periods of exposure to hypothetical triggers and much longer periods of unexposed time. The period during which the trigger increases the risk of the event is called the hazard period. Three types of information are needed: the time of disease onset; whether the trigger was present during a defined period immediately before onset (the case window); and the frequency of trigger exposure during a control period (the control window). The frequency of exposure in the case window is compared with the frequency of exposure in one or several control windows supplied by the same patient. Each patient serves as his or her own control, thus demanding a matched analysis (self-matching). The case and control windows are arbitrary units of observation. These are the windows one chooses to look into when one is stating a hypothesis, designing questions, or exploring the data. The length of the case and the control windows should be equal and correspond with the hazard period, and this is empirically established during the analytical process. In this study, the case and the control windows were also matched regarding the time of day to avoid bias.

To test the validity we chose three different ways of defining the control information from available control windows:

1. In our first analyses, we used the full information from the study by comparing each case window from every attack with

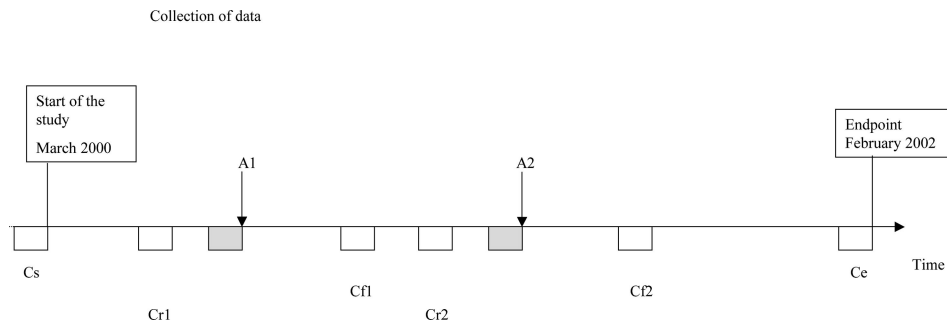


Fig. 2. Data collection from one individual patient with two reported attacks. Cs = starting point of the study when a control questionnaire was answered. A1 and A2 = onset of consecutive attacks of Menière's disease. An attack questionnaire was answered after each attack. Cr1-Cr2 = randomly chosen control periods, when control questionnaires were answered. Cf1-Cf2 = a date 22 days after an attack of Menière's disease when follow-up control questionnaires were answered. Ce = end of the study when a final control questionnaire was answered. The boxes illustrate the 48 hours (before the attack, respectively, before filling in the control questionnaire) that are covered by the questionnaires. Three different ways of selecting control windows were used: 1) 1:2 matched pair analysis: control windows were obtained from the two control questionnaires before and after each attack (in this case for attack A1 windows from the control questionnaires Cr1 and Cf1); 2) 1:n matched pair analysis: for each attack, control windows were obtained from all control questionnaires available for the patient (different numbers for each patient) (in this case for attack A1 control questionnaires Cs, Cr1, Cr2, Cf1, Cf2, and Ce); 3) an analysis based on the usual frequency approach: the usual frequency of exposure was calculated for each attack from all available control questionnaires. The 24 hours before the filling in were used as the control window. It was expressed as an expected exposure odds based on the proportion exposed time of the total time.

all control windows from all available control questionnaires of the same patient (1:n matched pair analysis).

2. We also conducted an analysis in which the case window of each attack was compared with a control window from the control questionnaire answered before the attack and a control window from the control questionnaire answered some time after the attack (1:2 matched pair analysis).

3. Finally, we used the so-called usual frequency approach in which we compared the observed exposure odds in the case window with an expected exposure odds, calculated from all available control questionnaires of the same patient. A usual frequency of trigger exposure was derived from all episodes of exposure during the 24 hours before answering the questionnaires. The expected exposure odds were based on the proportion of exposed time of the total time covered by the control questionnaires.

Statistical Analysis

An episode of stress was assumed to have a short duration and occur infrequently enough for hazard periods not to overlap. The matched pair approach was analyzed with conditional logistic regression.^{6,10} The usual frequency approach was analyzed with standard Mantel-Haenzel methods⁶ for follow-up studies with sparse data in each stratum. The effect was measured as a relative risk, estimated by the average incidence rate ratio (the ratio between the observed and the expected exposure odds). The length of the hazard period was investigated by separate analyses of different intervals covering the assumed induction period and beyond, controlling for subsequent exposure. Calculations were made with SAS version 8.1 (Cary, NC).

RESULTS

The material comprises 17 men and 29 women (Table I). Mean age was 53 (24–75) years. Almost all patients had some kind of medical treatment, most commonly diuretics or betahistine combined with antiemetics used in acute attacks. Two of the patients had been subjected to endolymphatic sac surgery (ELS) before the study.

During the study period, 24 of the 46 (52%) patients reported a total of 153 attacks. The mean number of attacks per patient was 3.3 (range 0–29). The total number

TABLE I.
Personal Characteristics of the Sample.

