Depressive Symptoms in Machado-Joseph Disease (SCA3) Patients and Their Relatives

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Key Words
Machado-Joseph disease · Spinocerebellar ataxias · Polyglutamines · Depressive symptoms · Multiple sclerosis

Abstract

Objectives: It was the aim of this study to determine the depression scores of Machado-Joseph disease (MJD) patients, their spouses, and individuals at 50% risk for MJD, and second, to verify the existence of a correlation between depressive symptoms and the degree of motor incapacitation. Subjects and Methods: Two hundred and forty-six individuals aged \geq 18 years were studied: 79 MJD patients (group 1), 43 spouses of MJD patients (group 2), 80 individuals at risk for MJD (group 3), and a control group (group 4) composed of 44 patients with multiple sclerosis (MS). The following two tools were applied: the Beck Depression Inventory and the Barthel index of physical incapacitation, both in an adapted Brazilian Portuguese version. Results: Moderate to severe depressive scores were found in 33.5% of patients in the MJD families, in 16.3% of the spouses, and in 6.3% of the individuals at risk. This linear reduction between MJD family members was statistically significant (p < 0.0001, ANOVA). Depressive scores were also associated with age and the female sex. A direct correlation between Beck Depression Inventory scores and motor incapacitation was found in MJD patients (r = 0.507, Pearson correlation, p < 0.0001). Although the depressive symptoms in the control group with MS were higher than those found in MJD patients (59% of MS patients showed moderate to severe scores), depression did not correlate with physical incapacitation, age, or education attainment in the MS group. Conclusions: Depressive symptoms are rather common in MJD patients and in their spouses (caregivers). In this condition, depression seemed to be more reactive than primarily related to the disease process itself.

Introduction

Machado-Joseph disease (MJD/SCA3) is an autosomal dominant degenerative disorder of the central nervous system, characterized by spinocerebellar ataxia (SCA), and was first reported in North American families of Portuguese-Azorean descent [1–3].

The gene associated with MJD is located on chromosome 14q32.1 [4] and contains a CAG repeat in the 5’ region of the coding sequence, which is expanded in MJD.
MJD is a highly disabling disease. The onset of its clinical manifestations usually occurs during adulthood, and the mean age (±SD) of onset is 32 ± 12 years for Brazilian patients [8]. First, patients are confined to a wheelchair, and later, they become bedridden [4]. The distribution of age of onset is very wide, ranging from 5 to 73 years in Portuguese patients [2]. Penetrance is high but incomplete, since rare obligate carriers free of symptoms have been seen until as late as the age of 90 [3]. Median survival time after onset varies from 14 to 17 years [2, 8].

Clinical manifestations include (1) cerebellar ataxia affecting gait, limb movements, speech articulation and deglutition, (2) a pyramidal syndrome with brisk deep tendon reflexes, Babinski sign and spasticity, (3) a progressive external ophthalmoplegia of supranuclear origin, with early limitation of upward gaze and convergence, and less frequently nuclear ophthalmoplegia, (4) extrapyramidal signs, including dystonia, rigidity and bradykinesia, (5) lower motor neuron disease, with fasciculation and amyotrophy, (6) sensitive loss, and (7) eyelid retraction, contraction fasciculation, weight loss, and sleep disorders [2].

In our experience, although rarely mentioned in the literature, depressive symptoms are quite common in MJD patients. It is widely known that a depressive mood can worsen several disease manifestations. Therefore, recognizing depressive disorders and potential needs of treatment would benefit MJD patients and their families.

The objectives of the present study were (1) to determine the depression scores of MJD patients, their spouses, and individuals at 50% risk for MJD, (2) to evaluate whether depressive symptoms correlate with the degree of motor disability, and (3) to compare these findings with a control group of patients with multiple sclerosis (MS).

