INSTITUTO DE PSIQUIATRIA- IPUB

Centro de Ciências da Saúde- CCS

Universidade Federal do Rio de Janeiro

Alterações Neuropsiquiátricas da Esclerose Múltipla

Tese de Doutorado submetida ao Corpo Docente do

Programa de Pós-Graduação em Psiquiatria e Saúde Mental -

PROPSAM do Instituto de Psiquiatria da Universidade Federal

do Rio de Janeiro, como parte dos requisitos necessários para obtenção do

Grau de Doutor em Ciências da Saúde - Área de

Concentração em Psiquiatria.

Orientador: Professor Antonio Egídio Nardi

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RIO DE JANEIRO

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ANA CLAUDIA RODRIGUES DE CERQUEIRA

Tese de Doutorado submetida ao Corpo Docente do Programa de Pós-Graduação em Psiquiatria e Saúde Mental - PROPSAM do Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro, como parte dos requisitos necessários para a obtenção do Grau de Doutor em Ciências da Saúde - Área de Concentração em Psiquiatria.

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1. Neuropsiquiatria, Esclerose Múltipla

I. Título: Aspectos Neuropsiquiátricos da Esclerose Múltipla.

II. Tese de Doutorado

DEDICATÓRIA

Aos meus pais, pelo amor incondicional em todos os momentos da minha vida.

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Ao Professor Antonio Egídio Nardi, orientador desta tese, por tudo que me ensinou e principalmente pelo crescimento profissional que me proporcionou.

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Ao CNPq pelo apoio financeiro de bolsa e financiamento de pesquisa.

"Nosso cérebro é o melhor brinquedo já criado: nele se encontram todos os segredos, inclusive o da felicidade."

Charles Chaplin

RESUMO: O objetivo deste estudo foi avaliar a freqüência de transtornos psiquiátricos, especialmente transtornos de humor e ansiedade, em uma amostra ambulatorial de pacientes com esclerose múltipla (EM), correlacionar os resultados com dados sociodemográficos e clínicos, e determinar o impacto da fadiga e da depressão na qualidade de vida (QV). Métodos: Foi realizado um estudo transversal em pacientes ambulatoriais com o diagnostico de EM avaliados consecutivamente. O diagnóstico de transtornos psiquiátricos foi realizado por meio de entrevista estruturada *Mini International Neuropsychiatry Interview* (MINI), a gravidade dos sintomas de depressão e ansiedade foram avaliadas através dos inventário de Beck. A QV foi avaliada através do SF-36, a gravidade da fadiga foi detectada utilizando a escala de impacto da fadiga na vida diária (D-FIS). Resultados: A prevalência de depressão maior ao longo da vida na população estudada foi alta, assim como o risco de suicídio. Foi detectada associação entre depressão e grau de incapacidade da doença (EDSS). Em relação a QV avaliada pelo SF-36, foi encontrado piora significativa da QV em pacientes com fadiga e depressão. Conclusão: A prevalência de transtornos de humor é alta na EM. A depressão deve ser cuidadosamente investigada em pacientes com EM porque é um importante fator relacionado ao risco de suicídio nesta população, e exerce impacto negativo na QV de pacientes com EM.

Palavras-chave: esclerose múltipla, distúrbios psiquiátricos, depressão, suicídio, qualidade de vida, fadiga.

Abstract: The aim of this study was to evaluate the frequency of psychiatric disorders, particularly mood disorders and anxiety, in an outpatient sample of patients with multiple sclerosis in Brazil and correlate the results with sociodemographic and clinical data, and to determine the impact of fatigue and depression on QOL. Methods: Cross-sectional study, patients evaluated consecutively. The prevalence of psychiatric disorders was evaluated using structured interviews (MINI), while the severity of symptoms of depression and anxiety was evaluated using the Beck inventory. For QOL was used SF-36, prevalence of fatigue was used D-FIS. Results: The prevalence of major lifelong depression in this population was high and suicide risk. There was detectable correlation between depression and degree of disability. Regarding QOL as assessed by the SF-36, deterioration in QOL in patients with fatigue and depression was detected. Conclusion: The prevalence of mood disorders is high in MS. Depression is an important factor related to the risk of suicide and should be carefully screened for in patients with MS because they are highly associated, and because the depression can determine negative impact QOL of patients with MS.

Keywords: multiple sclerosis, psychiatric disorders, depression, suicide, quality of life, fatigue.

Sumário

APRESENTAÇÃO

O interesse pelo estudo do comportamento humano foi importante na escolha de minha primeira graduação, em psicologia. No entanto, foi durante este curso que tive os primeiros contatos com a psiquiatria, através da disciplina de psicopatologia especial, ministrada pelo saudoso Professor João Ferreira Filho. A partir deste momento, o sonho de fazer medicina começou a surgir. Já nos primeiros anos do curso de medicina na Universidade Federal Fluminense (UFF), fiz estágio de iniciação científica por quatro anos na área de neuroquímica, sob a orientação do Professor Roberto Paes de Carvalho. Os meus primeiros contatos com a neurociência e pesquisa básica iniciaram-se neste período.

