Evaluation of the association between sexual dysfunction and demyelinating plaque location and number in female multiple sclerosis patients

Volkan Solmaz, Hatice Kose Ozlece, Aydin Him, Ayfer Guenes, Christian Cordano, Durdane Aksoy & Yahya Celik

To cite this article: Volkan Solmaz, Hatice Kose Ozlece, Aydin Him, Ayfer Guenes, Christian Cordano, Durdane Aksoy & Yahya Celik (2018): Evaluation of the association between sexual dysfunction and demyelinating plaque location and number in female multiple sclerosis patients, Neurological Research, DOI: 10.1080/01616412.2018.1462752

To link to this article: https://doi.org/10.1080/01616412.2018.1462752

Published online: 17 Apr 2018.

Submit your article to this journal

View related articles

View Crossmark data
Evaluation of the association between sexual dysfunction and demyelinating plaque location and number in female multiple sclerosis patients

Volkan Solmaz\textsuperscript{a}, Hatice Kose Ozlece\textsuperscript{a}, Aydin Him\textsuperscript{b}, Ayfer Gunes\textsuperscript{a}, Christian Cordano\textsuperscript{c}, Durdane Aksoy\textsuperscript{d} and Yahya Celik\textsuperscript{a}

\textsuperscript{a}Department of Neurology, Trakya University Medical Faculty, Edirne, Turkey; \textsuperscript{b}Department of Physiology, Ondokuzmayis University Medical Faculty, Samsun, Turkey; \textsuperscript{c}Department of Neurology, Multiple Sclerosis Center, University of California, San Francisco, CA, USA; \textsuperscript{d}Department of Neurology, Gaziosmanpasa University Medical Faculty, Tokat, Turkey

\textbf{ABSTRACT}

\textbf{Purpose:} To investigate the frequency of sexual dysfunction (SD) in female multiple sclerosis (MS) patients and to explore its association with the location and number of demyelinating lesions.

\textbf{Material and Methods:} We evaluated 42 female patients and 41 healthy subjects. All patients underwent neurological examination and 1.5 T brain and full spinal MRI. All subjects completed the female sexual function index (FSFI), Beck Depression Inventory (BDI), Beck Anxiety Inventory (BAI), and Short-Form 36 Quality of Life Scale (SF-36). All participants were also evaluated for serum thyroid stimulating hormone (TSH), T4, estradiol, and total testosterone.

\textbf{Results:} No statistically significant differences between the MS and control groups were found for age, body mass index (BMI), serum TSH, T4, E2, and total testosterone level. MS patients had a statistically significantly lower FSFI and SF-36 scores and higher BDI and BAI scores compared with healthy subjects. The location and number of demyelinating lesions were not associated with SD.

\textbf{Conclusion:} In our cohort, this difference in SD appears unrelated to the location and number of demyelinating lesions. These findings highlight the importance of the assessment and treatment of psychiatric comorbidities, such as depression and anxiety, in MS patients reporting SD.

\section{1. Introduction}

Multiple sclerosis (MS) is an autoimmune neurodegenerative disease with a high incidence in young adult females \cite{1}. MS is the second most frequent cause of disability in adults in developed countries. Higher relapse rates correlate with increased neurological and psychiatric dysfunction, such as relapse frequency, severity, recovery, progression rate, depression, and anxiety \cite{2–4}. Different organic and psychiatric conditions can cause sexual dysfunction (SD). SD is a frequently underestimated symptom due to the deep intimacy of this matter, combined with the social and cultural factors impacting the relationship between neurologist and patient. Despite these diagnostic difficulties, SD is a frequent symptom of MS, and it seriously impacts the quality of life of MS patients. Normal sexual functioning requires intact neural, endocrine, psychiatric, and hormonal mechanisms. The hypothalamus–hypophyseal axis plays a fundamental role in controlling sex hormone release and quantity \cite{5}.

We performed a review of the literature regarding SD in female MS patients, and found that there are a very limited number of studies evaluating the association between SD and demyelinating lesions, and none of them included an accompanying neuropsychiatric assessment.

