Remission of chronic headache: An 11-year follow-up study. Data from the Nord-Trøndelag Health Surveys 1995–1997 and 2006–2008

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Objectives: To estimate remission rates of chronic headache (CH) and predictors of remission.

Methods In this longitudinal population-based cohort study, we used validated headache questionnaire data from the second (1995-1997, baseline; n=51,856 aged ≥ 20 years, response rate: 55%) and third wave (2006-2008, follow-up, response rate: 42%) of the Nord-Trøndelag Health Study. CH was defined as ≥ 15 headache days/months during the last year. CH remission was defined as headache less than 15 days/month at follow-up. Potential predictors of remission were evaluated using logistic regression.

Results At baseline, 1266 (2.4%) participants reported CH. Of these, 605 (48%) answered headache questions at follow-up. Remission was observed in 452 (74.7%), the proportion being almost identical in men and women (74.4% vs. 74.9, p=0.92). In analyses adjusting for age, gender and education level, remission at follow-up was more than two times more likely among individuals without medication overuse headache (OR=2.4, 95% CI 1.7-3.6) and without chronic musculoskeletal complaints (OR=2.9, 95% CI 1.5-5.0) at baseline.

Conclusions In this longitudinal population-based cohort study three-quarters of CH participants remitted from CH. Remission was associated with no medication overuse headache and no chronic musculoskeletal complaints at baseline.

Introduction

2-5% of adults in the general population have chronic headache (CH) defined as headache on 15 days or more per month for at least 3 months (1-9). CH has a huge impact on quality of life and is responsible for much sick leave (10-12). 1-2% of adults (i.e. approximately 50% of persons with CH) have medication-overuse headache (MOH) (2, 3, 5, 9, 11, 13). Frequent use of analgesics is an important risk factor of CH (13, 14), and several other risk factors for CH have also been identified (14, 15).

To optimize treatment and better understand the pathophysiology of CH, it is important to identify risk factors as well as protective factors against CH (14). However, until now, relatively few prospective population-based studies have evaluated remission rate (3, 5, 16-21) and predictors of remission of CH (5, 20, 21).

We report here an analysis of historical data collected from a large population with follow-up after approximately 11 years. Our purpose was to estimate remission rates of chronic headache (CH) and predictors of remission.

Methods

Study design

This is a longitudinal cohort study utilizing historical data from the Nord-Trøndelag Health (HUNT) Study.

The HUNT study

The HUNT Study is a longitudinal cohort study in which all inhabitants ≥ 20 years old in Nord-Trøndelag have been invited to participate. Subjects were examined three times; 1984 to 1986 (HUNT1), 1995 to 1997 (HUNT2) and 2006 to 2008 (HUNT3)

(22). The two last surveys covered many health-related items in two different questionnaires (Q1 and Q2), and the participants were also invited to clinical consultations which included non-fasting blood samples and measurements of blood pressure, height and weight (22).

HUNT2

Among a wide range of topics of HUNT2 were questionnaire-based information of education, smoking, physical activity, depression measured by the Hospital Anxiety and Depression Scale (HADS) (14, 23), and chronic musculoskeletal complaints (CMSCs) (14, 23). Individuals who answered “yes” to the question “During the last year, have you had pain and/or stiffness in your muscles and/or joints that has lasted for at least 3 consecutive months?" were defined as having CMSCs. Q2 included a modified Norwegian version of the CAGE alcohol screening questionnaire. In Q2 participants were also asked whether, during the last 12 months, they had used medication (for any condition) of any type daily or almost daily. Those responding positively were asked whether, and for how many months, they had taken analgesics (for any condition), either prescription or over-the-counter (OCT) drugs (14). They were separately asked whether, and for how many months, they had taken tranquilizers and/or sleep-inducing medication (14). In addition, Q2 included two items on problems with onset and/or maintenance of sleep during the previous month, and an insomnia score was computed by summing the scores of these two questions. Those with a score ≤1 were defined as insomnia-free, and those with a score of ≥4 as having severe insomnia (14).

