PAINFUL MUSCULOSCELETAL DISORDERS AND DEPRESSION AMONG WORKING AGED MIGRAINEURS

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Running title:

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ABSTRACT

Objective: Musculoskeletal disorders and depression are common among migraineurs. The aim of our study is to evaluate the occurrence of these disorders among working aged migraineurs.

Material and Methods: The risk for fibromyalgia, rheumatoid arthritis (RA), osteoarthrosis (OA), sciatic syndrome and the occurrence of depression were studied among cases who reported about these conditions and migraine in working aged Finnish population in The Health and Social Support Study (HeSSup) based on postal questionnaire in 2012. Group differences were tested by Chi-square test. Odds ratios (ORs with 95% CI) adjusted for age, gender, education level and depression were calculated with logistic regression analysis.

Results: Total of 1505 migraineurs (13%) and 8092 controls were included among the 11 596 responders in 2012. Age and gender adjusted OR's, 2.37 (95% CI 1.81 − 3.09) for fibromyalgia, 1.46 (1.10 − 1.95) for RA, 1.58 (1.38 − 1.80) for OA and 2.09 (1.84 − 2.37) for sciatic syndrome were significant. At least moderate depression was more common among migraineurs (7.3%) than among controls (3.4%) ($p < 0.001$).

Conclusion: Recognition of comorbid musculoskeletal disorders and mood disorders among migraineurs need targeted outreach in working aged population. The acute and preventive treatments to control for neuronal sensitization in migraine and comorbid pain disorders may benefit of individual treatment plan and tailored use of antidepressants.

Key words: Migraine – Comorbidity – Musculoskeletal disorders – Fibromyalgia

1 Introduction

Migraine is a common disorder in working aged population and the occurrence peaks in the late teens and around 50 years of age. [1] The sociodemographic correlates have been stable for over 50 years and across studies the estimates of the 12-month prevalence yield a total of 18.5%. [1]

Pathophysiology of migraine is complex [2], including neuroinflammatory mechanisms and both peripheral and central sensitization. [3] Migraine is among the rare neurological conditions accompanying fibromyalgia. [4] The reported comorbidity is high and associates with anxiety, depression, and insomnia. [5,6] Pathophysiology linking these painful disorders remains poorly understood; suggested mechanisms include involvement of peripheral and central sensitization disturbances. [3,7] Neural sensitization has also been shown in other comorbid painful conditions in migraine, such as rheumatoid arthritis (RA) and osteoarthritis (OA) [8,9] .

The aim of our study is to evaluate the occurrence and risk of some comorbid and common painful musculoskeletal disorders such as fibromyalgia, osteoarthrosis, sciatic syndrome, rheumatoid arthritis and depression among migraineurs in a working aged population in Finland. The aim is relevant as depression and the pain conditions under study are reported to be common disabling conditions in the workforce. [10,11]

Material and methods

Health and Social Support Study

The Health and Social Support Study (HeSSup) is a prospective follow-up study on psychosocial health of Finnish working-age population. The Turku University Central Hospital Ethics Committee approved the study. Respondents' permission was also requested to collate the information with official registers. The questionnaire screens the self-reported health related factors and disturbances. It includes 33 items and several common disorders among working aged population. First postal questionnaire was sent in 1998 to a random sample of 64 797 individuals drawn from the Finnish Population Register, followed by follow-up questionnaires in 2003 and 2012 sent to those responding to the first HeSSup survey, excluding those who had died, moved abroad or whose present addresses were unknown. According to the non-response analysis in 1998 respondents and non-respondents were comparable with respect to the most important demographic variables including gender and age distribution [12] and the differences in physical health between participants and the general population were minor. [12,13]

Algorithm of responder distribution in the three surveys is shown in Figure 1. In 1998 altogether 25 895 responded and the respond rate was 40%. These participants were inquired whether a doctor had told them they have or have had migraine. Of them 25 691 (99.2%) responded to the question on migraine.

The International Headache Society International Classification of Headache Disorders criteria for migraine diagnosis are followed among doctors in Finland. Triptans are used and reimbursed as acute migraine treatment in Finland from 1993. The registers of The Finnish Social Insurance Institution (SII) were used to study the prescribed and reimbursed triptan medications between

1998 and 2013. A search for prescribed medications was carried out by linking the HeSSup and SII registers using the personal identification code given to all Finnish citizens as a key.