Pre\'vinaire et al. describe the etiology, diagnostic methods and treatment of sexual dysfunction in MS patients. In this review, the authors describe the multifactorial diagnosis of SD in MS, explaining that treatment should be shaped by the etiological basis of the symptoms \cite{6}. Winder et al. reported that demyelinating plaque number in the left temporal periventricular and right inferior occipital regions correlates with orgasmic dysfunction in female MS patients \cite{7}. Barak et al. found that SD is more frequent in both male and female MS patients than in healthy controls and found a relationship with depression but no association between SD and brain lesion number \cite{8}. The aim of our study was to assess SD in female MS patients and its possible association with the location (cranial and spinal cord) and number of demyelinating lesions.
2. Materials and method

In this study, 402 female MS patients, who were followed in our university neuroimmunology clinic, were evaluated (between January 2016 and December 2016, with a diagnosis of MS according with the McDonald 2010 criteria) [9]. The local ethics committee of the university approved the study (app. No: TÜTF-BAEK 2016/91). The inclusion criteria were as follows: female gender, older than 18 years old, sexually active, and in remission. Exclusion criteria were as follows: the presence of other conditions possibly underlying SD, such as hypothyroidism, diabetes mellitus, systemic rheumatological diseases, malignancies, antidepressant medication use, and alcohol and cigarette addiction. Forty-two patients meeting the above criteria and 41 healthy subjects were included in the study. The healthy subjects were recruited from our hospital staff.

After a complete neurological examination the patients’ sociodemographic status, use of medications, MS onset time, Expanded Disability Status Scale (EDSS) scores, comorbid diseases, height and weight were noted. All the participants completed the 19 question-long Female Sexual Function Index (FSFI). This questionnaire includes six parts, with questions regarding sexual arousal, orgasm, satisfaction, pain, desire, and lubrication in the last four weeks. Every question has 6 items and is scored from 0 or 1 to 5. The total possible score is 36. FSFI was validated in Turkish populations by Oksuz and Malhan in 2005 [10]. The cutoff value for diagnosis of SD is a total FSFI score of 26.55 or greater [11]. All the enrolled subjects completed the Beck Depression Index-Ia (BDI-Ia), Beck Anxiety Index (BAI) and Short Form 36 Questionnaire (SF-36) to assess their neuropsychiatric status. BDI-Ia consists of 21 questions with a score of 16 points or greater suggesting depression [12]. BAI also consists of 21 questions and evaluates anxiety levels [13]. The SF-36 questionnaire is commonly used to test a patient’s health status and is subdivided into two subgroups: physical (Physical Health Component Summary Scale – PCS), and mental (Mental Health Component Summary Scale – MCS) [14]. All participants underwent a 1.5 T brain and cervical/thoracic spine MRI, including T1, T2 weighted and FLAIR sequences with gadolinium. This 1.5 tesla (Signa HDx; GE Healthcare, Milwaukee, Wisconsin) MRI device has standard coils (8 channels). All participants were also evaluated for serum thyroid stimulating hormone (TSH), free T4, estradiol (E2) and total testosterone.

3. Statistical analyses

The SPSS (Statistical Package for Social Sciences) 15.0 for Windows program was used for statistical analysis. A Chi-square test was used to compare qualitative data, including symptoms and results of the physical examination. Prior to performing calculations on the non-qualitative data, the Kolmogorov-Smirnov test was used to determine whether the data were normally distributed. The nonparametric Mann-Whitney U and Kruskal-Wallis tests were used for non-normal data, while the parametric Student t and one-way analysis of variance (ANOVA) tests were used for normally distributed data. The results are presented as the mean ± standard deviation for numeric values and as ‘n’ and ‘%’ for the qualitative values. Values of p < 0.05 were accepted as significant. As this was an exploratory study, no correction for multiple comparisons was made.

4. Results

The mean age was 41.9 ± 8.06 in MS patients and 39.7 ± 7.3 in the control group. The BMI scores were 24.8 ± 3.9 for MS patients and 26.4 ± 4.04 for the control group. There were no significant differences between groups in terms of age (p = 0.195) and BMI (p = 0.069). We enrolled 34 relapsing remitting (RR) MS patients, 7 secondary progressive (SP) MS patients and 1 primary progressive (PP) MS patient. The patients’ average disease duration was 8.9 years (max: 25, min: 1 year), with a median range of EDSS score of 2.2 (min: 0, max: 7). At the time of enrollment, 7 patients were taking interferon beta 1a (Rebif), 9 were taking interferon beta 1b (Betaferon), 6 were taking interferon beta 1 a (Avonex), 4 were taking glatiramer acetate (Copaxone), 1 was taking natalizumab (Tysabri), 2 were taking dimethyl fumarate (Tecfidera), 8 were taking fingolimod (Gilenya) and 2 were taking teriflunomide (Eubagio). Three patients were not taking any disease modifying drugs for MS. (Table 1). When we compared the MS and control groups in terms of total and subgroup FSFI scores, there were statistically significant differences between groups (for each subgroup p = 0.0001) (Figure 1). Interestingly, according to the above mentioned cutoff value (FSFI total score: 26.55) of the entire 42 MS subjects, only 5% (n = 2) of MS patients did not have SD. The Beck Depression (p = 0.014) and Beck Anxiety (p = 0.0001).

