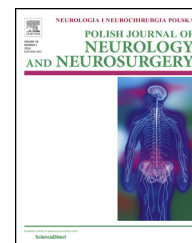


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## Original research article

## Psychiatric comorbidity in multiple sclerosis

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## ABSTRACT

**Aim:** To study the prevalence of psychiatric comorbidities in patients of multiple sclerosis and their association to the degree of disability.

**Method:** Psychiatric symptoms were assessed in 90 patients of multiple sclerosis using GHQ-12, MMSE, HADS, Beck Depression Inventory and AUDIT. Neurological disability was assessed using Expanded Disability Status Scale. Correlations were determined between EDSS scores and psychiatric scale scores.

**Result:** 61% of patients had significant psychological distress. Depression was most common (38.8%) which was followed by anxiety symptoms (27.8%). Cognitive functioning was relatively intact in patients with mild to moderate neurological disability. Alcohol abuse was mostly restricted to male gender.

**Conclusion:** Psychiatric illness is highly prevalent in patients of multiple sclerosis leading to poor quality of life and significant distress. Psychiatric disability was higher in patients who had greater deterioration in neurological function. All cases of MS should be assessed for psychiatric morbidities as can be alleviated by appropriate intervention.

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## 1. Introduction

Multiple sclerosis (MS) is an autoimmune condition causing inflammatory demyelination of the central nervous system. MS by affecting the adult in the prime of their productive life exerts a considerable socioeconomic burden on society. Psychiatric symptoms in MS are highly prevalent and frequently overlooked in clinical settings [1]. Changes in mood, personality, and cognitive functioning are among the most disabling and distressing symptoms for individuals diagnosed with MS, yet patients and their families receive little understanding or help with these problems [2]. Studies have

shown that prevalence of psychiatric comorbidity is high even at the time of MS diagnosis, and rises during the course of disease. Further, depression, anxiety, and bipolar disorder occur substantially more often in the MS population compared to general population [3].

Although psychiatric manifestations are relatively common among patients with MS, there is paucity studies on prevalence and impact of depression, anxiety, substance use, cognitive impairment bipolar mood disorders/schizophrenia in patients of MS. Keeping in view the above, this study was undertaken in a tertiary care hospital of India. Though the main objective is to measure the depression, anxiety, cognitive disability and alcohol abuse, it is also intended to incorporate

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as far as possible its association with neurological disability due to MS.

## 2. Materials and methods

### 2.1. Sample and procedure

All consecutive diagnosed patients of Multiple sclerosis taking treatment from Neurology Unit of our hospital consenting for the study were considered. The study received approval by the Institutional Ethics Committee. A total of 90 patients were assessed during the 18-month period. Most of the cases interviewed were from neurology OPD (both old and new cases). 20 patients were interviewed from neurology ward. The patients were diagnosed as per 2010 McDonald criteria (current practiced guideline) [4] and greater than 18 years of age. Patients who declined to participate in the study, medically too ill to participate, who were neither conversant in Hindi nor English and psychotic patients were excluded. Patients requiring psychiatric care were given option to seek consultation and detailed evaluation at psychiatric center which is co-located.

### 2.2. Measures

All patients fitting the inclusion criteria were assessed by administration of the following questionnaires and scales:

- (a) *Kurtzke Expanded Disability Status Scale (EDSS)*. It was used to rate the degree of neurological disability. This scale is considered the standard for quantifying disability in patients with MS. Score range from 0–10 with higher scores indicating more severe disability [5].

MS patients were divided into three groups based on their EDSS scores:

- i. Scoring 0–1.5 (with neurological symptoms but not disabled)
- ii. Scoring 2–4.5 (with neurological symptoms at disability level but still fully ambulatory)
- iii. Scoring 5.0–8.0 (in need of a cane, walker or wheelchair due to lack of ambulation or wheelchair dependent)

- (b) *Hindi version of General Health Questionnaire-12 (GHQ-12)*

GHQ is a self-administered screening questionnaire which has been widely used to detect non psychotic psychiatric disturbances in a variety of settings [6]. Standardization of Hindi version of Goldberg's GHQ on Indian population was done by Gautam et al. in 1987 [7]. Each item is rated on a four-point scale. A total score of 3 or more was considered abnormal.