	Total (n = 46)	Attacks (n = 24)	No Attacks (n = 22)
Age			
Mean	53	55	50
(Range)	(24–75)	(27–71)	(24–75)
Sex (%)			
Men	17 (37)	6 (25)	11 (50)
Women	29 (63)	18 (75)	11 (50)
Family (%)			
Married	30 (65)	15 (62)	15 (68)
Single	16 (35)	9 (38)	7 (32)
Working situation (%)			
Active work	23 (50)	11 (46)	12 (55)
Sick leave	4 (9)	4 (17)	0
Retired	8 (17)	4 (17)	4 (18)
Other	11 (24)	5 (21)	6 (27)
Duration of disease			
Mean	11 years	11 years	7 years
(Range)	(1–45)	(1–45)	(1–44)

of control questionnaires collected from the patients having at least one attack was 259 (mean 10.8 questionnaires per patient, range 4–29).

The length of the hazard period after an episode of stress was investigated in separate analyses of each of the 6 hours before the attacks (Table II). The increased risk from emotional stress reached a peak value during the first hour, but it appeared to remain elevated for 3 hours. Twelve of the 153 (8%) attacks were preceded by emotional stress 0 to 3 hours earlier. These 12 attacks were distributed among 7 patients (29% of all patients with attacks), and this group of patients had had between 4 to

TABLE II.
Relative Risk (RR) of having an Attack of Menière's Disease after being Exposed to Emotional, Mental, or Physical Stress.

Hazard Period	Emotional Stress RR (CI)	Number of Exposed Attacks	Mental Stress RR (CI)	Number of Exposed Attacks	Physical Stress RR (CI)	Number of Exposed Attacks
0–60 minutes	6.61 (2.70–16.17)	8	4.16 (1.47–11.84)	5	—	0
60–120 minutes	1.73 (0.36–8.42)	3	—	0	2.64 (0.24–29.25)	1
120–180 minutes	2.78 (0.53–14.5)	3	—	0	0	0
180–240 minutes	1.14 (0.13–9.69)	1	—	0	0	0
240–300 minutes	0.88 (0.11–7.01)	1	—	0	—	0
300–360 minutes	—	0	—	0	—	0

Multiple control periods selected from the same patient and matched according to time of day of the attack (CI = 95% confidence interval).

29 attacks in total. Five of the seven patients had only one exposed attack, but the patient having experienced 29 attacks reported that 4 of those had been preceded by emotional stress. None of the 12 patients in the study who only reported one to three attacks during the study period had had an attack after exposure to emotional stress.

The hazard period for mental stress was just 1 hour (Table II), and mental stress was reported to have preceded five (3%) of the attacks by less than an hour. All of these five attacks were in different patients. Two of the five attacks occurred after exposure to both mental and emotional stress. Physical stress had preceded only one of the attacks. This attack had also been exposed to emotional stress.

Table III shows that the relative risk of having an attack of Menière's disease was 5.10 (95% confidence interval [CI] 2.37–10.98) during a period of 3 hours after being exposed to emotional stress in the analysis using information from control windows in all available control questionnaires. The relative risk of having a Menière's attack was 4.16 (95% CI 1.46–11.83) during the first hour after being exposed to mental stress. Physical stress was not found to trigger Menière's attacks (Table III). When testing two other kinds of control information, the usual

frequency and two control periods (before and after the attack), we saw that they did not result in substantially changed point estimates of the relative risk.

DISCUSSION

Our study demonstrates that emotional stress increases the risk of having Menière's attacks, and it suggests that the hazard period could be extended to the first 3 hours after stress exposure. The relative risk of triggering an attack of Menière's disease was also increased after mental stress, but it was not possible to demonstrate any increase in risk after physical stress. This finding is supported by the patients' own notion of triggering factors. Sixty-one percent of the 46 patients in the study spontaneously mentioned "stress" when asked about potential triggers they were aware of. However, exposed attacks were found in only less than a third of the patients and in approximately one tenth of the attacks. This may be caused by avoidance of stressful situations by this group of patients, but only 15% of the patients actually reported that they tried to avoid stressful situations, despite the fact that they suspected triggering effects.

TABLE III.
Relative Risk (RR) of having an Attack of Menière's Disease after being Exposed to Emotional, Mental, or Physical Stress, Analysed with Different Approaches of Sampling Control Information.

Type of Stress Exposure	Hazard Period	Number of Exposed Attacks	Matched-Pair, 1:2	Matched-Pair, 1:n	Usual Frequency
			RR (CI)	RR (CI)	RR (CI)
Emotional stress	0–180 minutes	12	5.31	5.10	3.81
			(1.7–16.7)	(2.37–10.98)	(2.20–6.62)
Mental stress	0–60 minutes	5	9.99	4.16	5.27
			(1.17–11.83)	(1.46–11.83)	(2.17–12.8)
Physical stress	0–120 minutes	1	1.00	0.80	1.19
			(0.09–11.0)	(0.10–6.74)	(0.17–8.19)

CI = 95% confidence interval; n = number of control periods available for each patient.