<table>
<thead>
<tr>
<th>Table 1. Clinical and demographic features of the groups.</th>
<th>MS (n = 42)</th>
<th>Control (n = 41)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>41.9 ± 8.06</td>
<td>39.7 ± 7.3</td>
<td>0.195</td>
</tr>
<tr>
<td>BMI</td>
<td>24.8 ± 3.9</td>
<td>26.4 ± 4.04</td>
<td>0.069</td>
</tr>
<tr>
<td>TSH</td>
<td>10.8 ± 8.1</td>
<td>7.3 ± 4.07</td>
<td>0.014</td>
</tr>
<tr>
<td>T4</td>
<td>15.1 ± 10.3</td>
<td>2.3 ± 4.6</td>
<td>0.001</td>
</tr>
<tr>
<td>SF-36</td>
<td>431.5 ± 143.3</td>
<td>657.6 ± 50.97</td>
<td>0.0001</td>
</tr>
<tr>
<td>E2</td>
<td>10.76 ± 3.6</td>
<td>10.36 ± 4.80</td>
<td>0.65</td>
</tr>
<tr>
<td>TSH</td>
<td>1.75 ± 1.2</td>
<td>1.74 ± 0.7</td>
<td>0.986</td>
</tr>
<tr>
<td>FSFI</td>
<td>15.84 ± 6.33</td>
<td>31.01 ± 3.53</td>
<td>0.0001</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Civil servant</td>
<td>4(9.5)</td>
<td>6(14.6)</td>
<td></td>
</tr>
<tr>
<td>Self employed</td>
<td>8(19.6)</td>
<td>6(14.7)</td>
<td></td>
</tr>
</tbody>
</table>
| Note: MS: Multiple sclerosis BMI: Body mass index FSFI: Female sexual dysfunction index BDS: Beck Depression scale, BAI, Beck anxiety scale, SF-36: short form 36.
scores were significantly higher in MS patients, and the SF-36 (total and subgroups scores) were significantly lower in the MS group than the control group (for each group $p = 0.0001$) (Table 2).

Pearson correlation analyses showed that there was no correlation between FSFI and EDSS scores, or disease duration and FSFI scores. We found that higher depression and anxiety scores were associated with lower FSFI scores (respectively $r = 0.565, p = 0.03$, $r = 0.585, p = 0.0001$), and higher SF-36 scores were associated with higher FSFI scores ($r = 0.654, p = 0.0001$). Serum TSH, T4, E2, and total testosterone levels were similar in both groups (each $p > 0.05$). Analyzing the location of demyelinating lesions, we found that the FSFI scores of patients who had only supratentorial plaques and of patients with both supra and infratentorial lesions were not different ($p = 0.491$). Similarly, the FSFI scores of patients with only brain lesions were similar to the scores of patient who had both brain and cervical lesions ($p = 0.361$) and lesions in all the areas analyzed (brain, cervical, and thoracic spine) ($p = 0.296$) (Figure 2). There were no correlations between total plaque number and FSFI scores ($p = 0.26$, $r = 0.758$), and there were no significant differences between black hole positive and black hole negative MS patients in terms of FSFI scores ($p = 0.392$). Moreover, one-way ANOVA showed that immunomodulator drugs did not have significant effects on sexual function in MS patients ($F = 0.341, p = 848$)

5. Discussion

Our results show a much higher incidence of sexual dysfunction in female MS patients than in healthy subjects. We did not find a correlation between lesion location and sexual dysfunction, and the patients’ hormonal status (E2, Thyroid hormones and total testosterone) did not seem to play a role. The novel finding of this study is the strong correlation with depression and anxiety. In addition to these findings, we also found that female MS patients’ SF-36 scores were correlated with a significant negative impact on mental and physical daily life, which could be due to MS itself, or complications of disease such as sexual dysfunction, depression, and anxiety.