Headache classification based on HUNT2 and HUNT3

The headache questions in HUNT2 and HUNT3 were designed mainly to determine

whether the participants suffered from headache, the frequency of headache, and to diagnose migraine and medication overuse headache (MOH). More details of the headache questionnaire in HUNT2 and HUNT3 have been published elsewhere (4, 9, 24, 25). Both HUNT2 and HUNT3 questionnaires included the screening question "Have you suffered from headache during the last 12 months?" In HUNT2, the question regarding headache frequency during the last year had three response options; less than 7 days/month, 7-14 days/month, or more than 14 days/month. CH was defined as headache occurring on ≥15 days/month during the last year. In HUNT2 modified ICHD-I diagnostic criteria of migraine were used (24). Headache that did not satisfy the criteria of migraine was classified as non-migrainous headache (mutually exclusive). Medication overuse headache (MOH) was defined as CH occurring in association with use of analgesics daily or almost daily for ≥1 month during the previous 12 months (13, 14).

In HUNT3, the question about headache frequency had four response options; less than 1 day/month, 1-7 days/month, 7-14 days/month, or more than 14 days/month. CH was defined as headache occurring on ≥15 days/month during the last year (as in HUNT2), whereas remission was defined as no headache or headache less than 15 days/month in HUNT3 in those who had CH in HUNT2.

The validity of the diagnostic criteria used in HUNT2 and HUNT3 has been reported previously (23, 24). In HUNT2 the questionnaire-based diagnosis of CH was made with a sensitivity of 38%, specificity of 97%, and kappa value of 0.44 (95% CI 0.21-0.67) (24). For migraine, sensitivity was 69% and specificity 89% (kappa value 0.59, 95% CI 0.47-0.71); and for non-migraineurs, the sensitivity was 61%, and specificity 81% (kappa 0.43, 95CI 0.29-0.57). In HUNT3, the diagnosis of CH was made with a sensitivity of 69%, specificity of ≥99%, and kappa value of 0.75 (95% CI 95% CI 0.56-0.94) (25).

Study participants

In HUNT2, 65,237 persons out of 93,898 invited (70%) participated, and 51,856 (55%) of them indicated whether they suffered from headache or not. In HUNT3 93,860 persons were invited, whereof 50,807 (54%) participated, and 39,690 of them (42%) answered the headache questions. Among the 65,237 persons who participated in HUNT 2, 8,545 had died and 4,357 moved out of the county during the period before HUNT3.

A total of 37,061 persons participated in both HUNT2 and HUNT3, and 26,197 participants answered questions regarding headache in both HUNT2 and HUNT3 (Figure 1).

The present study is based on individuals who reported CH in HUNT2, and who also responded to the headache questions in HUNT3.

Statistical analysis

Differences between responders and non-responders to the headache questions in HUNT3 were tested with one-way analysis-of-variance for continuous variables, and with Chi-squared test for categorical variables. The level of significance was set at $p<0.05$.

In the population with CH at baseline, we evaluated the relative influence of baseline factors on the occurrence of remission by the time of HUNT3 by multivariate analyses using logistic regression with 95% confidence intervals (CIs). The baseline factors included demographic variables (age, education, gender); headache diagnoses; self-reported complaints (CMSC, gastrointestinal complains, insomnia, and anxiety and depression), measured variables (body mass index (BMI), and systolic blood pressure (BP); lifestyle factors (smoking, alcohol use, and physical activity); and other

health-related information (use of medication and sick leave). The multivariate analyses were evaluated by a preplanned strategy based on our previous findings (14, 23). Because over-adjustment bias is a potential problem in epidemiological studies (26), adjustment was made for age (continuous variable), gender and education level in all analyses. Thus, because all different baseline factors were evaluated in a similar way, it may be possible to evaluate the relative impact of each factor by inspection of estimated odds ratio (OR). Subjects with incomplete data regarding education level (n=12) were included in the analysis to reduce the impact of possible bias.