- (c) *Hospital Anxiety and Depression Scale*

The Hospital Anxiety and Depression Scale (HADS) is a 14-item self-report screening scale that was originally developed to indicate the possible presence of anxiety and depressive states in the setting of a medical out-patient clinic [8]. It contains two 7 item scales: one for anxiety and one for depression both with a score range of 0–21. Each of the items can be scored from 0 to 3 based on severity of distress. A cut off score of  $\geq 8$  was fixed for anxiety or depression.

- (d) *Beck Depression Inventory (BDI)*

It is one of the most widely used and well-validated self-report inventory to assess the intensity of depression in psychiatric patients and for detecting possible depression in normal populations. There are 21 groups of statements which can be rated on a 4-point scale ranging from 0 to 3 in terms of severity making maximum total score of 63 [9]. A cut-off of 10 was fixed for depression.

- (e) *Mini-Mental State Examination (MMSE)*

Since its introduction in 1975, MMSE has become a widely used brief, standardized method to grade patients' cognitive mental status. As per Folstein et al., any score greater than or equal to 25 points (out of 30) indicates a normal cognition. Score of 25 was taken as cut-off [10].

- (f) *Alcohol Use Disorders Identification Test (AUDIT)*

The AUDIT was developed by the World Health Organization (WHO) as a simple method of screening for excessive drinking and to assist in brief assessment. There is a total of 10 questions with score ranging from 0–40. Based on WHO guidelines for use of AUDIT score more than 8 was taken as cut off [11].

### 2.3. Statistical analysis

Statistical analysis was carried out by using Statistical Package for Social Sciences (SPSS) – 22. Our data has been analyzed basically using categorical data. For each such character frequencies and percentages have been computed. Therefore, for testing for association we have used Chi square test based on frequencies along with probability of significance (Table 3). For all statistical tests a *p*-value of 0.05 or less indicates significance (rejection of null hypothesis of agreement).

## 3. Results

During the period of study, a total of 94 patients were approached. 2 of them expressed unwillingness to participate in the study. There were 2 dropouts who left the study during the evaluation process.

In Table 1 shows count and percentage of discrete variables age group, sex, type of MS, MMSE, GHQ-12, HADS-A, HADS-D, BDI and AUDIT and EDSS categorized into various classes as explained in methodology. In Table 2 descriptive statistics with respect to all variables for which numerical values were available are recorded. It shows the values of mean, Standard deviation, Standard error of mean, minimum and maximum of each variable.

Average age of all subjects was 38.07 years which ranged from 18 to 65. Out of 90 patients, 54 patients were female and 36 were male. Incidentally there is only one patient in category PP (primary progressive MS) and 6 patients in category SP (Secondary progressive MS) as depicted in Table 1. The maximum subjects were of category RR (Relapsing remitting MS).

The average score in GHQ-12 came out to be 2.04 with SD of 1.52. 43 (47.78%) patients scored 3 or more which was taken as cut off. On HADS, 25 patients (27.78%) had anxiety symptoms whose scores lied above the cut off. When the data was further

**Table 1 – Tally: discrete variables: age group, sex, type of MS, MMSE, GHQ-12, HADS-A, HADS-D, BDI, AUDIT and EDSS.**

Attribute	Class	Count	Percent
Age group	18–28	19	21.10
	29–39	34	37.78
	40–49	24	26.67
	50–65	13	14.44
Sex	Male	36	40.00
	Female	54	60.00
Type of MS	RRMS	83	92.22
	SPMS	6	6.67
	PPMS	1	1.11
MMSE	Abnormal	11	12.22
	Normal	79	87.78
GHQ-12	Abnormal	55	61.11
	Normal	35	38.89
HADS-A	Abnormal	25	27.78
	Normal	65	72.22
HADS-D	Abnormal	32	35.96
	Normal	58	64.04
BDI	Abnormal	35	38.89
	Normal	55	61.11
AUDIT	Abnormal	14	15.56
	Normal	76	84.44
EDSS	Not disabled	18	20.00
	Ambulatory	51	56.67
	Not ambulatory	21	23.33