No entanto, a minha formação em psicologia sempre esteve presente e me influenciou no modo de enxergar o paciente, observando que não só os fatores físicos, mas os emocionais e psíquicos interferem na sua saúde. Foram nesses quase vinte anos de exercício da medicina, que pude perceber que a prevalência de transtornos psiquiátricos, particularmente a depressão em populações clínicas é alta, principalmente nos portadores das diversas condições neurológicas.

Durante o período da Residência médica em Neurologia, na Universidade do Estado do Rio de Janeiro (UERJ) fez parte do meu treinamento, o atendimento aos pacientes portadores de esclerose múltipla (EM), no ambulatório de neuroimunologia do Hospital Pedro Ernesto (HUPE/UERJ), sob supervisão do Professor José Maurício Godoy Barreiros. O interesse em estudar EM ocorreu não apenas pela exuberante sintomatologia neurológica apresentada pelos pacientes, mas pelos aspectos neuropsiquiátricos relacionados a esta condição.

A escolha em fazer a Pós-graduação no Instituto de Psiquiatria da UFRJ (IPUB-UFRJ) ocorreu por se tratar de um centro de pesquisa reconhecido internacionalmente, através de seus pesquisadores, entre eles o Professor Antonio Egídio Nardi, orientador desta tese, e principalmente pela possibilidade em desenvolver uma linha de pesquisa com a qual me identificava.

Desta forma, foi elaborado o projeto de pesquisa que visava avaliar aspectos neuropsiquiátricos em pacientes com esclerose múltipla, este projeto teve forte aceitação pelos professores da UERJ, José Maurício Godoy Barreiros e José Marcelo Ferreira Bezerra, o que possibilitou o desenvolvimento desta linha de pesquisa, resultando em diversos trabalhos apresentados em congressos nacionais, e publicados em periódicos nacionais e internacionais.

Ao longo desses anos, aprendi que o grande segredo para ser um grande pesquisador consiste em trabalhar em colaboração com outros pesquisadores. Durante o doutorado conheci o Professor Antonio Lúcio Teixeira Júnior, da Universidade Federal de Minas Gerais (UFMG), e por me identificar com as linhas de pesquisa desenvolvidas por ele, resolvi convidá-lo para ser coorientador desta tese. A partir desta colaboração, surgiu o desejo de ampliar esta linha de pesquisa, e incluir o estudo do impacto da depressão sobre as funções cognitivas, e o estudo da correlação entre biomarcadores periféricos (incluindo fatores inflamatórios e fatores neurotróficos) e depressão maior em pacientes com EM. Este projeto encontra-se em pleno desenvolvimento, possibilitará identificar possíveis biomarcadores de sintomas de humor em pacientes com EM.

1. INTRODUÇÃO

A esclerose múltipla (EM) é uma doença crônica e inflamatória do sistema nervoso central (SNC), que atinge predominantemente a substância branca através de lesões que promovem a destruição da mielina, oligodendrócitos, e axônios. A etiologia é desconhecida, algumas teorias sugerem uma interação entre fatores imunológicos, genéticos, ambientais e infecciosos. A fisiopatologia da EM ainda não está completamente esclarecida. Trata-se de uma doença imunomediada, na qual ocorre uma resposta autoimune contra vários antígenos proteicos e lipídicos presentes na mielina do SNC. A prevalência varia nas diversas regiões do mundo, porém na América do Sul é considerada baixa, com menos de 15 casos por 100.000 habitantes. A incidência é maior no sexo feminino com uma proporção de 2:1.[1,2]

O diagnóstico da EM é baseado na ocorrência de dois eventos neurológicos consistentes com desmielinização no SNC que são separados temporal e anatomicamente, demonstrado através de evidências clínicas e para-clínicas. O início dos sintomas ocorre principalmente em indivíduos jovens na faixa etária entre 20-40 anos, e a longa duração da doença resulta em elevados custos sociais com redução da capacidade laborativa e na qualidade de vida (QV). As manifestações clínicas incluem: alterações sensitivas; déficit motor; alterações esfincterianas; neurite óptica; diplopia e sinais cerebelares.[1,2]

A observação de que a evolução da doença segue determinados padrões clínicos, levou à descrição de “tipos” ou formas clínicas da EM. Sendo

assim, a doença pode ser classificada em varias formas de acordo com critérios clínicos caracterizados pela ocorrência de *surtos* e *progressão*: recorrente-remitente, primariamente progressiva, secundariamente progressiva, progressiva com surtos. [1,2]

A presença de sintomas psiquiátricos na EM é conhecida desde a primeira descrição clínica da *sclérose en plaques* por *Jean Martin Charcot* no Hospital Pitiê-*Salpêtrière* no século XIX, em Paris. Os sintomas neuropsiquiátricos descritos por *Charcot* incluem: choro e riso patológico; euforia; mania; alucinações; e depressão.[3]

O principal objetivo deste trabalho foi estudar as principais alterações neuropsiquiátricas em pacientes com EM, especialmente transtornos de humor e de ansiedade. Os objetivos secundários foram avaliar possíveis fatores de risco associados a depressão nesta população, e o impacto da depressão sobre a QV em pacientes com EM.

