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Anxiety and depression in multiple sclerosis. A comparative population-based study in Nord-Trøndelag County, Norway

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Abstract

Anxiety and depression are widely distributed symptoms among multiple sclerosis patients and in the general population. We assessed the prevalence of anxiety and depression in the multiple sclerosis population in Nord-Trøndelag County, Norway compared with Norway's general population. The Hospital Anxiety and Depression Scale questionnaire was completed by 172 MS patients and 56,000 controls. A cut-off of ≥ 8 was used to define significant symptoms of anxiety and depression. Fatigue was measured using Krupp's Fatigue Severity Scale, with a mean cut-off of >4. Among men, 31.1% of the multiple sclerosis patients reported anxiety, while only 12.1% of the control population reported this symptom ($p = 0.002$). For women, the prevalence of anxiety was 29.7% versus 17.4% ($p < 0.001$). Depression was reported by 26.2% of the men with multiple sclerosis compared with 10.8% of the controls ($p < 0.001$). The corresponding figures for women were 25.2% versus 10.4% ($p < 0.001$). Anxiety and depression were not correlated with duration of disease or disability measured by the Expanded Disability Status Scale. Among women, fatigue was associated with anxiety ($p \leq 0.010$) and depression ($p = 0.007$). No such association was found among men. Anxiety and depression occur more frequently in multiple sclerosis patients than in the general population. Fatigue was associated with these neuropsychiatric manifestations in only women.

Keywords

Multiple sclerosis, anxiety, depression, fatigue

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Introduction

Multiple sclerosis (MS) is the most common disabling neurological illness among young people. The prevalence is about twice as high in women as in men. Norway is a high-risk area, and MS is especially frequent in Nord-Trøndelag County.[1] Early on in the course the disease, the prognosis is difficult to predict, although some prognostic factors are known.[2–4] After 15–20 years 10–20% of the patients have a good outcome.[2,5–7]

Living with a chronic disease with an unpredictable outcome may cause anxiety. Few studies have been carried out on anxiety in MS patients. The Hopkins Symptom Checklist-25 was used as the outcome measure for anxiety in a recent Norwegian study[8] where 19.3% of persons with MS in the study reported anxiety. In a recent study on determinants of disability and quality of life in patients with Parkinson disease,[9] in which the Hospital Anxiety and Depression Scale (HADS) was used, the authors reported that 30.5% of the patients had symptoms indicating significant anxiety.

Several studies report a higher prevalence of depression among MS patients compared with the general population.[10–14] During the course of the disease, most MS patients experience a decline in their physical function. Most studies conclude that worse physical

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function leads to more depression,[10,12,13,15] others have not found such a correlation.[14]

As depression can give symptoms that are quite common in MS, such as fatigue, lack of energy and problems with memory and concentration, depression in an MS patient can be overlooked. It is important to detect significant depression because it is one of the most important determining factors of quality of life.[16] The treatment of clinical depression may make it easier to live with the chronic disease. Unfortunately, anxiety and depression are clinical manifestations that are not routinely and systematically evaluated in MS patients. The aim of this study was to find the prevalence of symptoms of anxiety and depression in the MS population in Nord-Trøndelag County, Norway. We also wanted to analyse how anxiety and depression correlate with physical function, fatigue and duration of disease.

Table 1. Characteristics of the study population

		Patients	Controls
Men	*N*	61	26,788
	Mean age in years (min–max)	51.7 (26–72)	46.6 (20–89)
	Mean duration of MS in years (min–max)	17.0 (2–42)	
	Mean EDSS score (min–max)	4.1 (0–0.5)	
Women	*N*	111	25,233
	Mean age in years (min–max)	48.5 (23–82)	45.9 (20–89)
	Mean duration of MS in years (min–max)	16.2 (1–44)	
	Mean EDSS score (min–max)	3.5 (0–9.0)	

MS, multiple sclerosis; EDSS, Expanded Disability Status Scale.

Material and methods

Populations

The included MS patients were examined neurologically by the lead author (OPD) as part of a previously published population-based epidemiological study in the county.[1] The study identified 208 MS patients (130 women and 78 men) of whom 200 accepted the invitation to participate in a new neurological examination. Based on the neurological examination, the patients were scored using the Expanded Disability Status Scale (EDSS). In addition, the patients were asked to fill in the HADS questionnaire, and 172 patients did so.