Supplementary analyses were made to evaluate alternative definitions of remission. Firstly, remission was defined as headache less than 7 days/month, omitting individuals with 7-14 headache days/month from the analyses. Secondly, we also subdivided persons with remission into two subgroups; those with "excellent remission" defined as headache less than 1 days/month at follow-up, and those with "partial remission" defined as headache 1-14 days/month at follow-up.

Data analyses were performed with the IBM Statistical Package for the Social Sciences, version 22 (SPSS, Chicago, Illinois, USA)

Ethics

This study was approved by the Regional Committee for Ethics in Medical Research, and the HUNT Study was in addition approved by the Norwegian Data Inspectorate.

Results

Of the 51,856 individuals who answered the headache questions in HUNT2, 1266 (2.4%) reported CH. Among these, 605 persons also responded to the headache questions in HUNT3 (48%). Responders were younger, more educated, had lower systolic blood pressure, lower BMI, and were also less likely to use sleep medication

and tranquilizers than the non-responders (n=661) (Table 1). On the other hand, the responders were more likely to report sick leave more than 2 weeks the previous year than the non-responders.

Remission in HUNT3

Remission from CH was observed in 452 persons in HUNT3 (74.7%), the proportion being almost identical in men and women (74.4% vs. 74.9, p=0.92). Remission was more likely among individuals without MOH (81.5% vs. 65.4, p<0.001) and CMSCs (86.6% vs. 71.1, p<0.001) in HUNT2.

Among the 452 persons with remission at follow-up, 177 (39%) had "excellent remission" (i.e. less than 1 headache day/month), whereas 275 (61%) reported "partial remission" (i.e.1-14 headache day/month).

Predictors of remission

In crude analyses remission in HUNT3 was more likely among individuals without migraine, MOH, CMSCs, or daily use of tranquilizers at baseline in HUNT2 (Table 2). No significant association with remission was found e.g. regarding gender, age, level of education, life style factors, anxiety and depression measured by HADS score, or insomnia score (Table 2).

As demonstrated in Table 2, supplementary analyses adjusting for age, gender and education, did not changed the ORs substantially. Thus, remission was still more than twice as likely among individuals without MOH (OR=2.4, 95% CI 1.7-3.6) or CMSCs (OR=2.9, 95% CI 1.5-5.0) at baseline. However, in the adjusted analyses we failed to find significant association with remission for individuals without daily or nearly daily use of tranquilizers (OR=2.0, 95% CI 0.9-4.3).

The impact of headache frequency at follow-up was evaluated in supplementary analyses. First, eliminating the 94 individuals with 7-14 headache days/month from the remission group increased the strength of the association to being without MOH (OR=2.9, 95% CI 2.0-4.4) and CMSCs (OR=3.3, 95% CI 1.9-5.9) at baseline. In Table 3, adjusted analyses are reported for persons with "partial remission" defined as headache 1-14 days/month, and "excellent remission" defined as headache less than 1 days/moth at follow-up. For both subtypes remission was significantly more likely among individuals without MOH and CMSCs. Excellent remission was also more likely for individuals with non-migrainous headache (OR=3.2, 95% CI 1.8-5.7), low insomnia score (OR 3.8, 95% CI 1.8-8.1), being without gastrointestinal complaints (1.8, 95% CI 1.1-3.0), and not using sleep-inducing medication (OR 4.6, 95% CI 1.5-13.7) or tranquilizers (OR 7.6, 95% CI 2.4-24.5) at baseline.

4. Discussion

In this population-based 11-year follow-up study, three-quarters of CH participants remitted from CH. Remission at follow-up was more likely among individuals without MOH and CMSCs at baseline.

As demonstrated in Table 4, the proportion of individuals with remission from CH in other population-based studies have varied between 26% and 88% (3, 5, 15-20) (Table 4). However, direct comparisons between these studies should be done with caution because of methodological differences regarding included age groups, follow-up time, number of respondents, and participation rate (17, 20).