**Subjects and Methods**

MJD patients were previously diagnosed in a reference center and were invited to participate, along with their relatives, through phone calls. After individuals agreed to participate, a structured interview was conducted. If necessary, a second interview was scheduled. Individuals were told that they were completely free to break off the conversation at any moment, without any influence on their future treatment. Since it was easy for individuals not to answer the phone or not to permit the interview to be conducted over the phone, participation in the study was completely free. On the other hand, telephone calls reached individuals that otherwise would never come to interviews in our outpatient clinics. Recruitment was based on a registry of MJD families, which counted 60 families at the time of the study. Individuals were subdivided into three groups: MJD patients (group 1), i.e. symptomatic individuals who already had a molecular diagnosis, spouses of MJD patients (group 2), and healthy individuals at 50% risk for MJD (group 3), i.e. either siblings or children of molecularly identified patients. Other neurological patients, all with MS, were recruited as a control group (group 4); these patients had been diagnosed in the same hospital according to the diagnostic criteria of Poser et al. [9]. Both symptomatic groups, i.e. MJD patients (group 1) and MS patients (group 4), were contacted at least 1 year after receiving the diagnosis. Data such as age, sex, education attainment, and marital status were also collected. Only individuals aged ≥ 18 years were included in the study. The present study was approved by the local institutional research board, as well as by the national board (CONEP). Two different tools were used in this study: the Beck Depression Inventory (BDI), in its Brazilian version, to quantify the depressive symptoms [10–12], and the Barthel index (BI) of physical incapacitation [13], in an adapted Brazilian Portuguese version. The severity of neurological disease (MJD and MS) was assessed by the BI. The BI is an ordinal scale that measures functional independence in the domains of personal care and mobility. A score range from 0 to 45 indicates severe disability (marked or complete neurological disturbance), a score range from 50 to 70 corresponds to moderate disability, and a score range from 75 to 100 indicates minimal or absent neurological disturbance. A patient with a BI score of 100 is independent in performing daily activities. He is continent, feeds and dresses himself, gets out of bed and chairs, bathes himself, walks at least a block, and can ascend and descend stairs [13].

The BDI depression scores are usually interpreted as follows: 0–10 (absence or subtle depression), 10–18 (mild depression), 19–29 (moderate depression), and 30–63 (severe depression). Average ± SD BDI scores in control populations range from 6.47 ± 5.6 to 9.98 ± 7.8 [11, 12, 14]. In the present study, psychotherapeutic evaluation was offered to individuals with a BDI score of 19 or higher.

The BDI scores of the MJD subgroups were compared using ANOVA with a linearity test. The possible association between the BDI score and incapacitation scores (BI) was tested using Spearman’s correlation test, first in MJD patients, and then in MS patients. Confounding variables between MJD subgroups, such as sex, age and education attainment, were controlled using a multiple linear regression. The significance level was 0.05.

**Results**

At least 1 patient of each family of the local registry was contacted, and all individuals that were contacted agreed to participate. A total of 246 individuals participated in the present study: 79 MJD symptomatic patients (group 1), 43 spouses of MJD patients (group 2), and 80 individuals at risk for MJD (group 3). The neurological
control group was composed of 44 MS patients (group 4). The clinical characteristics of these subgroups are presented in table 1. The number of spouses was lower than the number of patients, mainly because several patients were single or divorced (only 47 of 79 patients were married).

**Results among Individuals of MJD Families (Groups 1, 2 and 3)**

Mean BDI scores (± SD) are shown in table 1. Depressive scores in group 1 were significantly higher when compared with the other two groups. Differences in depressive symptoms between groups were both statistically significant (p < 0.0001, ANOVA) and showed a clear trend towards linear worsening from individuals at risk to spouses and to MJD symptomatic patients (fig. 1).

Age, sex and education attainment could be confounding factors, since the three MJD subgroups differed in these respects (table 1). However, multivariate analysis showed that in all the MJD samples (groups 1, 2 and 3), age, sex and education attainment were all independently associated with depressive scores (p = 0.001, p = 0.03, and p = 0.0001, respectively).