Nord-Trøndelag County is located in central Norway at latitude 64° north. The population, mostly rural, is scattered with only six persons per square kilometre. The largest of the six small towns has 21,000 inhabitants. The total population of the county was 127,108 on 1 January 2000. The average income, the prevalence of people with higher education and the average number of current smokers in the county are slightly lower than the national averages in Norway. In most other respects, however, the county is fairly representative of Norway in terms of geography, economy and industry, sources of income, age distribution, morbidity and mortality.

Approximately 3% of the Norwegian population live in Nord-Trøndelag County, which is a stable population with low net migration (0.3% per year in 1996–2000) and a homogenous composition (<3% non-Caucasian).

The Nord-Trøndelag health study (HUNT) is one of the largest health studies ever performed. It is a unique database of personal and family medical histories collected during three intensive studies. All people in Nord-Trøndelag 20 years or older were invited to participate in the HUNT 2 study. This study included several health questionnaires and a physical examination. Of the 92,100 people between 20 and 89 eligible for the study, 65,648 (71.3%) participated. Of these, 53,526 (81.5%) completed the anxiety part of HADS and 58,698 (89.4%) completed the depression part. These large samples from the county population form the control groups in the present study.[17]

A major strength of the HUNT 2 study is the high level of participation. All the MS patients are residents in the same county. Several aspects of depression and anxiety in this large population-based sample have been presented by Stordal et al. in previous publications.[18] The characteristics of the study population and controls are summarized in Table 1.

Measures

The symptoms of anxiety and depression were measured using the HADS. HADS is a self-report instrument that was originally designed to measure anxiety and depression in patients with somatic diseases and mental problems.[19] Subsequently, HADS became a commonly used and validated self-report instrument for evaluating anxiety and depression in large populations. The Norwegian HADS version has been extensively applied to the HUNT population and has shown robust psychometric properties.[20] This self-rating questionnaire contains seven questions that focus on symptoms of anxiety (HADS-A) and seven questions that address depressive symptoms (HADS-D). The scoring scale for each item runs from 0 (not present) to 3 (highly present). The HADS questionnaire

specifically asks about symptoms that appeared during the last week prior to answering the questionnaire. The minimum score is 0 and the maximum score is 21 for both scales. A cut-off value of ≥ 8 on both scales indicates clinically significant symptoms of anxiety or depression. This cut-off value has demonstrated reasonable screening properties for identifying anxiety disorders and major depressive disorder, yielding a sensitivity and specificity of approximately 0.8.[21]

We chose to use the HADS instrument in the MS population as we had access to the large control population in the county (HUNT 2) where this had been used.[22]

The EDSS was developed and published in 1983[23] and has been widely used in clinical trials and other MS studies in the last 25 years, although the scale has inherent weaknesses. The scale comprises seven subscales (for example, Functional Systems): pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual (or optic) and cerebral (or mental) functions. The ordinal scale ranges from 0 to 10 in half-point steps where 0 means a normal neurological status and 10 means death due to MS. The lower the score, the better the function: a score from 0 to 4.0 means no restriction in ambulation, a score from 4.5 to 7.0 means increased need for ambulation help and a score >7.5 means restricted to a wheelchair.

Fatigue was measured by using a Norwegian version of Krupp's Fatigue Severity Scale (FSS).[24] The FSS consists of 9 items in a Likert scale from 1 to 7. The minimum score is 9 and the maximum is 63; the higher score, the more pronounced the fatigue. The Norwegian version of this scale is well validated.[25] Most studies use a mean value >4 as an indication of a significant level of fatigue,[26] others use mean values >5.[25] We used a mean value >4 as cut-off for a significant fatigue level in this study.

Ethics

All participants signed a written informed consent. The study was approved by the Regional Committee for Medical Research Ethics in central Norway.

Statistics

Prevalence differences in anxiety and depression were analysed by 95% confidence intervals (CI) for the difference (Newcombe method) and Pearson's chi square test. Possible confounding effects of age, duration of MS symptoms and EDSS score were evaluated using logistic regression analysis with anxiety or depression as dependent variables. All analyses were done separately for women and men. SPSS 15 (SPSS Inc., Chicago, IL, USA) and CIA[27] were used for the analyses.