In the literature, there are very limited studies about the location of demyelinating lesions and sexual dysfunction in female MS patients [7,15], and the most important limitation of these studies is a lack of assessment of possible causes of these symptoms, such as psychiatric disorders and endocrinological illnesses. Unlike these studies, we evaluated the patients’ psychiatric and

![Figure 1. Comparison of patients and healthy groups in terms of FSFI.](image)
endocrinological status in addition to lesion location. One of the most important causes of SD in MS is cranial and spinal atrophy, a feature that occurs from the earliest disease stages onward [16–18]. Our results showed that psychiatric status is the most prominent cause of SD in female MS subjects; however, we did not make a volumetric assessment of the brain and spinal cord in our study.

SD is one of the most common MS complications, and it has a strong impact on quality of life. Many studies report a higher incidence of SD in MS, and MS is considered one of the most common causes of SD among neurological disorders [19–21]. Recently, a few studies investigated the association between demyelinating lesions and SD in MS. Winder et al., studying the association between orgasmic dysfunction and demyelinating lesion volume and location, found a weak but significant negative correlation between orgasmic dysfunction and lesion number/volume in the right visual association area and the left temporal periventricular white matter. Interestingly, participants who had lesions in temporal, frontal and midbrain regions had improved orgasmic function compared to other patients. The psychiatric and metabolic status of the subjects was not assessed [7]. A second study from the same research group reported an association between occipital cortex lesions and decreased sexual arousal, while insular cortex lesions were associated with decreased lubrication. Arousal and lubrication scores did not correlate with patient age, disease duration, BDI scores, EDSS scores and total volume of cerebral MS lesions [15]. These findings are similar to the ones described in our work, but Winder and collaborators also found no difference in arousal and lubrication scores between patients with and without depression. In addition to depression, we also evaluated the daily life quality (SF 36 questionnaire) and anxiety levels (BAI), with both revealing scores indicative of pathology (Table 2). Chronic diseases such as MS may cause sexual disorders in patients due to despair, desperation, guilt, and fear of death or pain. Additionally, in chronic diseases, sexual energy, as well as mental and physical energy, correlates with survival and coping, and we think psychiatric symptoms are commonly an underestimated cause of SD in MS.

Depression and anxiety disorders are important risk factors for sexual dysfunction [22–24]. Gromisch et al. showed that both depression and anxiety disorders are significant risk factors for sexual dysfunction in a multicenter trial, while Gümüş et al. reported that SD is significantly more frequent in MS patients, negatively correlated with BDI scores, and strongly associated with psychiatric disorders [19]. In a large prospective study, with 2062 participants enrolled, depression was found to be a major risk factor for SD in MS patients [23].

Thyroid function tests, E2 and total testosterone did not differ between healthy controls and MS patients. These findings are consistent with the literature; in 2017, Villalpando and collaborators obtained similar results in two different cohorts of MS patients [25].

Our work includes several limitations, consisting mainly of the absence of a lumbar MRI execution, a detailed lesion mapping, and urinary incontinence assessment with urodynamics. The lack of a fatigue assessment is another limitation of this study; according to recent findings, fatigue may negatively impact...
quality of life and may significantly contribute to SD, as well [26].

Despite these limitations, we think that our results, showing a strong association between SD and depression and anxiety, and an absence of correlation with location and number of demyelinating brain and spinal cord lesions, demonstrate the importance of assessing psychiatric disorders in MS patients. Additional studies are needed to replicate these results and indicate the role of lumbar cord lesions.

Disclosure statement
No potential conflict of interest was reported by the authors.

Notes on contributors

Volkan Solmaz is assistant professor in Trakya University Medical Faculty Department of Neurology (Turkey). He is the principal investigator of the research and he has published various studies in neurological disorders like neurodegenerative diseases.

Hatice Kose Ozlece is assistant professor in Trakya University Medical Faculty Department of Neurology (Turkey), some of her studies are published in J Clin Neurophysiology. She contributed during study writing and data collecting.

Aydn Him is an associate professor in Ondokuz Mayas University Medical Faculty Department of Physiology (Turkey) and some of his studies are published in J Membr Biology. He contributed during study writing and designing.

Ayfer Güneş is research assistant in Trakya University Medical Faculty Department of Neurology (Turkey). She collected the data and designed the manuscript.

Christian Cordano is research fellow in University of California, Dept. of Neurology, Multiple Sclerosis Center, San Francisco, U.S.A. He designed the manuscript and evaluated the results.

Dürdane Aksoy is an associate professor in Gaziosmanpasa University Medical Faculty Department of Neurology and some of her researches are published in Am J Med Sci. She evaluated the results and statistical analyses and also she evaluated the literature about the topic.

Yahya Çelik is professor in Trakya University Medical Faculty Department of Neurology and Neuroimmunology, and he is the senior author of the research.

References