When the three MJD subgroups were separately analyzed, we found that the BDI scores were significantly higher for the women of groups 1 and 2 (table 2). These results indicate that both female patients and healthy wives of MJD patients are more prone to depression than men.

Education attainment seemed to be different in the three MJD groups: patients were less educated, and individuals at risk were more educated than the average of all MJD cases (table 1). This probably reflects the trend towards higher education attainment in the younger generations. In any case, education attainment did not influence depressive scores (multivariate analysis).

The BDI scores from 19 to 29 are interpreted as indicators of moderate depression, and from 30 to 63, of severe depression. Moderate to severe depressive scores, in the BDI, are clinically significant and are used as a screening for depressive disorders. They were found in 33.5% of the patients of group 1, in 16.2% of group 2 (spouses, i.e. caregivers), and in 6.2% of group 3 (individuals at risk for MJD). In fact, both the mean BDI score and the pro-

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**Table 1. Characteristics of the individuals studied**

<table>
<thead>
<tr>
<th>Group</th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total sample</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>79</td>
<td>43</td>
<td>80</td>
<td>44</td>
<td>246</td>
<td></td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>45/34 (57/43%)</td>
<td>14/29 (32.6/67.4%)</td>
<td>20/60 (25/75%)</td>
<td>13/31 (30/70%)</td>
<td>92/154 (37.4/62.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Age, years</td>
<td>42.1 ± 11.9</td>
<td>48.4 ± 13.5</td>
<td>30.5 ± 9.7</td>
<td>43.6 ± 8.3</td>
<td>39.7 ± 12.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Education attainment, years</td>
<td>7.4 ± 3.6</td>
<td>7.5 ± 3.8</td>
<td>8.9 ± 3.2</td>
<td>8.5 ± 3.7</td>
<td>&lt;0.052 (between MJD groups)</td>
<td></td>
</tr>
<tr>
<td>BDI scores</td>
<td>15.6 ± 9.9</td>
<td>10.5 ± 9.8</td>
<td>5.6 ± 6.9</td>
<td>21.6 ± 8.7</td>
<td>12.5 ± 10.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BDI scores (&gt;30 years old)</td>
<td>16.2 ± 10.2 (n = 64)</td>
<td>11.2 ± 10.4 (n = 35)</td>
<td>6.3 ± 8.17 (n = 34)</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barthel incapacitation scores</td>
<td>87.1 ± 15.2</td>
<td>97.9 ± 6.9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data are given as mean ± SD. Group 1: MJD, symptomatic patients; group 2: spouses of MJD patients; group 3: individuals at 50% risk for MJD; group 4: MS controls.
portion of moderate and severe scores found in group 3 were comparable with those found in the general population in Brazil [11, 12, 14].

CAG repeat lengths (CAGn) in patients of group 1 varied from 68 to 81, with an average of 74 repeats, while the mean age of onset of neurological symptoms was 34 ± 10.5 years. The number of CAG repeats did not correlate with the BDI scores. The same lack of correlation was found between age of onset of MJD symptoms and the BDI and BI scores.

**Results Comparing MJD (Group 1) and MS (Group 4) Patients: Correlation between Depressive Symptoms and Physical Incapacitation**

In MJD patients (group 1), the BI of physical incapacitation varied from 7 to 100 points, with a mean score of 87.1 ± 15.7. A positive correlation was found between physical incapacitation and depressive symptoms in MJD patients (r = 0.494, Spearman correlation, p < 0.0001).

MS patients showed important differences in their depressive characteristics when compared with MJD patients: MS patients were more depressed, but less incapacitated. The MS group had significantly higher depression scores (average BDI score 21.61 ± 8.73), whereas the score of MJD patients was 15.62 ± 9.9 (p < 0.001, t test). These findings are also seen in the different rates of patients with moderate and severe depressive scores: 33% of MJD patients had moderate to severe depression versus 59% of MS patients (fig. 2). On the other hand, the BI was better in MS patients than in MJD patients (97.9 ± 6.9 and 87 ± 15.2, respectively; p < 0.001, t test) and was not associated with depressive symptoms in MS (fig. 3).