Criticism has been raised to studies evaluating remission between two points in time because of random variation in headache activity over time and the potential of regression to the mean (27-29). Based on mathematical simulation, illusory

remission rates of 10.3% to 23.5% can been expected simply due to random variations of headache frequency (28). In order to reflect stable headache complaints a long recall period for headache complaints is recommended, reducing the risk of temporal sampling error (27). In the present study, we used identical headache screening question at baseline and follow-up, asking for headache complaints during last year, which accords with the ICHD-3β, recommending that patients receive a diagnosis according to the headache type they have presented during the last year (30). In addition, the phrasing of the question about headache frequency was similar. The impact of follow-up time on random variation of headache frequency is not stated (27-29), but most likely, the risk of random variation is lower in studies with long follow-up time.

In our previous 11-year follow-up study evaluating risk factors for developing CH, the strongest associations were found for headache frequency (OR=10.9), use of transquilizers (OR=2.4), and having the combination of CMSCs, gastrointestinal complaints and HADS score > 11 (OR= 2.8) (14). In the present study, we found that remission at follow-up consistently was more likely among individuals without MOH and CMSCs at baseline. In accordance, remission was associated with no medication overuse in a recent population-based study from Germany (21). Furthermore, in a systematic review of prognostic factors for CH, medication overuse was highlighted to predict poor prognosis (31).

In two previous studies, lower headache frequency at baseline has been associated with remission (20, 21). In the present study headache frequency > 14/days/month was the upper response option at baseline in HUNT2. Consequently, we could not evaluate the influence of headache frequency at baseline as predictor of remission. However, in supplementary analyses we found that being without MOH

and CMSCs at baseline was associated both with excellent remission defined as <1 headache days/month) and partial remission defined as 1-14 headache days/month.

Other studies have reported that remission has been associated with e.g. younger age, higher education (16), and female sex (21). In accordance, in our previous study, all these factors were more likely among individuals who developed CH (14). However, in the present study no consistent association with remission was found for young age, gender, migraine , high education level, or other modifiable lifestyle factors.

Interpretation

Based on our main results, one may speculate whether the degree of central sensitisation is the main determinant of long-term prognosis of CH. Central sensitisation is associated with MOH (32) and probably also with CMSCs, most likely in the widespread form of CMSCs (33, 34). Thus, if true, the results suggest that remission is more likely in the absence of central sensitisation. It may be of relevance that absence of allodynia has been shown to be associated with remission (20). Although it is not definitely known whether MOH and CMSC are cause or consequence of central sensitization, measures to avoid MOH and to treat CMSCs may be of great importance in preventing the risk and persistence of CH.

We have previously reported an increasing risk of chronic daily headache and MOH in those less than 50 years of age. Correspondingly, in the present study excellent remission tended to be more likely among those aged ≥ 50 years. This may reflect the natural course of headache, because we know that headache prevalence decreases with increasing age (4, 9).

Strengths and weaknesses

Major strengths of this study are the large and unselected population, the prospective design with a long follow-up of 11 years, the use of validated headache diagnoses and data on many potential predictors of remission. The sample size of patients with CH is larger than most of other studies (3, 5, 16-21) and provide enough power to test several predefined factors.

Some limitations should be considered. First, headache diagnoses were based on responses to a questionnaire and not on clinical diagnoses. However, in the present study, we focused on CH regardless of headache type, making the potential problem with co-existence of several headache diagnoses less. The validity of the CH and MOH diagnosis has nonetheless been demonstrated to be good in HUNT2. Second there was a relatively low participation rate at baseline in HUNT2 (56%), and only 48% of persons with CH in HUNT2 (63% of eligible subjects in HUNT3) responded to the headache questions in HUNT3. Thus, a selection bias cannot be ruled out, but the wide scope of the HUNT studies makes bias with specific relevance to headache less likely.

In conclusion, in this longitudinal population-based cohort study three-quarters of CH participants remitted from CH. Remission was associated with no MOH and no CMSC at baseline.

Clinical implications

- Three-quarters of participants with chronic headache remitted from chronic headache during 11-year follow-up.
- Remission from chronic headache was highest in patients without medication-overuse headache and without chronic musculoskeletal complaints at baseline.
- The present results may be of relevance for the ongoing debate about pathophysiology of chronic headache

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