Results

Patients

Two hundred MS patients (121 women and 79 men) were given a standard neurological examination and were scored on the EDSS scale. One hundred and seventy two MS patients (86%) completed the HADS questionnaires, of which 111 (64.5%) were women and 61 were men. Five patients were not able to answer the questionnaire due to weak cognitive function. Four patients were unable to write and thus unable to fill in the questionnaire. Nineteen patients refused to complete the questionnaire for unspecified reasons. There was no significant difference in the EDSS score between the groups who had a clinically significant score of anxiety or depression symptoms and those who did not have these symptoms.

Group characteristics

In the HUNT 2 study, we identified 53,502 individuals (27,567 women, 25,935 men) who had completed the HADS anxiety questionnaire and 58,688 (30,894 women, 27,794 men) who had completed the HADS depression questionnaire. The 116 MS patients who were identified as participants in the HUNT 2 study were excluded from the control group.

Among the MS patients there was no difference in age between those who had answered the HADS questionnaire and those who had not answered it. In the control group, however, the people who had not filled in the HADS questionnaire were older than the people who did fill in this questionnaire (men 62.0 years old *vs.* 46.6 years old and women 63.3 years old *vs.* 45.9 years old, $p < 0.001$).

The mean age of the MS patients was 51.7 years old for men and 48.5 years old for women. In the control group the mean age was 46.6 years old for men and 45.9 years old for women. The mean duration of MS was 17.0 years in men (median 15.0) and 16.2 years in women (median 15.0). Mean EDSS score was 4.1 for men and 3.5 for women.

Anxiety

Anxiety was reported more frequently in the MS patients than in the general population. There was greater difference among men (31.1% *vs.* 12.1%, $p < 0.001$) than among women (30.0% *vs.* 17.4%, $p = 0.013$) as shown in Table 2. The effect of being an MS patient with anxiety remained practically unchanged when adjusted for age (logistic regression, results not shown). We found a higher prevalence of anxiety among MS patients with fatigue than among those without, though significant only in women.

Table 2. Prevalence differences in anxiety and depression by gender

	n/N (%)		Differences (%)		
	MS-patients	Controls	Estimate	95% CI	*p*-values
Anxiety					
Men	19/61 (31.1)	3135/25935 (12.1)	19.1	8.8 to 31.5	0.002
Women	33/111 (29.7)	4788/27567 (17.4)	12.4	4.6 to 21.4	<0.001
Total	52/172 (30.2)	7923/53502 (14.8)	15.4	9.0 to 22.7	<0.001
Depression					
Men	16/61 (26.2)	3012/27794 (10.8)	15.4	6.0 to 27.6	<0.001
Women	28/111 (25.2)	3216/30894 (10.4)	14.8	7.6 to 23.6	<0.001
Total	44/172 (25.6)	6228/58688 (10.6)	15.0	9.0 to 22.0	<0.001

Table 3. Fatigue in multiple sclerosis patients with anxiety and depression by gender

Fatigue and anxiety in multiple sclerosis		
	Men $N = 47$	Women $N = 87$
Fatigue with anxiety (%)	17/47 (36)	31/87 (36)
Fatigue without anxiety (%)	2/14 (14)	2/24 (8)
95% CI	-7 to 39	7 to 40
p values	0.120	0.010
Fatigue and depression in multiple sclerosis		
Fatigue with depression (%)	14/47 (30)	27/87 (31)
Fatigue without depression (%)	2/14 (14)	1/24 (4)
95% CI	-12 to 33	9 to 38
p values	0.25	0.007

CI, confidence interval.

In men the prevalence was 36% (17/47) among patients with fatigue versus 14% (2/14) in males without fatigue (95% CI for difference -7% to 39%, $p = 0.12$). In women, the prevalence was 36% (31/87) and 8% (2/24) respectively, as shown in Table 3 (95% CI for difference 7% to 40%, $p = 0.010$). Duration of illness was not associated with anxiety.

Depression

The MS patients reported depressive symptoms significantly more frequently than people in the general population: 25.7% in MS patients versus 10.6% in controls ($p < 0.001$) according to HADS-D when the cut-off value was ≥8. The difference between MS patients and controls was approximately the same in women, 25.2% *vs.* 10.4% ($p < 0.001$), as in men, 26.2% *vs.* 10.8% ($p = 0.003$) (Table 2). The effect of being an MS patient with depression remained practically unchanged when adjusted for age (logistic regression, results not shown).