analyzed for level of anxiety, the results showed 8 (8.9%) patients had mild anxiety and 17 (18.9%) patients had significant anxiety. In present study HADS-A score of 11 or more was significant anxiety. On depression subscale of HADS we found that out of total 90 subjects, 32 (35.96%) of patients had significant depressive symptoms. The findings from BDI corroborated with the results obtained from HADS-D. 35 (38.89%) patients had scores above the cut off. Among 35 patients having significant depressive symptoms, 11 patients had mild level of depression (scores 11–16), 20 patients had moderate level of depression (scores 17–29) and 4 patients had severe level of depression (scores 30 and above).

MMSE, used to access the cognitive function, showed an average score of 27.54 with SD of 2.19. 11 out of 90 patients (12.22%) had MMSE scores of 24 or below which was kept as cut off. AUDIT clinical procedure showed 14 patients had problematic alcohol use requiring further assessment and possible intervention.

EDSS scores varied from a minimum of 1–7.5 with a mean score of 3.45 with SD of 1.683. In Table 1 as depicted, 18 patients (20%) were not disabled or had minimal disability, 51 patients

(56.67%) were disabled but were ambulatory and 21 patients (23.33%) were non-ambulatory.

There was strong association of EDSS with age of patients ( $p = 0.0001$ ). As age increased, the count of cases increases from not disabled to disabled. However, there was no significant association between sex and EDSS ( $p = 0.562$ ). There was significant association between type of MS and EDSS scores. Subjects suffering from progressive MS had higher EDSS scores compared to subjects of RRMS ( $p = 0.03$ ).

There was strong association between EDSS and MMSE depicted by chi-square value of 8.06 with  $p = 0.018$ . As EDSS score increased, there was deterioration of cognitive function as reflected by decrease in MMSE scores.

Again, there was a strong association of GHQ-12 on EDSS (chi-square value of 10.255,  $p = 0.006$ ). It indicates that there is increasing psychological distress in subjects with increasing physical disability.

Chi-square analysis of EDSS with HADS-A shows that there is an association between the 2 variables, but it failed to reach statistical significance (chi-square = 5.687,  $p = 0.058$ ). There was a statistically significant association between HADS-D and EDSS (chi-square = 7.004 with  $p = 0.03$ ) meaning the depressive symptoms was higher in patients with high physical disability. Similar significant association was obtained between BDI and EDSS (chi-square = 7.722 with  $p = 0.021$ ). As physical disability increased, there is also an increase in BDI scores.

Alcohol abuse in patients of MS, assessed with AUDIT, failed to show any association with degree of disability. There was no significant association detected with age and AUDIT. However, when we analyzed the effect of sex on AUDIT, we found a highly significant association with chi-square value of 14.436 and  $p = 0.0001$ . There were only 2 out of 54 females screened positive for alcohol abuse compared to 12 out of 26 males.

#### 4. Discussion

Multiple sclerosis is an autoimmune condition causing inflammatory demyelination of the CNS. MS exerts a considerable socioeconomic burden on society by affecting the adult in the prime of their productive life. Psychiatric symptoms in MS are highly prevalent and frequently overlooked in clinical settings [1].

This study was a cross sectional descriptive study incorporating diagnosed cases of multiple sclerosis as per 2010 McDonald's criteria. In this study it was aimed to detect the prevalence of psychiatric comorbidities in patients of multiple sclerosis and their association to the

**Table 2 – Descriptive statistics: age, EDSS, MMSE, GHQ-12, HADS-A, HADS-D, BDI, AUDIT.**

Variable	N	Mean	St dev	SE mean	Minimum	Maximum
Age	90	38.070	10.470	1.100	18.000	65.000
EDSS	90	3.450	1.683	0.177	1.000	7.500
MMSE	90	27.544	2.194	0.231	21.000	30.000
GHQ-12	90	2.044	1.528	0.161	0.000	6.000
HADS-A	90	6.067	4.334	0.457	0.000	16.000
HADS-D	90	5.722	4.414	0.465	0.000	17.000
BDI	90	11.644	8.556	0.902	2.000	37.000
AUDIT	90	2.133	3.601	0.380	0.000	14.000