Desta forma esta tese é composta de cinco artigos que abordam os diferentes aspectos neuropsiquiátricos da EM como depressão maior, transtorno bipolar, transtornos de ansiedade, suicídio, fadiga e QV.

No primeiro artigo, " **Depression and multiple sclerosis: on overview "**, publicado na *Revista Brasileira de Neurologia,* fizemos uma revisão sistemática detalhada, abordando os principais aspectos relacionados à depressão maior na EM.

No segundo artigo, **Psychiatric Disorders in Patients with Multiple Sclerosis,** *in press* no periódico *Comprehensive Psychiatry*, realizamos um estudo transversal onde foi avaliada a frequência de transtornos psiquiátricos, principalmente do humor e de ansiedade em uma amostra clínica de pacientes com EM.

No terceiro artigo, **Bipolar disorder and multiple sclerosis: comorbity and risk factors**, publicado na *Revista Brasileira de Psiquiatria*, discutimos a associação entre transtorno bipolar e EM.

No quarto artigo, **Depression and multiple sclerosis: A cross-sectional study** , submetido à publicação, demonstramos correlação positiva entre depressão e o grau de incapacidade na EM.

Por fim, no quinto artigo, **Quality of life in multiple sclerosis: The impact of fatigue and depression**, submetido à publicação, avaliamos o impacto da fadiga e da depressão na QV de pacientes com EM.

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Depressão e esclerose múltipla: Uma visão geral

Depression and multiple sclerosis: on overview

*Ana Claudia Rodrigues de Cerqueira[1]
Antônio Egídio Nardi[2]

Resumo

O risco de depressão em pacientes com esclerose múltipla (EM) é de aproximadamente 50% ao longo da vida. A depressão acarreta sofrimento psíquico, diminui a aderência ao tratamento, piora a qualidade de vida, e aumenta o risco de suicídio em pacientes com EM. ***Objetivo****: Conduzir uma revisão de estudos apresentando uma visão geral abordando aspectos relevantes relacionado à depressão e esclerose múltipla tais como prevalência, aspectos neurobiológicos, implicações clínicas e estratégias terapêuticas.* ***Métodos****: A base de dados PubMed / Medline foi pesquisada sem limite de data para todos os artigos publicados escritos em inglês, utilizando os descritores "depression", "mood disorders" e "múltipla sclerosis". Somente artigos originais e com rigor metodológico na seleção dos pacientes foram relacionados aos objetivos desta revisão foram incluídos.* ***Resultados****: Foram apresentados de forma descritiva e concisa achados relevantes referentes às associações entre prevalência da depressão/ risco de suicídio e EM, aspectos neurobiológicos relacionados à depressão, manifestações neuropsiquiátricas induzidas por medicamentos, relação entre depressão e funções cognitivas, assim como depressão e fadiga, além de aspectos relacionados ao tratamento da depressão na EM.* ***Conclusão****: A prevalência de transtornos depressivos é alta em pacientes com EM, portanto, deve ser investigado de forma sistemática, tendo em vista o elevado risco de suicídio nesta população, o impacto negativo no tratamento e na evolução da doença. Estratégias terapêuticas utilizadas no tratamento da depressão em pacientes com EM incluem o uso de antidepressivos e terapia cognitivo comportamental.*

Palavras-chave*: esclerose múltipla, depressão e transtornos do humor.*

Abstract

The risk of depression in patients with multiple sclerosis (MS) is approximately 50% lifetime. Depression leads to psychological distress, decreased adherence to treatment, worsening the quality of life, and increases the risk of suicide in patients with MS. ***Objective****: To conduct a systematic of studies showing an overview addressing relevant issues related to depression and multiple sclerosis such as prevalence, neurobiological aspects, clinical implications and therapeutic strategies.* ***Methods:*** *A PubMed / Medline was searched without limit date for all published articles written in English using the keywords "depression", "mood disorders" and "multiple sclerosis". Only original articles and methodological rigor in the selection of patients were related to the objectives of this review were included.* ***Results****: We presented a descriptive and concise relevant findings regarding the associations between prevalence of depression / suicide and risk of MS, neurobiological aspects related to depression, drug-induced neuropsychiatric symptoms, the relationship between depression and cognitive functions as well as depression and fatigue, as related to treatment of depression in MS.* ***Conclusion****: The prevalence of depressive disorders is high for patients with MS, therefore, should be investigated in a systematic way in view of the high risk of suicide in this population, the negative impact in the treatment and disease progression. Therapeutic strategies used in the treatment of depression in MS patients include the use of antidepressants and cognitive behavioral therapy.*