We found a higher prevalence of depression among MS patients with fatigue than among those without, though significant only in women. In men, the prevalence of depression was 30% (14/47) among patients with fatigue versus 14% (2/14) in males without fatigue (95% CI for difference -12% to 33%, $p = 0.25$). In women, the prevalence was 31% (27/87) and 4% (1/24), respectively (95% CI for difference 9% to 38%, $p = 0.007$) (Table 3).

Duration of illness was not associated with depression. Anxiety and depression were positively associated. Ten of 19 men with symptoms of anxiety also reported symptoms of depression ($p = 0.003$). Among women, 21 of 33 reported symptoms in both neuropsychiatric domains ($p < 0.001$). There is no report of suicide among the MS patients included in the study. Disability as measured by the EDSS score was not associated with anxiety or depression (logistic regression, results not shown).

Discussion

The present study shows that people with MS report symptoms of anxiety in a statistically significantly higher proportion than the normal population (30.2% *vs.* 14.8%). Men with MS reported slightly more symptoms of anxiety than women (31.1% *vs.* 29.7%), but the gender difference did not reach statistical significance. Men are also somewhat more disabled than women (mean EDSS 4.2 *vs.* 3.9), but the difference did not reach statistical significance. We did not find significant associations between anxiety and age, duration of disease or disability as measured by EDSS.

There are few robust epidemiological studies addressing anxiety in MS using standardized and validated outcome measures.[28] Nicholl and co-workers present a review of past research on emotional problems in people who have MS in addition to their own results. The most striking features in the review, altogether

15 studies published from 1980 to 2000, are the small sample sizes and the inherent selection bias. In their own study, Nicholl and co-workers classified the patients into two categories: those who maybe in need of intervention (cases) and those who were not in need of intervention. They found that 39% were case level on HADS-A with a cut-off value of 7–8. With a cut-off value of 10–11 on HADS-A, the percentage of case level MS patients fell to 18. In a British study using the HADS, 34% of MS patients were case level for anxiety on HADS-A when standard cut-off levels were applied.[29]

In two Dutch studies[30,31] the authors concluded that MS patients suffer a substantial emotional burden of disease. Eight months after diagnosis of MS, 34% of the patients reported that they experienced high levels of anxiety; they used the HADS-A as the outcome measure. In a follow-up study two years later they showed that 69% of persons with MS with high anxiety scores at baseline had high scores after two years.

In a Canadian study[32] using both the Structured Clinical Interview for DSM-IV disorders (SCID-IV) and the HADS self-report instrument, the authors concluded that anxiety disorders are common, but frequently overlooked and under-treated in people with MS. The lifetime prevalence of anxiety disorders was 35.7%, and in the Canadian study, 20.7% of the people with MS had clinically relevant self-reported anxiety. In a recent Norwegian study[8] using the Hopkins Symptom Checklist-25 (HSCL-25), 19.3% of the MS patients reported anxiety. A univariate analysis showed that anxiety was associated with fatigue, pain, younger age at onset and lower disability (EDSS <3). After the multiple regression analysis, however, lower disability lost significance, but fatigue, pain and younger age at onset remained significantly associated with anxiety. Thus, our results correspond with published figures and corroborate previous studies showing a high occurrence of anxiety symptoms in people with MS.

A substantial proportion of people with MS in our study reported symptoms of depression when compared with the large population-based control group (25.7% *vs.* 10.6%). We found no association between the reporting of depressive symptoms and disability (EDSS), nor between depression and age or duration of disease. There were no statistically significant gender differences in the MS patients, though women tended to report more depressive symptoms than men.

The persons with MS in the study who did not fill in the HADS questionnaire were significantly more disabled than those who completed the questionnaire (mean EDSS 5.5 *vs.* 3.7, $p < 0.001$). This difference may result in an underestimation of depressive symptoms; many studies report a rather consistent association between depression in MS and a more advanced neurological disability as measured by EDSS.[33,34]

Patten and co-workers found the frequency of an annual major depression among MS patients to be 15.7% compared with 6.8% in the general population in a large, population-based Canadian study[13] with a sample selected from the Canadian Community Health Survey and using the Composite International Diagnostic Interview Short Form for Major Depression (CIDI-SFMD) as the outcome measure. They found more depression in women than in men (16.7% *vs.* 13.1%). The prevalence estimates were lower after exclusion of fatigue and cognitive function from the scoring, but still remained more elevated in those with MS compared with controls.