The final sample on included cases comprises those individuals who had reported migraine in all three questionnaires (N=11 596) and they were regarded as migraineurs. The respective control group includes cases who have responded negatively to all inquiries on migraine (N=8 176). Cases with triptan prescription in the control group, 84 individuals, were excluded as no self-reported migraine was recorded. The final control group thus comprised 8 092 individuals.

For the purposes in this survey we focused on following comorbid items in the questionnaire: painful disorders such as fibromyalgia, RA, OA and sciatic syndrome. We did not include less common syndromes in our estimates (e.g. myofascial pain syndromes, temporomandibular disorders) or other musculoskeletal disorders (e.g. traumatic or other neck or back pain). Respondents were inquired whether a doctor had told them they have or have had these conditions. Those who reported about these conditions in 2012 were included in the analyses. Severity or pain score was not assessed.

Beck's depression inventory (BDI) scores were included and assessed. If a responder scored more than 18 points in BDI he/she was considered as having at least moderate depression. Information on marital status and education was collected and assessed as lower or higher according to having passed the Finnish matriculation examination.

Data were analyzed using the IBM SPSS Statistics version 23. Statistical significances were tested by chi-square test. Odds ratios (ORs with 95% CI) for migraine as dependent and other painful

disorders as covariates were calculated with separate logistic regression analyses. These analyses were first calculated with no adjusting (Model 1) and then with adjusting for age and gender (Model 2). In Model 3 the calculations were made with adjusting for both age and gender and education (matriculation examination). Finally, in Model 4 the calculations were made with adjusting for age, gender, education and at least moderate depression (Beck > 18).

Results

Migraine was reported by 1 505 (13%) cases versus the 8 092 cases who did not report migraine nor had been prescribed for any triptan medication among the included 11 596 responders in 2012. The female (77.4%) to male ratio was 1228/277 in the migraine group and 4581/3 511 (56.6%) in the control group. Majority of all migraine cases, 32.2 %, belonged to the oldest and 20.2 % to the youngest age group. (Table 1.)

The self-reported severity of depression by BDI scores was higher and statistically different between migraineurs and controls, ($p<0.001$). The difference in mean scores of BDIs among migraineurs (7.1 points) and controls (5.4) and at least moderate depression (Beck >18) was reported by 7.3% and 3.4% respectively ($p<0.001$). Depression was as common among older and younger migraineurs. Lower education status was more common among migraineurs but no difference was observed for the marital status as compared to controls. (Table 1) Triptans were prescribed in 522 migraine cases, 34.7%.

All four painful musculoskeletal disorders, fibromyalgia, RA, OA and sciatic syndrome, were reported more often among migraineurs than among controls. One in three migraineurs reported sciatic syndrome and OA compared to one in five among controls. (Table 2)

In the two oldest age groups all four reported disorders were more common among female and also OA among male migraineurs compared to controls. In the two youngest age groups OA, sciatic syndrome and fibromyalgia among women and sciatic syndrome among men were more common. Almost half of female and one third of male migraineurs reported OA while the rate in the younger age groups was only one in ten. (Table 3)

Musculoskeletal disorders reported by migraineurs showed a higher and statistically significant risk in both univariate and multivariable models. Odds ratio (OR) with 95% CIs in logistics regression analysis were 2.37 (95% CI 1.81 − 3.09) for fibromyalgia, 1.46 (1.10 − 1.95), for RA, 1.58 (1.38 − 1.80) for OA and 2.09 (1.84 − 2.37) for sciatic syndrome in the age and gender adjusted Model 2. In separate logistics regression analyses in Models 3. and 4. adjustment for age, gender, education and at least moderate depression had only slight influence, the ORs were high for all four musculoskeletal disorders, and the association with migraine was statistically significant. (Table 4)

Discussion

The key finding in this study was that several common painful musculoskeletal disorders, such as rheumatoid arthritis, fibromyalgia, osteoarthrosis and sciatic syndrome were reported significantly

more often in the working aged migraine than in the control population. Migraineurs reported more often a lower education level and at least moderate depression compared to the controls. The risk for all four musculoskeletal disorders was high and statistically significant after adjustment for age and gender, as well as with education and at least moderate depression.