**Table 3 – Tests of association using Chi-square test.**

Attribute	Chi-square	Degree of freedom	P value
EDSS vs age	28.810	6	0.0001
EDSS vs sex	1.152	2	0.562
EDSS vs MS	10.676	4	0.030
EDSS vs MMSE	8.016	2	0.018
EDSS vs GHQ12	10.255	2	0.006
EDSS vs HADS-A	5.687	2	0.058
EDSS vs HADS-D	7.004	2	0.030
EDSS vs BDI	7.722	2	0.021
EDSS vs AUDIT	1.191	2	0.551
Age vs AUDIT	0.882	3	0.830
Sex vs AUDIT	14.436	1	0.0001

degree of disability. The mean age of our patients was 38 years. Amato et al. in 1998 in a study on 106 patients found mean age to be 44.89 with youngest patient aged 21 years and oldest 69 years [12]. Sarisoy et al. in 2010 studied 79 patients of MS in Turkey and reported mean age of patients to be 37.84 years [13]. A study conducted in India by Singhal et al. reported mean age of the patients at the time of presentation was  $33.3 \pm 9.2$  years [14].

In our study, majority of patients were female. Many diseases with auto-immune etiology are known to have a skewed sex distribution. Review of population studies reveals that the preponderance of women in MS is almost constant. In a large scale community survey by Chwastiak et al. on 719 patients found that 77.9% were females [15]. A study conducted in Mangalore, India also shows a female preponderance in which out of 35 patients, 22 were females [16]. The skewed sex distribution in MS could be attributed to the known hormonal and gender influences on the immune response, as well as to genetic influences [17].

The relapsing remitting MS is the most common type of MS worldwide comprising about 80% of cases [18]. Our result was consistent with study by Karadayi et al. in 2014 in which MS group composed of 90.3% RRMS [19].

Neurological disability as assessed by EDSS showed that most of the patients (80%) had some form of significant physical disability. Physical disability was higher in patients who were older and had progressive MS. These observations were statistically significant. A recent study done by Sarisoy et al. has shown a mean EDSS score of 2.58 [13]. A study conducted at NIMHANS, Bangalore on 31 patients showed mean EDSS score to be 3.5 [20]. There was very strong association between EDSS and age. As age increased, the count of cases increases from not disabled to disabled. This is akin to the study done by Chwastiak et al. in 2005 which has shown as duration of illness increases, there is an increase in the disability [15].

Psychiatric disorders seem to have profound effects on wide-ranging aspects of the lives of persons who have MS. The prevalence of psychiatric comorbidity is high even at the time of MS diagnosis, and rises over the course of the disease. In present study, we attempted to assess common psychiatric comorbidities.

12.22% of patients had impaired cognitive function. Patients with greater physical disability had poor cognitive functioning which was reflected by decrease in MMSE scores with increase in EDSS scores ( $p = 0.018$ ). This is in concurrence with previous studies where it found that EDSS was significant

predictor of cognitive deficits. The results were akin to the results from a study by Amato et al. in sample of 103 patients. The study found an average MMSE score was 27.26 with SD of 2.78 [12]. Another study from Turkey by Karadayi et al. assessed cognitive function on 31 patients of MS using MMSE, showed mean score to be 28.29. The study also showed significant impairment in selective attention, cognitive flexibility and processing speed compared to controls which was measured by stroop test. [19]. Considering all previous studies, the percentage of subjects screened positive for cognitive impairment varied depending on screening tool used and characteristics of subjects, however all studies have shown significant impairment in cognitive function in patients of MS irrespective of methodology used.

A clear majority of patients (47.78%) had some form of psychological distress which was reflected by GHQ-12. Also, we found in our study that distress increased with increasing physical disability ( $p = .006$ ). Lincoln et al. screened 311 patients of MS in 2011 at Nottingham, UK on GHQ-12, out of which 221 (71%) had significant amount of distress [21].