Assuming that people with MS reflect the general population in all psychological aspects with the exception of having a chronic neurological disease, one might argue that depressive symptoms by gender should be distributed as they are in the general population. True to this assumption, the lack of difference in symptoms of depression between men and women with MS is consistent with the results from the large population-based Nord-Trøndelag Health Study 2 (HUNT 2)[35] where the gender differences are minimal when HADS-D is applied as the outcome measure. However, in the Hordaland Health Study,[36] another population-based Norwegian study that used HADS-D as the outcome measure, men appear to be more depressed than women. The authors of this cross-sectional study with 22,317 participants from 40 to 47 years of age argue that HADS-D overestimates the prevalence of depression in men or underestimates depressive symptoms in women. Their argument is based on the perception of the two items in the questionnaire that relate to interest in personal appearance and ability to enjoy television, radio and books, which may not be considered gender neutral topics by some.

In a study of predominantly male US veterans with MS,[37] the authors reported a prevalence of 22.2% with a current major depressive episode. When combining major and minor depressive episodes, 32.2% reported such symptoms on the Patient Health Questionnaire (PHQ). Of the nine items concerning depression on the PHQ, fatigue and low energy were more frequently reported. The population studied was mainly male (86%), yet the authors argue that men and women with MS appear to have similar risk for depressive symptoms because the frequency of depression is equally high in their sample as in predominantly female MS populations.

In a quantitative review Dalton and Heinrichs[11] assessed 41 studies making two separate comparisons between people with MS and healthy individuals and people with MS and people with other chronic

conditions. The results from the first meta-analysis indicate that mildly or moderately disabled people with MS have more depressive symptoms than healthy people. For people with other chronic conditions, however, the results are more heterogeneous with higher, lower and equivalent levels of depressive symptoms in comparison with the MS patients. Thus, they conclude that the link between MS and depression are multifaceted and unspecific.

In another less formal review, Siegert and Abernethy[14] conclude that depression is a common co-morbidity in MS with annual prevalence rates around 20% and lifetime prevalence rates of 50%. They also assessed the association between the lesion sites in the central nervous system and the occurrence of depressive symptoms, and pointed out that this association is weak. The controversy as to whether depressive symptoms in MS are due to the disease itself or are a consequence of living with an unpredictable chronic disorder is not resolved. Most likely there are a number of interactions between structural abnormalities in the brain, neuroimmunological aberrations and depressive symptoms in MS, but so far no definitive conclusions can be drawn.[38]

Depressive symptoms in MS cause significant suffering and add to the existing disability. Our study shows that one of four persons with MS experiences significant depressive symptoms; it is important to detect and treat these patients.

Mohr and co-workers[39] have suggested that just two screening questions that address mood and anhedonia in people with MS may be adequate to identify depressed MS patients, and this would make it possible to improve the treatment these patients are offered. This American research group[40–42] has also shown that targeted treatment strategies improve function and quality of life for MS patients.

The present comparative cohort study is entirely population-based, thus, a possible selection bias is reduced to a minimum. However, the loss of some patients due to advanced disease causing severe dysfunction in both cognitive and motor skills might lead to an underestimation of reported symptoms of anxiety and particularly depression.

In a relatively small German study, however, cognitive impairment in MS did not affect reliability and validity of self-report health measures, which includes the HADS scale.[43] One of the limitations of the HADS scale as an outcome measure is that it measures only self-reported symptoms of anxiety and depression, not actual psychiatric diagnoses. However, the instrument has been shown to have robust psychometric properties applied across a wide spectrum of sub samples.[20,21]

In conclusion, our population-based study shows significant levels of anxiety and depression in people with MS compared with the normal population. Women with MS suffering from anxiety and depression are also significantly more fatigued compared with women with MS who do not have these neuropsychiatric symptoms. It is important to identify these clinical manifestations early and offer suitable treatment. Systematic use of HADS as a quick, clinical screening instrument could be useful in daily clinical practice to identify MS patients suffering from anxiety and/or depression.

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