Article

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Anxiety and depressive symptoms in clinically isolated syndrome and multiple sclerosis

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ABSTRACT

Depression and anxiety have been reported in patients with multiple sclerosis (MS) and in patients with clinically isolated syndrome (CIS). However, the precise mechanisms that lead to depressive and anxiety symptoms in these patients are still unclear. In this study we evaluated with the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI) patients with MS and CIS and compared them to controls. We also correlated BDI and BAI scores with clinical parameters. Kruskall-Wallis followed by Dunn's Multiple Comparison Test, Chi-square and Spearman test were used. Patients with MS had higher depressive and anxiety scores than controls. The BDI and BAI scores of patients with CIS were not significantly different from controls. There was a positive correlation between BDI, BAI and EDSS. Our results corroborate the view that MS patients have higher depression and anxiety levels than control subjects. Anxiety and depressive symptoms also seem to progress according to the severity of the disease.

Key words: clinically isolated syndrome, multiple sclerosis, anxiety, depression.

Ansiedade e depressão em pacientes com síndrome clínica isolada e esclerose múltipla

RESUMO

A depressão e a ansiedade têm sido descritas em pacientes com esclerose múltipla (EM) e síndrome clinicamente isolada (CIS). Entretanto, os mecanismos precisos que determinam o surgimento de depressão e ansiedade ainda não estão elucidados. No presente estudo, foram utilizadas as escalas de Beck para depressão (BDI) e ansiedade (BAI) em pacientes com EM, CIS e controles. O grau de comprometimento funcional dos pacientes e o tempo de doença foram correlacionados com parâmetros clínicos. Foram utilizados os testes de Kruskall-Wallis seguido do teste de múltiplas comparações (Dunn's Test), qui-quadrado e o teste de Spearman. Pacientes com EM apresentam escores mais elevados de depressão e ansiedade do que controles. Houve correlação positiva entre os escores do BDI e do BAI com o grau de comprometimento funcional avaliado pela EDSS. Nossos resultados corroboram a visão de que pacientes com EM exibem mais ansiedade e depressão que controles. Sintomas ansiosos e depressivos parecem progredir com a gravidade da doença.

Palavras-Chave: síndrome clínica isolada, esclerose múltipla, ansiedade, depressão.

Multiple sclerosis (MS) is a chronic demyelinating central nervous system disease with time and space disseminated lesions. MS lesions usually have a relapsing remitting couse and affect periventricular region, optical nerves, and spinal cord[1].

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Clinically isolated syndrome (CIS) represents the first neurological demyelinating event. CIS patients may convert to MS, representing, in most cases, the first manifestation of MS[2].

Until recently, the MS impact was measured only taken into account motor, visual, sensitive, and autonomic symptoms. In recent years a large number of studies involving neuropsychological and neuropsychiatric manifestations in MS and CIS has been performed[3-6]. Depression was found in up to 40% of MS patients[3,6]. Anxiety was also frequently reported in MS[6-8]. It was shown that the presence of such psychiatric comorbidities has a great impact in general health status and quality of life of MS patients[9-11]. However, little is known about these neuropsychiatric comorbidities in patients with CIS[12].

Some studies have found that neuropsychiatric symptoms in MS are related with the degree of functional disability and with disease duration[13,14]. If depression and anxiety are related with the degree of functional impairment and with disease duration it is possible that patients with MS have more depression and anxiety than patients with CIS. In this study we compared anxiety and depression symptoms in patients with CIS and in patients with MS. We also correlated anxiety and depression symptoms with clinical parameters such as EDSS.

METHOD

Subjects

The patients were recruited in the Multiple Sclerosis Clinic of Santa Casa de Misericórdia de Vitória, ES. The control group was composed of randomly selected healthy subjects paired by age and gender, with no neurological disease. Patients and controls with evidence of severe cognitive impairment or using psychotropic drugs were not included.

The study received full approval by the Ethics Committee on Research of the Escola Superior de Ciências da Santa Casa de Vitória (EMESCAM), Vitória ES, Brazil and informed consent was obtained from each participant.

Data collection

The diagnosis of MS and CIS were all done by a neurologist and were based on revised McDonald criteria[15]. The neurologic evaluation included clinical history, neurologic evaluation including Expanded Disability Status Scale (EDSS), and magnetic resonance imaging.

Anxiety was evaluated with Beck Anxiety Inventory (BAI)[16,17]. BAI contains 21 items related with anxiety symptoms. The respondent is asked to rate how much he or she has been bothered by each symptom over the past week on a 4-point scale ranging from 0 to 3. The items are summed to obtain a total score that can range from 0 to 63. If the score is up to nine points there is no indication of anxiety. Mild anxiety is suggested if the score is between 10 to 16 points. BAI suggests moderate anxiety symptoms if the score is between 17 and 29 and severe anxiety symptoms if the score is between 30 and 63[16,17].