Keywords*: multiple sclerosis, depression and mood disorders*

[1]Doutoranda; [2]Professor Titular; Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (IPUB/ UFRJ); Laboratório de Pânico & Respiração

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Introdução

A esclerose múltipla (EM) é uma doença crônica e inflamatória do sistema nervoso central (SNC), que atinge predominantemente a substância branca, através de lesões que promovem a destruição da mielina, oligodendrócitos e axônios. A etiologia é desconhecida, algumas teorias sugerem uma interação entre fatores imunológicos, genéticos, ambientais e infecciosos. A prevalência varia nas diversas regiões do mundo, na América do Sul é considerada baixa, com menos de 5 casos por 100.000 habitantes, ocorre com maior frequência no sexo feminino, em uma proporção de 2:1, acomete principalmente indivíduos jovens na faixa entre 20-40 anos. As principais manifestações clínicas incluem: alterações sensitivas; déficit motor; alterações esfincterianas; neurite óptica unilateral; diplopia; sinais cerebelares, e disfunção cognitiva. O diagnóstico é baseado na ocorrência de pelo menos dois eventos neurológicos consistentes com desmielinização no SNC, separados temporalmente e anatomicamente, demonstrado através de evidências clínicas e para-clínicas.[1,2]

A presença de sintomas psiquiátricos é conhecida desde a primeira descrição clínica detalhada da sclérose en plaques por *Charcot* na *Salpêtrière* no século XIX, estes incluem: choro e riso patológico, euforia, mania, alucinações e depressão[3].No entanto, os primeiros estudos sobre a prevalência da depressão iniciaram-se em 1927 por Cottrell e Wilson's, estes autores detectaram sintomas de depressão em 10% dos pacientes com EM avaliados consecutivamente[4].

Estudos recentes mostram que o risco de depressão em pacientes com EM é de aproximadamente 50% ao longo da vida, enquanto que na população em geral é em torno de 10%[5].A depressão acarreta sofrimento psíquico, diminui a aderência ao tratamento[6],piora a qualidade de vida[7],e aumenta o risco de suicídio em pacientes com EM[8]. O objetivo desta revisão é fornecer uma visão geral abordando aspectos relevantes relacionado à depressão na EM.

Métodos

A base de dados *PubMed / Medline* foi pesquisada sem limite de data para todos os artigos publicados escritos em inglês, utilizando os descritores "*depression*", "*mood disorders*", e "*multiple sclerosis*". Somente artigos originais e com rigor metodológico na seleção dos pacientes foram relacionados aos objetivos desta revisão foram incluídos. No total foram encontrados 310 artigos, sendo que 120 eram originais. As listas de referências dos artigos identificados foram examinadas para selecionar estudos adicionais de interesse. Foram selecionados 32 artigos originais de acordo com os objetivos desta pesquisa.

Prevalência da depressão em Esclerose Múltipla

Um estudo epidemiológico conduzido por *Patten et al.*[9] demonstrou que a prevalência de episódio depressivo por um período de doze meses é aproximadamente 25,7%, em pacientes com EM, e 8,9%, em pessoas sem EM, na faixa entre 18-45 anos. *Sadovnick et al.*[5] avaliando consecutivamente 221 pacientes no Canadá utilizando uma entrevista estruturada, constatou que a prevalência de episódio depressivo é de aproximadamente 50,3% em pacientes com EM. *Chwastiak et al.*[10] em um estudo epidemiológico utilizando a *Centre for Epidemiological Studies Depression Scale (CES-D)*, constatou que 42% dos entrevistados apresentavam sintomas depressivos clinicamente significativos, e destes 29% pontuaram na faixa entre moderado ou grave. Neste estudo, os autores encontraram correlação positiva entre grau de incapacidade funcional e gravidade dos sintomas depressivos, porém outros autores não demonstraram esta relação. Contudo, estes resultados devem ser interpretados com cuidado, tendo em vista a variabilidade de instrumentos empregados pelos pesquisadores para diagnosticar ou quantificar os sintomas depressivos.

Risco de suicídio

Estudos revelam que o risco de suicídio é alto em pacientes com EM. *Bronnum-Hansen et al.*[11] na Dinamarca constataram que o risco de suicídio é mais que o dobro quando comparados a população em geral. *Sandovnick et al*[12]. demonstraram no Canadá que a proporção de mortes por suicídios entre pacientes com EM foi 7,5 vezes maior do que para a população em geral. A diferença nos resultados destes estudos pode ser explicada em parte pelas diferentes metodologias e populações estudadas. *Feinstein*[8] demonstrou que a gravidade dos sintomas depressivos, o abuso de álcool, e o isolamento social parecem ser fatores importantes relacionados à ideação suicida e tentativa de suicídio. A prevalência de ideação suicida ao longo da vida foi de 28,6%, enquanto 6,4% haviam tentado suicídio. Um estudo realizado na Dinamarca por *Stenager et al.*[13] mostrou que o risco de suicídio é maior nos primeiros

cinco anos após o diagnóstico, em homens com início da doença antes dos 30 anos de idade, e diagnosticados antes dos 40 anos. Estes resultados realçam a importância na adoção de medidas preventivas em relação ao suicídio no atendimento a pacientes com EM.