Self-reported migraine is generally considered reliable, and this method is used in several observational studies. [14-16] In line with other studies we did not use diagnostic questions to identify individuals with different pain conditions. We used recall prompts which in case of migraine shows that the self-reported occurrence of migraine among Finnish working aged population in 2012 was 13%, being similar to rates observed in other studies. [1,15] Female majority and the observation of lower education level among migraineurs [16] were corroborated also in our cohort. It is known that the classification of a given primary headache disorder subtype may change in a quarter of cases and the diagnostic certainty of other pain conditions may vary significantly according to the doctor who made the diagnosis , e.g. general practitioners, other specialists. [17] Same limitation is true for musculoskeletal disorders in this and other studies using recall prompts. However, self-reporting of migraine is considered reliable and the included cases in this data had responded affirmatively to the inquiry on having migraine in all three questionnaires up to 2012 which further improves the reliability. Moreover, the proportion of migraineurs with prescribed triptans may be considered appropriate. [18]

A major strength of this study is the high response rates among migraineurs in the follow-up questionnaires comprising altogether 1 505 included cases in 2012. Baseline characteristics in both study groups were controlled for age and educational status. The possible differences in other comorbidities than painful comorbidities are not expected to affect results and conclusions in our

study. Exclusion of suspected 1% false negative migraine population according to triptan prescription data do not interfere with the inferences in this study.

Limitations of the results and inferences based on the data may be the fairly low general response rate in 1998 and the over presentation of older age groups. As migraine prevalence was not studied here we find the response rate and number of cases adequate for the purposes in this study. The sample size remained ample for statistical analyses to assess risk and occurrence of painful comorbidities. However, given the careful non-response analysis after the baseline study, where respondents and non-respondents were comparable with respect to the most important demographic variables [13], we strongly assume that the conclusions drawn from the statistical analyses may be considered reliable and random effects small. Also, the non-response analysis showed only minor differences in physical health between participants and the general population. [12,13] That's why results in this study may be generalizable in other migraine populations.

Association of migraine, painful musculoskeletal disorders and depression was shown in our working aged cohort. The affective components in pain response are recognized in everyday clinical practice and it may be argued that some of the pain syndromes under the study have a predominantly psychological etiology, whereas others have a predominantly biological etiology. Fibromyalgia was formerly classified as an inflammatory musculoskeletal disease but it is now regarded as a condition where pain processing is dysfunctional [19], and similar to migraine [20] both the ascending and descending pain pathways result in abnormal central amplification of pain signals. Fibromyalgia, migraine and some musculoskeletal pain conditions carry an increased risk for mood disorders and psychological distress [6, 21-23] Inferences according to current data [6, 24] suggest that in case of migraine there is an association with depression but the causal

direction of the relationship is unclear why it may be regarded as bidirectional.

The relative clinical and therapeutic implications in the complex relation of depression and painful conditions are recognized in clinical practice. The currently used antidepressants, serotonin-norepinephrine reuptake inhibitors (SNRI) and tricyclic antidepressants, treat both depression and the painful conditions, such as migraine and fibromyalgia, by activating the central descending inhibitory pain pathways and modulating pain transmission. [25,26] These medications may be the most promising agents for the modulation of pain symptoms, but their efficacy as headache preventive varies widely. Tricyclic antidepressants are more effective than SNRIs in migraine prophylaxis, but demonstrate dose-limiting side effects. [27,28] The use of antidepressants in the treatment of complex pain syndromes thus requires individual assessment. Assessment for the need of efficacious and tolerated treatments is warranted as these disorders are shown to exert a significant influence on working capacity [10,11] and health related quality of life (HRQol). Subjects with migraine selected from the general population have been shown to have a lower HRQol as measured by the SF-12 compared with the nonmigraine controls. [29] The same is true in fibromyalgia. [30]

Painful musculoskeletal comorbidities and depression associated to migraine as observed here increase the disease burden and are expected to decrease the quality of life and productivity in working aged population. Comorbidities should be taken into account when assessing the therapeutic needs of a patient. As physiological mechanisms modulating pain expression are further clarified in different age and gender groups, with and without comorbidities, improved pharmacological interventions for pain syndromes are expected. The characterization of specific pathophysiological changes underlying particular inflammatory diseases is set to produce

paradigms in pain management and future possibility of more specific diagnosis-based analgesic medication, such as calcitonin gene related peptide (CGRP) receptor antagonist use in migraine.[31]

Conflict of Interest:

Authors report no conflict of interest.