In MS patients, only gender was associated with the BDI scores (p = 0.024). This was not the case with age, education attainment and physical incapacitation (multiple linear regression, r² = 0.23).

**Discussion and Conclusions**

Depression is a rather common medical condition in primary care practice [15–17]. It is said to affect 4% of the general population [18], women being 2–3 times more affected than men [19]. Several organic diseases are associated with depressive symptoms, working either as risk factors or as determinants of depression. Indeed, depressive symptoms are present in 12–36% of individuals with general chronic conditions, such as, among others, diabetes, coronary artery disease, hypertension, and obesity. Since SCAs are chronic disorders, the finding of depressive symptoms in these patients is not surprising.
Neurodegenerative autosomal dominant conditions impose a considerable burden not only on patients, but also on their families, especially on spouses and the individuals at risk. These phenomena have been more extensively studied in Huntington’s disease. For instance, Tibben et al. [20] observed that spouses followed the same course of distress as carriers of Huntington’s disease. Individuals at risk have received extensive psychological support and have participated in worldwide follow-up studies, focusing mainly on adverse effects of predictive testing [21, 22]. Similar study designs have been reported in relation to other adult-onset disorders, such as Alzheimer’s disease [23] and breast/ovarian cancer [24, 25]. Most of these papers indicate that people most prone to distress are those individuals who seek genetic counseling (GC). Specific literature about individuals at risk for MJD is scarce. A recent study on this issue reported that the depressive scores of individuals at risk for MJD in the Azores were in the normal range [26].

Few studies based on quantitative analyses have examined psychological and behavioral aspects in MJD patients with established disease. These studies have demonstrated slow processing of visual information [27] and visual memory impairment [28], both possibly related to compromised executive and emotional functions [29]. Cognitive impairment and dementia have already been associated with SCAs in general [30] and MJD in particular [31], but more rarely with the latter. Depressive symptoms in MJD have also been reported, especially mood swings, irritability [32], and moderate to severe levels of depressive symptoms in the BDI-II [29]. However, these reports have been anecdotal or limited to few MJD cases. Possibly the best study about the psychological burden of MJD on patients and their relatives is that of Boutté [33]. According to this researcher, the stigma provides a definitive mark that brings discredit to the individual’s life projects, affecting patients, their descendants and spouses.

The present study was observational and compared depressive scores (BDI) between MJD patients, individuals at risk, and their non-related spouses. Depressive symptoms were quite frequent in the present sample of MJD patients, since 33.5% showed significantly high (moderate to severe) BDI scores. This finding confirms our hypothesis that depression, either organic or reactive, is associated with MJD.

Abnormally high BDI scores were also found for spouses (10.51 ± 9.8), at least when compared with a historical sample of a healthy population (6.47 ± 5), whereas individuals at risk for MJD did not show scores compatible with depression. Environmental factors seem to play an important role in the appearance of depressive symptoms in the present sample. Spouses, especially wives, are those who usually help MJD patients in their daily needs. As

Fig. 3. Correlation between physical incapacitation (BI) and depression scores (BDI) in groups 1 (a, MJD patients) and 4 (b, MS patients).
caregivers, they are probably more susceptible than other relatives to the frustrations of witnessing the downhill course of the disease. Thus, in spite of having no risk for MJD, spouses were more depressed than their children at risk.

The finding of normal BDI scores for individuals at risk (group 3) was a surprise. Individuals at risk can be divided into those who seek GC and those who decline GC. Research indicates that people who seek GC are in distress [25], but also that individuals who decline GC may be at increased risk for depressive symptoms [34, 35]. We think that the way individuals of the present study were recruited – by telephone calls – allowed us to sample, among others, people that would not otherwise go to an appointment in an outpatient clinic. In other words, it allowed us to sample both those individuals at risk who seek and those who decline GC. If this is true, the present sample is probably very representative of the general population at risk. Before conducting the study, we anticipated that being at risk for MJD would cause mild to moderate depressive symptoms. Evidence did not confirm this hypothesis, based on former experience with individuals at risk that seek medical care (mainly GC). Individuals that seek medical attention are probably more motivated, more informed, and/or more psychologically distressed. Therefore, we believe that the low percentage of depressive scores found for at-risk individuals is true and thus deserves some interpretation.