A neurobiologia da depressão

Os principais estudos que mostram uma associação entre fatores de risco neurobiológico e sintomas depressivos na EM, baseiam-se em estudos de neuroimagem. Um dos primeiros estudos sobre este tema foi realizado por *Rabins et al.*,[14] este autor concluiu que pacientes com EM e lesões que afetam o parênquima cerebral apresentaram mais transtornos depressivos, quando comparados aos indivíduos com lesões na medula espinhal. *Zorzon et al.*[15], utilizando ressonância nuclear magnética (RNM) mostrou correlação significativa entre gravidade dos sintomas depressivos e lesões nas regiões frontal e temporal à direita. *Feinstein et al.*[16] concluíram que pacientes deprimidos com EM apresentavam mais lesões nas regiões frontal e temporal esquerda. Os resultados destas pesquisas variam amplamente, portanto poucas conclusões podem ser feitas.

A associação entre neuroimunologia da EM e depressão tem sido pouco investigada, mas parece estar relacionada a mudanças importantes nos parâmetros imunológicos causados pela doença. Um estudo realizado por *Foley et al.*[17] avaliou prospectivamente pacientes com EM e depressão por dois anos, os autores demonstraram uma redução na contagem de linfócitos CD8, e aumento da relação CD4/CD8 nos períodos de maior depressão quando comparados ao grupo controle. Mohr et al.18 investigaram a produção de citocinas pró-inflamatórias interferon gama (IFN-γ) em pacientes com diagnóstico de EM, detectaram maior produção de IFN-γ em pacientes deprimidos, neste trabalho os autores comprovaram que o tratamento da depressão reduz a produção de IFN-γ.

Um estudo realizado por *Fassbender et al.*[19] com o objetivo de avaliar a associação entre anormalidades neuroendócrinas e sintomas depressivos em pacientes com EM, utilizando o teste de supressão com a dexametasona, demonstrou que pacientes deprimidos com EM apresentaram a não-supressão na liberação do cortisol pela dexametasona, semelhante ao que ocorre nos pacientes com depressão. Neste estudo também foi observado que pacientes com maior gravidade dos sintomas depressivos, apresentavam aumento na captação do contraste nos exames de RNM, portanto mais lesões inflamatórias em atividade, evidenciando associação entre atividade de doença e gravidade dos sintomas depressivos.

Manifestações neuropsiquiátricas induzidas por medicamentos

O tratamento farmacológico para EM inclui principalmente o uso de corticoesteróides, imunomoduladores e imunossupressores[1,2].Os corticoesteróides são utilizados em altas doses, por curto período, na fase aguda da doença, potencialmente podem causar várias manifestações psiquiátricas como sintomas psicóticos, delirium, depressão, e mania. No entanto, não existem estudos controlados avaliando os efeitos neuropsiquiátricos induzidos por estes em pacientes com EM. Os imunomoduladores são usados de forma contínua, reduzem à frequência e a gravidade dos surtos, assim como o aparecimento de novas lesões na EM, pode ser utilizado o interferon-beta ou o acetato de glatiramer[1,2]. Os primeiros estudos indicavam que o uso de interferon-beta poderia aumentar o risco de depressão nos primeiros meses do tratamento, porém estes resultados não foram confirmados em pesquisas rigorosas, e recomenda-se utilizá-lo com cautela em pacientes susceptíveis à depressão[20,21].O acetato de glatiramer pode provocar uma reação que consiste em rubor, sensação de aperto no peito, dispnéia, palpitações e grave ansiedade[22]. Por outro lado, drogas imunossupressoras como a azatioprina, ciclofosfamida e o mitroxantona não estão associados a efeitos neuropsiquiátricos. O uso de anticorpos monoclonais como o natalizumab parece não induzir sintomas psiquiátricos.

A relação entre depressão e fadiga

A fadiga é um dos sintomas mais frequentes e incapacitantes na EM, tem impacto negativo sobre o trabalho e a qualidade de vida. Um estudo epidemiológico conduzido por *Hadjimichael et al.*[23] avaliou a prevalência deste sintoma em 9077 pacientes com EM, e detectou a presença de fadiga grave em 74% dos entrevistados. A etiologia e a fisiopatologia são desconhecidas, assim como não existe nenhum marcador biológico reconhecido. Uma associação significativa entre fadiga e sintomas depressivos foi demonstrada por *Koch et al.*[24] em um estudo transversal que avaliou consecutivamente 412 pacientes com EM, porém neste

trabalho os autores não detectaram associação entre fadiga, depressão e incapacidade funcional.

A relação entre depressão e as funções cognitivas.