The Beck Depression Inventory (BDI)[18] is a 21-question, multiple-choice, self-report inventory for depression symptoms. It consists of 21 questions about how the subject has been feeling in the last week. Each question has a set of at least four possible answer choices, ranging in intensity. When the test is scored a value of 0 to 3 is assigned for each answer and then the total score is compared to a key to determine the severity of depression symptoms. The standart cut-offs are: 0-9 indicates no depression symptoms, 10-18 indicates mild depression, 19-29 indicates moderate depression, and 30-63 indicates severe depression[18,19].

Statistics

The Kruskall-Wallis test followed by Dunn's Multiple Comparison Test was used for the comparison of mean age, BAI, and BDI among the three groups (control, CIS, and MS). The Chi-square test was used to compare the proportion of individuals in each of the three groups for the following variables: gender, BAI groups, BDI groups. Spearman test was used to assess the correlation between the degree of functional disability of EDSS and the BDI and BAI scores. All the calculations were performed using GraphPad Prism version 4.00 for Windows software (GraphPad Software Inc., San Diego, CA, USA). The level of significance was set at $p<0.05$.

RESULTS

Nineteen patients with MS were evaluated. Fifteen (78.9%) were women. The mean age was 37±12.7 years. In the group of patients with MS 14 (73.7%) had relapsing remitting disease, 3 (15.8%) had secondary progressive disease, and 2 (10.5%) had primary progressive disease. The mean EDSS was 4.7±2.9. The mean time of disease was 7±3.9 years. Fifteen (78.8%) MS patients were using disease modifying drugs (DMDs), fourteen were using beta interferons and one was using azathioprine. Fourteen patients with CIS were included. Ten (71.4%) patients were women. The mean EDSS was 1±0.6. The mean age was 36±8.4 years. The CIS clinical manifestations were: optic neuritis, 8 patients (57.1%); myelopathy, 5 patients (35.7%); and lobar, 1 patient (7.2%). The mean time of disease of CIS patients was 0.5±2.9 years. Six (42.8%) CIS patients were using disease modifying drugs (DMDs), four were using beta interferons and two were using glatiramer acetate. Twenty nine subjects were included in the control group. The mean age was 38±7.3 years. There were not significant differences in age and gender distribution in the three groups.

Table 1. Proportion of individuals in the different BAI groups.

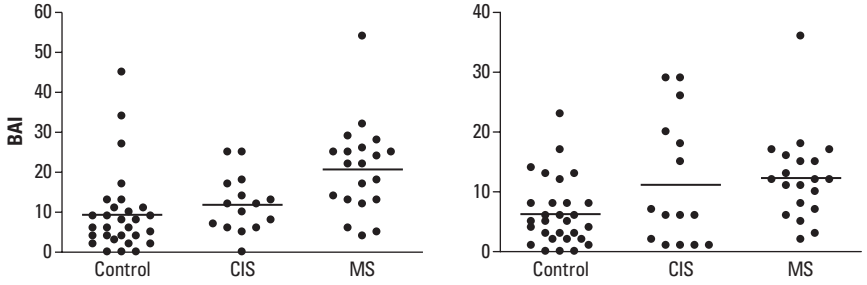
	CIS (n %)	MS (n %)	Control (n %)
BAI			
<10	6 (42.8)	3 (15.8)	20 (68.9)
10-16	5 (35.7)	4 (21)	5 (17.2)
17-29	3 (21.5)	10 (52.6)	2 (6.9)
>29	0	2 (10.6)	2 (6.9)
p value	0.09*	0.0005**	

MS: multiple sclerosis; CIS: clinically isolated syndrome; BAI: Beck anxiety inventory; *CIS versus control (not significant); **MS versus control (significant).

Table 2. Proportion of individuals in the different BDI groups.

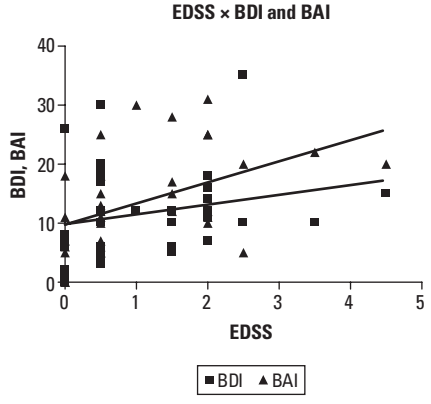
	CIS (n %)	MS (n %)	Control (n %)
BDI			
<10	9 (64.3)	6 (31.6)	23 (79.3)
10-18	2 (14.3)	12 (63.1)	5 (17.2)
19-29	3 (21.4)	0	1 (3.5)
>29	0	1 (5.3)	0
p value	0.16*	0.004**	

MS: multiple sclerosis; CIS: clinically isolated syndrome; BDI: Beck depression inventory; *CIS versus control (not significant); **MS versus control (significant).



MS: multiple sclerosis; CIS: clinically isolated syndrome; BAI: Beck anxiety inventory; CIS versus controls - not significant; CIS versus MS - not significant; MS versus controls - p<0.001.