Sources of Funding Statement: Nothing to declare.

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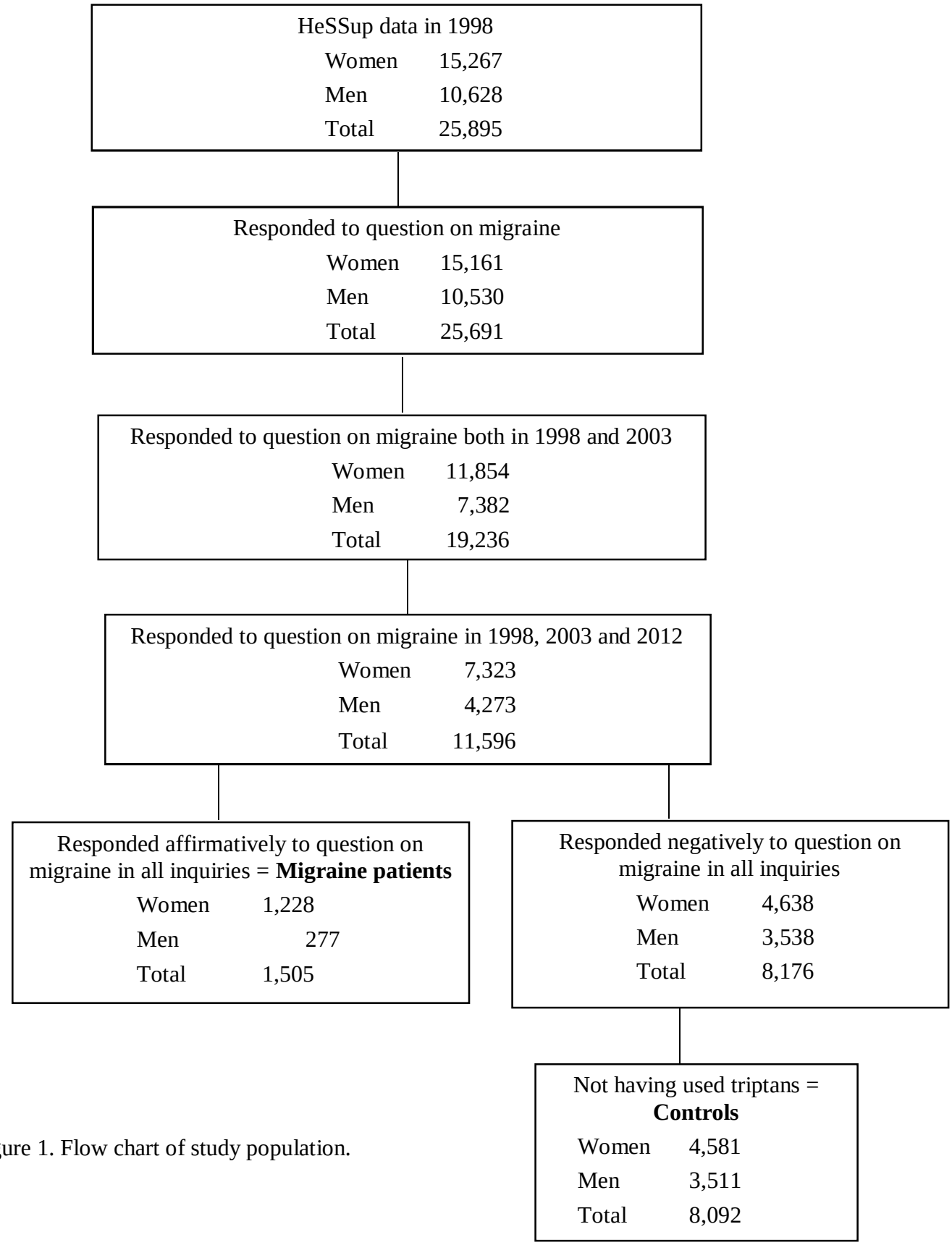

Figure 1. Flow chart of study population.