Estudos avaliando a associação entre a gravidade dos sintomas depressivos e o desempenho cognitivo em pacientes com EM, sugerem uma associação positiva entre depressão e disfunção cognitiva. A depressão moderada a grave parece comprometer principalmente a memória de trabalho, a velocidade no processamento das informações, e as funções executivas[25].No entanto, não existem pesquisas que comprovem que o tratamento da depressão na EM melhore o desempenho cognitivo. Um estudo recente conduzido por *Rabinowitz et al.*[26] mostrou que os déficits cognitivos em pacientes com EM podem prejudicar a capacidade de usar estratégias adaptativas de coping, portanto mais susceptíveis a depressão.

O tratamento da depressão na esclerose múltipla

A presença de sintomas depressivos em pacientes com EM não é diagnosticada por neurologistas, por isso poucos recebem tratamento adequado[27].Um estudo epidemiológico recente conduzido por *Cetin et al.*[28] realizado nos EUA, avaliou a prevalência de sintomas depressivos e o uso de antidepressivos em 542 pacientes com EM, destes 51% apresentavam sintomas depressivos clinicamente significativos, sendo que 35% faziam uso de pelo menos um antidepressivo, os mais utilizados eram fluoxetina, sertralina, citalopram e amitriptilina. Contudo, 10% destes não apresentavam sintomas depressivos, e estavam em uso de antidepressivos para tratamento de dor crônica. Neste estudo, os autores identificaram que apenas 41% dos pacientes com sintomas depressivos clinicamente significativos estavam em uso de antidepressivos.

O uso de antidepressivos tem demonstrado ser eficaz no tratamento da depressão em pacientes com EM, existem poucos estudos controlados que avaliaram o uso de tricíclicos. *Schiffer e Wineman*[29] em uma amostra pequena constataram que a desipramina apresenta eficácia moderada, porém a dose é limitada devido aos efeitos colaterais anticolinérgicos. A amitriptilina e a imipramina são bem toleradas, mas devem ser usadas com precaução em caso de aumento de dose, devido à retenção urinária em pacientes com bexiga neurogênica, aproximadamente 40% interrompem o tratamento devido a efeitos colaterais antes de atingir as doses necessárias para o tratamento da depressão. Um estudo realizado por *Barak et al.*[30] avaliando o uso do inibidor da monoaminoxidase moclobemida, mostrou melhora dos sintomas depressivos com doses entre 150 e 450mg, avaliados através da escala de Beck. Os inibidores da recaptação da serotonina (sertralina, fluoxetina) também têm demonstrado eficácia em estudos abertos com amostras pequenas.[31,32] Há evidências de que a depressão diminui a aderência ao uso de medicamentos auto-injetáveis, como os imunomoduladores. Por outro lado, o tratamento da depressão melhora a aderência ao tratamento.[33]

A terapia cognitiva-comportamental (TCC) é eficaz no tratamento da depressão em pacientes com EM, por isso o estudo do consenso *Goldmann Group*[34,35] recomenda usá-la de forma combinada ao uso de antidepressivos. Entretanto, portadores de EM geralmente apresentam dificuldade de locomoção, o que pode comprometer o tratamento psicoterápico regular. A terapia pelo telefone parece ajudar a superar esta dificuldade[36], um estudo recente realizado por Beckner et al.[37] comparou a eficácia da terapia cognitivo comportamental por telefone (TCC-T) e da terapia focada nas emoções por telefone (TFE-T) em 127 pacientes com EM e depressão. Neste estudo, os autores demonstraram que aqueles com maior suporte social e redes sociais apresentaram maior redução dos sintomas depressivos com a TCC-T. No entanto, indivíduos com baixo suporte social apresentaram resultados similares nas duas formas de psicoterapia, isto porque a abordagem terapêutica da TFE-T pode interferir de forma significativa no apoio social.

Conclusão

A prevalência de transtornos depressivos é alta em pacientes com EM, portanto, deve ser investigado de forma sistemática, tendo em vista o elevado risco de suicídio nesta população, o impacto negativo no tratamento e na evolução da doença. Os mecanismos neurobiológicos são desconhecidos, mas alguns fatores parecem predispor o surgimento de sintomas depressivos. Estratégias terapêuticas utilizadas no tratamento da depressão em pacientes com EM incluem o uso de antidepressivos e terapia cognitivo comportamental, que visam reduzir o sofrimento psíquico, o risco de suicídio e melhorar a qualidade de vida.

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Psychiatric disorders in patients with multiple sclerosis

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Abstract

The aim of this study was to evaluate the frequency of psychiatric disorders, particularly mood disorders and anxiety in an outpatient sample of patients with multiple sclerosis in Brazil, and correlate the result with sociodemographic and clinical data. Methods: Cross-sectional study, patients evaluated consecutively, for the clinical, demographic, prevalence of psychiatric disorders was used structured interview (MINI), severity of symptoms of depression and anxiety was used Beck inventory. Results: The prevalence of major lifelong depression in this population was 36.6%, and the risk of suicide was high. There was no detectable correlation between depression, degree of disability, or disease duration. Conclusion: The prevalence of mood disorders is high in MS. Depression is an important factor related to the risk of suicide and should be investigated systematically.