One explanation would be that the study sample was composed of young individuals, and that the effect of age could be influencing the depressive scores. In fact, the BDI depression scores were related to age in the whole sample. However, the multiple linear regression showed that age and being at risk act independently in the BDI scores. For this reason, the low BDI scores in group 3, which were even lower than those found in the general population, could not simply be attributed to the younger age of this group.

Psychodynamic mechanisms may be another explanation for the lower depression scores found in group 3. Living with uncertainty about one’s carrier state could lead a person to use denial as a defense mechanism against emotional suffering. According to Vincent [36], BDI scores lower than 4 are highly suggestive of denial, operating against depressive feelings. In favor of this interpretation is the fact that the level of adherence to predictive test programs was generally lower than expected [32]. In other words, most people at risk for autosomal dominant neurodegenerative diseases prefer not to know about their genetic status and this ‘not knowing’ attitude bears some resemblance to denial.

A positive and apparently biologically significant correlation was found between depressive scores and incapacitation levels in MJD patients. Of course, incapacitation and depression may reinforce one another.

The same cannot be said for MS patients: they were far less incapacitated and, at the same time, more depressed than MJD patients.

The MS group was studied in order to contrast some characteristics of depressive manifestations with those found in the MJD group. General clinical findings and psychological characteristics of MS, besides biological markers and therapeutic interventions, have been an object of intense investigation in the medical literature. Compared with MJD, MS is quite well known. MS has a different etiology and pathogenesis. To begin with, there is no major gene involved in MS. The only similarities shared with MJD are its chronic, long-term course and its neurological involvement. We compared groups 1 and 4, expecting that the possible differences observed would be attributable to the main differences between MJD and MS – etiology and pathogenesis – and not to their principal similarity – being a chronic, progressive neurological disease. This was done in order to test if the common prejudice is true, namely that having a progressive neurological disorder would fatalistically cause a depressive mood. The present findings show that depressive symptoms in these two disorders had a different pattern of associated risk factors, and this probably means that the nature of depressive symptoms in both MJD and MS is different.

For instance, one might argue that the finding of more severe depressive symptoms in MS patients was not a surprise, and that it could be due to a known effect of the pathogenic process of MS on higher mental functions. In fact, depression is common in MS, and the lifetime prevalence of a major depressive disorder after receiving a diagnosis of MS is above 50%. Although the etiology of depression certainly includes psychosocial factors, its high prevalence within MS also suggests organic MS-specific etiologies. Structural changes in the brain related to dysmyelination have been suggested as causative of or contributing to depression [37, 38].

The relative independence of depressive manifestations in MS of environmental markers (the lack of association with incapacity scores, age, and education attainment) argues in favor of depression being a direct consequence of the disease process. Nonetheless, a quite different relation between depression and physical inca-
Depressive Symptoms in MJD

In conclusion, depressive symptoms are quite frequent in MJD patients, as well as in their spouses. In both groups, these symptoms should be recognized so as to offer an appropriate support for these individuals.

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7. Maciel P, Costa MC, Ferro A, Rousseau M, Furtado S, Ribeiro R: The present work was partially supported by Comissão Nacional de Pesquisa (CNPq), Comissão de Aperfeiçoamento do Pessoal de Ensino Superior (CAPES), Fundação de Amparo à Pesquisa do Rio Grande do Sul (FAPERGS), Brazil. A grant was given by Instituto de Cooperação em Ciência e Tecnologia Internacional (ICCTI), Portugal. Prof. Jardim is supported by CNPq, Brazil.