Table 1. Demographic features of migraine patients and controls in the year 2012.

	Migraine patients		Controls		
	n	%	n	%	p-value
Gender					<0.001
women	1228	81.6	4581	56.6	
men	277	18.4	3511	43.4	
Born on years					<0.001
1944−1948 (age 64−68)	488	32.4	2602	32.2	
1954−1958 (age 54−58)	440	29.2	2163	26.7	
1964−1968 (age 44−48)	301	20.0	1680	20.8	
1974−1978 (age 34−38)	276	18.3	1647	20.4	
Marital status*					0.060
single, divorced or widowed	365	24.3	1874	23.3	
married or cohabiting	1135	75.7	6185	76.7	
Education*					<0.001
lower	850	56.5	4370	54.1	
higher**	655	43.5	3715	45.9	
Beck’s depression inventory*					<0.001
< 18	1377	92.7	7750	96.6	
≥ 18	108	7.3	272	3.4	

* All individuals did not respond to every question.

** At least matriculation examination.

Table 2. Proportion (%) of migraine patients and controls having reported painful musculoskeletal disorders in the year 2012.

	Migraine patients N=1494		Controls N=8067		
	n	%	n	%	p-value
Rheumatoid arthritis	67	4.5	212	2.6	<0.001
Osteoarthrosis	453	30.3	1587	19.7	<0.001
Sciatic syndrome	478	32.0	1503	18.6	<0.001
Fibromyalgia	91	6.1	165	2.0	<0.001

Table 3. Occurrence (%) of painful musculoskeletal disorders among old and young migraine patients and controls in the year 2012.

	Age groups 54−58 and 64−68										Age groups 34−38 and 44−48									
	Women					Men					Women					Men				
	Migraine N = 744		Controls N = 2521			Migraine N = 173		Controls N = 2226			Migraine N = 474		Controls N = 2047			Migraine N = 103		Controls N = 1276		
	n	%	n	%	p-value	n	%	n	%	p-value	n	%	n	%	p-value	n	%	n	%	p-value
Rheumatoid arthritis	48	6.5	114	4.5	0.032	5	2.9	57	2.6	0.781	13	2.7	35	1.7	0.137	1	1.0	6	0.5	0.492
Osteoarthrosis	341	45.8	889	35.3	<0.001	50	28.9	485	21.8	0.030	53	11.2	140	6.8	0.001	9	8.7	73	5.7	0.213
Sciatic syndrome	285	38.3	558	22.1	<0.001	52	30.1	550	24.7	0.109	116	24.5	240	11.7	<0.001	25	24.3	155	12.2	<0.001
Fibromyalgia	57	7.7	111	4.4	<0.001	4	2.3	27	1.2	0.207	30	6.3	26	1.3	<0.001	0	0.0	1	0.1	0.777

Table 4. Summary of separate logistic regression analyses of migraine (ORs with 95% CI) for different painful musculoskeletal disorders.

	Model 1	Model 2	Model 3	Model 4
Rheumatoid arthritis	1.74 (1.32 − 2.31)	1.46 (1.10 − 1.95)	1.44 (1.08 − 1.92)	1.43 (1.07 – 1.90)
Osteoarthrosis	1.78 (1.57 − 2.01)	1.58 (1.38 − 1.80)	1.57 (1.37 − 1.79)	1.52 (1.33 – 1.75)
Sciatic syndrome	2.06 (1.82 − 2.33)	2.09 (1.84 − 2.37)	2.07 (1.82 − 2.35)	2.00 (1.76 – 2.27)
Fibromyalgia	3.12 (2.40 − 4.06)	2.37 (1.81 − 3.09)	2.31 (1.77 − 3.02)	2.14 (1.63 – 2.82)

Model 1: Not adjusted

Model 2: Adjusted for age and gender

Model 3: Adjusted for age, gender and education

Model 4: Adjusted for age, gender, education and also for at least moderate depression (Beck > 18)