The presence of psychiatric symptoms in multiple sclerosis (MS) is known from the first clinical description of sclérose en plaques by Charcot at the Hospital Pitié-Salpêtrière in the nineteenth century. These symptoms include pathological crying and laughing, euphoria, hallucinations and depression [1]. The first studies on the prevalence of depression began in 1927 and were conducted by Cottrell and Wilson; these authors identified symptoms of depression in 10% of MS patients evaluated consecutively [2]. Studies have shown that MS patients have an increased risk of presenting with psychiatric disorders, particularly mood disorders. These disorders, if not identified and treated, can worsen patient functioning and quality of life, reduce treatment adherence and increase the risk of suicide. The prevalence of major depression throughout life is between 36% and 54%; bipolar disorder, 13%; and anxiety disorders, 35.7%. The risk of suicide is twice baseline rates in this population [3,4].

The objective of this study was to evaluate the frequency of psychiatric disorders, particularly mood and anxiety disorders, in an outpatient sample of patients with multiple sclerosis in Brazil and to correlate with sociodemographic and clinical data.

1. Material and methods

Between January 2012 and December 2013, a cross-sectional study with a convenience sample of consecutive multiple sclerosis patients was performed at a public university-based outpatient service for Neuroimmunology in Rio de Janeiro, Brazil. In this study, all patients with the diagnosis of multiple sclerosis according to the criteria of McDonald et al. were invited to participate. Exclusion criteria were patients with exacerbation of the disease in the last three months, age under 18 and over 65, higher degree of disability EDSS (Expanded Status Scale Kurtze Disability) > 7.5, schooling less than four years, and patients with other neurological diseases that could potentially interfere with the assessment, such as epilepsy, history of traumatic brain injury (TBI) or stroke.

A complete medical history focusing on the disease, the use of medications, and socio-demographic data was obtained concurrently. A clinical evaluation was performed by neurologists to quantify the degree of incapacity by EDSS

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(Expanded Status Scale Kurtze Disability). The psychiatric evaluation was performed concurrently. For this purpose, we used version 5.0 of the Mini International Neuropsychiatric Interview, a short structured interview designed to explore each of the necessary criteria for the main diagnoses of DSM-IV Axis (American Psychiatric Association, 1994), which was the principal diagnostic instrument. This instrument also contains one specific section that allows for suicide risk assessment [5].

The severity of depressive symptoms was assessed using the Beck Depression Inventory (BDI), and the severity of symptoms of anxiety was assessed through the Beck Inventory for Anxiety (BAI). Patients signed a written informed consent to participate in the study, which was approved by our local Research Ethics Committee.

Pearson χ^2 was performed for categorical univariate analysis, and Student t-tests for independent samples were used for the univariate analysis of continuous variables. SPSS version 18 (SPSS Inc., Chicago, IL, USA) was used to conduct all analyses.

2. Results

A total of 70 patients with MS were invited to participate in the study but 10 were excluded according to the exclusion criteria: 1 due to Parkinson's disease, 1 due to epilepsy, 1 due to brain injury, 1 due to dementia, 2 due to a degree of disability greater than 7.5 obtained in EDSS, 2 due to present age younger than 18 years, and 2 due to lower education level than four years.

In total, 60 patients with MS participated in the study. The sample included 46 (76.7%) female and 14 (23.3%) male patients. Their ages ranged from 19 to 65 years, with a mean of 43 (SD = 11.8). Seventy-five percent of the sample had a degree of education in excess of 11 years. The relapsing–remitting form was found in 49 (81.7%) MS patients. Disease duration ranged from 1 to 28 years, with a mean of 9.6 (SD = 6.8). The degree of disability ranged from 0 to 7.5, with a mean of 2.9 (SD = 2.2). Regarding treatment for MS, 47 (78.3%) were using interferon beta 1A.

Regarding the frequency of mood disorders, 36.6% had depression throughout life, while 13.3% had bipolar disorder (BD). In relation to the frequency of anxiety disorders, generalized anxiety disorder (GAD) was the most frequent, detected in 16.7%, followed by panic disorder (PD) diagnosed in 3.3%. Other anxiety disorders such as obsessive–compulsive disorder (OCD), social phobia (SP) disorder and post-traumatic stress disorder (PTSD) were not detected in this population. For other mental disorders, 1 patient had bulimia nervosa, 1 exhibited dependency and abuse of marijuana and cocaine, and 1 presented psychotic symptoms (Table 1). It is important to mention that 11 patients used some type of antidepressant for several indications; 9 (15%) were using the following antidepressants in therapeutic doses for the treatment of major depression: amitriptyline 75 mg (n = 1), venlafaxine 75 mg (n = 1), fluoxetine 30 mg (n = 1), fluoxetine 20 mg (n = 6). In total, 6 (10%) were diagnosed to be in a current depressive episode, and 3 (5%) had passed from depression, so they had recently recovered. The use of benzodiazepines was reported by 8 patients (13.3%). In total, 31.6% were using some psychoactive drug.