Fig 1. [A] BAI scores in the three groups (p=0.0003). [B] BDI scores in the three groups (p=0.01).



MS: multiple sclerosis; CIS: clinically isolated syndrome; BAI: beck anxiety inventory; BDI: beck depression inventory; EDSS: expanded disability status scale.

Fig 2. Correlation between EDSS of patients with CIS and MS with BAI (p=0.002) and BDI (p=0.04).

There was a significant difference in the proportion of subjects in the four BAI cutoffs when comparing the three groups (control, CIS, and MS) (p=0.003). When comparing controls versus CIS, controls versus MS, and CIS versus MS the only significant difference was found between control and MS patients (p=0.0005). There was not a significant difference between CIS and controls (p=0.09) (Table 1).

The mean BAI scores were: controls 6±10.2, CIS 12±7.14, and MS 22±11.3. There was also a significant difference in the mean BAI scores in the three groups (p=0.0003). In post-hoc analysis the only mean BAI significant difference was found between controls and MS patients (p<0.001) (Fig 1A). There was a significant correlation between EDSS and BAI (p=0.002) (Fig 2).

There was a significant difference in the proportion of subjects in the four BDI cutoffs when comparing the three groups (control, CIS, and MS) (p=0.0001). In post-hoc analysis controls versus MS showed significant difference (p=0.004) but there was not a significant difference between CIS and MS (p=0.16) and between CIS and controls (p=0.07) (Table 2). The mean BDI scores were: controls 5±5.56, CIS 6±10.65, and MS 12±7.28. There was a significant difference in the mean BDI scores in the three groups (p=0.01). In post-hoc analysis the only mean BDI significant difference was between controls and MS patients (p<0.01) (Fig 1B). There was a positive correlation between EDSS and BDI (p=0.04) (Fig 2).

DISCUSSION

Our data are in line with previous reports showing higher prevalence of depressive symptoms in MS patients in comparison with controls[20-22]. The precise explanation of depression in MS patients has not been fully

established. A previous study showed that depression in more frequent in MS than in other chronic diseases[6]. Therefore the explanation may not rely only on psychological consequences of having a chronic disease[21,22]. It is possible that neuroinflammatory changes are involved in the pathogenesis of depression in MS[23]. It was shown that the burden of demyelinating lesions is related with the severity of depression[24]. Another possibility is that the use of disease modifiable drugs (DMDs), especially interferon-β, may determine depression[25]. Some studies have suggested that depression severity is related with the progression of the disease while other studies have described depression since the early stages of the disease[20,26]. In our study the BDI score was not related with the time of the disease or EDSS suggesting that the progression of depressive symptoms occurs independently of the functional disability but further and prospective studies are necessary to better understand the evolution of depressive symptoms in MS.

We found significant difference in BAI scores in MS patients when comparing to controls. The mean BAI score was 22±11.3 and most MS patients had moderate anxiety BAI scores. In fact anxiety symptoms have been frequently found in MS patients, with a prevalence ranging from 14% to 41%[6-8]. It was shown that the severity of anxiety symptoms are related with the EDSS score, suggesting that anxiety worsens as the disease progresses[27]. Our data are in accordance with this view since there was a significant correlation of BAI scores, time of the disease, and EDSS. Most of the explanations of anxiety in MS patients has relied on psychological aspects[28]. It is possible that the increased anxiety level in more advanced disease is related with the psychological consequences resulting from progressive neurologic deficits and, hence, limitations imposed by MS.

Some studies have reported depression and anxiety in patients with CIS[6,7]. Di Legge et al. reported anxiety and depression in CIS patients with a tendency towards normalization after a relapse free period. These authors suggested that besides psychological aspects, organic features may be involved in the pathogenesis psychiatric disorders in CIS since they found a correlation between temporal lobe lesion load and depressive scores[29]. In our study depressive and anxiety scores in CIS patients were not significantly different from controls. One possible explanation is that the low number of CIS patients in our study did not allow that a significant difference between CIS and controls was shown. But it is also possible that the lower functional impact of CIS when comparing to MS may explain the lower anxiety and depressive scores in CIS than in MS. The positive correlation between anxiety and scores and EDSS supports this hypothesis.

Our study has some limitations. The sample size may be considered small. However, this sample is representative of the state population, which is one of the smallest in the country. There are no official figures but it is estimated that less than one hundred patients are on MS and CIS treatment with disease modifying drugs (DMDs) in Espírito Santo. The diagnoses of anxiety and depression were not based on psychiatric clinical evaluation. However, Beck inventories for anxiety and depression are largely used both in clinical practice and research.

In conclusion, our data confirm that anxiety and depressive symptoms are more frequent in MS patients than in healthy controls. As depression and anxiety may negatively impact quality of life and reduce the compliance of the patients to the treatment[30], the recognition and treatment of these neuropsychiatric syndromes are of paramount importance for a better MS outcome and an improved quality of life.

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