27.78% of patients had significant anxiety symptoms on HADS screening tool. The association with EDSS and HADS-A was near significant ( $p = 0.058$ ). We found that that in young people with less physical disability, anxiety was comparatively higher to subjects who were not ambulatory. This is consistent with the study of Da Silva et al., where they reported 26.6% of patients were having significant anxiety [22]. In contrast to the present study, Watson et al in a study conducted at United Kingdom reported high levels of anxiety in which 47% ( $n = 34$ ) of subjects had scores more than 7 on HADS-A [23]. Korostil et al. took score of 10 on HADS as cut off and found prevalence of anxiety disorders to be 14% [24]. Depending on method of assessment used and sample population, prevalence of anxiety varied across studies. Considering all studies, the prevalence of diagnosed anxiety ranged from 1.24% to 36% [22,25,26].

A substantial number of subjects had prominent depressive symptoms and as physical disability increased, there was also an increase in the depressive symptoms which was reflected by statistically significant association between HADS-D and BDI with EDSS ( $p = 0.03$  and  $0.021$ ) respectively. This finding agrees with studies in the literature scanning depressive symptoms in MS patients. Depressive symptoms were more prevalent in the progressive-course MS group in our study. Since progressive MS is a more severe form of the disease, this is an expected finding. Watson et al in a study conducted at United Kingdom reported high levels of depression in which 50% ( $n = 34$ ) of subjects had scores more than 7 on HADS-D [23]. Da Silva et al. studied 325 patients of MS in Portugal and measured depression using HADS. They reported 30.4% of patients were having significant depression [22]. Saadat et al. in a population-based study of 160 subjects conducted in Iran measured depression using BDI. They have reported 69.4% were having depressive symptoms [27]. Mattioli et al. demonstrated the prevalence of depressive symptoms to be 25% in a sample of Italian MS patients, which was lower than what we actually found [28]. This difference in results might be due to the use of various diagnostic or screening tools for the detection of depression, or the use of different cut-off points for screen tools. Other possible explanations for this could be related to study design or population sampling.

Alcohol abuse was present in 15.56% of patients. Alcohol abuse was significantly higher in male gender ( $p = 0.0001$ ). This is in correlation with similar studies conducted earlier which has shown that men endorsed higher rate of alcohol use than women. It can also be inferred that the alcohol abuse is lower in women than in men in the community from where these subjects were taken. Bombardier et al. in 2003 surveyed 1374 persons with MS and found 14% screened positive for possible alcohol abuse or dependence. Alcohol abuse was associated with younger age and less severe MS related disability [29]. Turner et al. used the AUDIT for their study and reported that 13.9% of their veteran population of MS individuals met criteria for excessive drinking. One possible explanation for this finding is the sampled population. It was noted in the literature that excessive drinkers tend to be younger, employed and less disabled than their non-drinking peers [30].

The strengths of the study were a large sample size considering the prevalence of multiple sclerosis. Only the patients satisfying well-defined diagnostic criteria for multiple sclerosis were taken. The scales used to screen for psychiatric disability were validated for the study population. This study had several limitations. As with any other cross-sectional study, our study lacked temporality for determining causal associations. Recall bias and reporting bias cannot be excluded as most of the questionnaires are self-reporting. The findings of the study can only be extrapolated to hospital patients. Patients with low MMSE scores received help for completing other measurements. Also, patients not conversant with Hindi received help in completing GHQ. Data related to immediate reason for hospitalization or seeking outpatient care was not collected. The association of relapses affecting EDSS scores cannot be ascertained from present study.

## 5. Conclusions

From the study it can be reasonably concluded that psychiatric illness is highly prevalent in patients of multiple sclerosis leading to poor quality of life and significant distress. Depression is the common symptom which is followed by anxiety. A modest number of patients had poor cognitive function and alcohol abuse were mostly restricted to male gender. We can also conclude that psychiatric disability was higher in patients who had greater deterioration in neurological function. All cases of MS should be assessed for psychiatric morbidities. Psychiatric morbidity increases distress in patients of MS and worsens the quality of life. This can be alleviated by appropriate intervention.

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## Conflict of interest

None declared.

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