Limitations of this Study

Recall bias is a potential limitation in case-crossover studies because of the different ways of obtaining the case and the control information. To avoid differential memory problems, we used control information from separate days with identical questions, asking for information 48 hours back. Furthermore, despite different ways of sampling the control information, the results from the analyses were quite similar. We have also used the elaborate data collection method in this study to examine the importance of differential exposure misclassification.¹¹ Comparisons with control-crossover analyses showed that neither outcome-dependent misclassification nor differential misclassification of exposure caused by fading memory over time seemed to be a major problem.

The design automatically controls for confounding from ordinary long-term risk factors because the analyses are individually matched. Confounding from other triggers is difficult to ascertain because few risk factors triggering attacks of Menière's disease are identified.

The fact that 3 of the 15 attacks exposed to stress were preceded by more than one of the three stress dimensions we asked for should probably not be understood as potential confounding but as conceptual and methodological ambiguity regarding stress perception. If the two patients who reported emotional and mental stress simultaneously during the 0 to 60 minutes before the attack were omitted, the relative risk for emotional stress would be 4.75 (1.78–16.68). If you omit the patient who reported both emotional and physical stress during the period 60 to 120 minutes before the attack, the relative risk for emotional stress would be 1.41 (0.16–12.35). It therefore seems fair to conclude that the emotional aspect of the stressors was the most important.

Menière's patients were recruited by clinicians unaware of the hypotheses in the study. Therefore, bias from exposure-dependent selection should not be a problem. The questionnaires contained questions on a number of potential triggers, and we did not have any indication that nonparticipation of the patients depended on earlier stress exposure and its association with attacks. Another form of self-selection is possible in that patients susceptible to the triggering effects of stress try to avoid stress and therefore experience no attacks. However, this form of selection does not bias the results; it only decreases the power of the study. The unit of analysis is the attack, but the attacks are not totally independent because they cluster in patients. The exposed attacks are, as shown earlier, broadly distributed among the patients and not confined to just a few special cases. This hierarchical nature of the data implies a slight underestimation of the variance when using ordinary logistic regression methods, but because the lower bounds of the CIs for the main results are well above unity, this should not be problem.

Relation to Previous Studies

In a study by Crary and Wexler,² Menière's patients kept diaries to record stress and vertigo. The presence of stress within 5 days before the onset of vertigo was compared with stress the day vertigo occurred and with stress identified within 5 days after the onset of vertigo. The

results show that most episodes of vertigo occurred in the absence of stress. Their data also show that stress within 5 days before as well as 5 days after stress was almost equal to the stress that occurred on the same day as vertigo. However, because of the different time spans, these results can be interpreted as such that the occurrence of stress the same day as the vertigo was in fact was five times higher. Andersson et al.'s⁴ time-series analysis also shows an increased incidence of stress on the same day as vertigo. Sawada et al.⁵ used a retrospective stress questionnaire in a study on antidiuretic hormone (ADH) and Menière's disease. They reported that 78% of 46 cases were conscious of stress before an attack of vertigo, but no information about the time span between stress exposure and the attack was presented.

Relationships between stress and attacks in other diseases have been demonstrated. In a recent study of patients with multiple sclerosis, the experience of at least one stressful event during a period of 4 weeks was associated with double risk of an exacerbation within the next week.¹²

Possible Mechanisms

Literature clearly indicates that the effect of stress on Menière's disease is not a psychologic by-product, but that stress might very well cause inner ear pathology.³ The mechanism behind the relation between stress and Menière's attacks might be mediated through the hypothalamus. Stress leads to an increased secretion of the adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland followed by an increased adrenocortical production of glucocorticoids (cortisol and corticosterone) and mineral corticoids (aldosterone). In animal experiments, the relationship between circulating adrenal steroids and activity in the inner ear has been showed,¹³ but so far, this has not been confirmed in clinical studies. Aldosterone levels have been studied,¹⁴ but the Menière's patients' plasma levels of aldosterone were not elevated compared with normal subjects. The reason for this might have been that the samples were collected during hospital admission, and none of the patients had an attack during that period. In a recent study, serum ADH levels were studied in a group of patients with unilateral Menière's disease. The samples were drawn within 1 week of an acute episode of vertigo. However, no significant elevation of ADH levels was demonstrated.¹⁵

The present study is the first to be able to demonstrate emotional stress as a trigger of Menière's disease attacks. Further studies on the aldosterone levels within 24 hours after a Menière's attack, as well as ADH levels in cases of bilateral disease, might contribute to better understanding of the mechanisms behind attacks of Menière's disease.

CONCLUSION

Being exposed to emotional stress increases the risk of getting an attack of Menière's disease during the next hour, and the hazard period is possibly extended up to 3 hours. The impact of mental stress is less clear. Physical stress was not found to trigger attacks of Menière's disease.

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