Table 1
Psychiatric disorders in patients with multiple sclerosis.

Psychiatric disorder	N	%
Depression		
Absent	38	63.3
Current depression	11	18.3
Past depressive episode	11	18.3
Bipolar Disorder		
Without bipolar disorder	52	86.7
Hypomania	6	10
Mania	2	3.3
Anxiety disorders		
Absent	48	80
GAD	10	16.7
PD	2	3.3
OCD	–	–
PTSD	–	–
Social phobia	–	–
Alcohol abuse/dependence	–	–
Substance abuse/addiction	1	1.6
Psychotic episode	1	1.6
Eating disorders		
Anorexia nervosa	–	–
Bulimia nervosa	1	1.6
Antisocial personality disorder	–	–

GAD, generalized anxiety disorder; PD, panic disorder; OCD, obsessive–compulsive disorder; PTSD, post-traumatic stress disorder.

In this study, we compared the demographic and clinical characteristics between the groups who were and were not experiencing a current depressive episode (Table 2). The results indicate no significant differences in relation to gender, age or disease duration. The results showed that the severity of symptoms of MS did not seem to be related to major depression.

The risk of suicide was investigated through a MINI-specific section. Of the 60 patients, suicide risk was detected in 16.6%. Of these 8.8% had attempted suicide in the past,

Table 2
Prevalence of depressive and anxiety symptoms in patients with MS.

	N	%
Depressive Symptoms (BDI)		
Absent (0–10)	45	75
Mild (11–18)	11	18.3
Moderate (19–29)	2	3.3
Severe (30–63)	2	3.3
Anxiety Symtoms (BAI)		
Absent (0–7)	39	65
Mild (8–15)	8	13.3
Moderate (16–25)	12	20
Severe (26–63)	1	1.7

and 8.8% were at risk of current suicide, and 1 (10%) low risk, 3 (30%) moderate risk, 1 (10%) high risk. All patients who were at risk of suicide were experiencing a current depressive episode.

The severity of depressive symptoms measured by the BDI showed that 15 (24.9%) patients had depressive symptoms ranging from mild to severe. Their BDI scores ranged from 1 to 45 points, with a mean of 7.7 (SD = 7.7) (Table 3). Our analysis of receiver operating characteristic (ROC) curves indicated that a cutoff point at 10.5 BDI was able to discriminate between patients undergoing a current depressive episode and patients not currently depressed (sensitivity 100%, specificity 61%). The area under the curve was 0.99 (95% CI: 0.0–1.0), indicating good discriminatory power for the instrument (Fig. 1). The severity of anxiety symptoms measured by the BAI showed that 34% patients had anxiety symptoms ranging from mild to severe. Their BAI scores ranged from 0 to 55 points, with a mean of 9.6 (SD = 8.8) (Table 3).

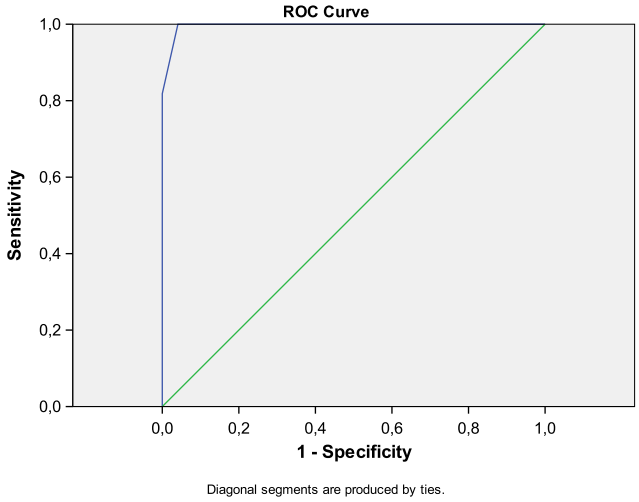

Fig. 1. ROC Beck Depression Inventory curve for the diagnosis of current depression. Cutoff point of 10.5.

3. Discussion

Few studies have evaluated psychiatric comorbidity in clinical samples using structured interviews with a diagnosis consistent with DSM-IV. Feinstein, in Canada, used a Structured Clinical Interview for Axis I DSM-IV Disorders (SCID-I) to evaluate 100 patients with MS; depression was detected in 17% of patients [6]. Using the SCID-I to evaluate 50 patients with the relapsing–remitting form [7], Galeazzi et al., in Italy, identified major depression in 46%, bipolar disorder (BD) in 6%, and anxiety disorders in 37%. Korostil and Feinstein, in Canada, used the SCID-I to assess the prevalence of anxiety disorders in 140 patients with MS; they found that the lifetime prevalence of any anxiety disorder was 35.7%, with panic disorder (PD) 10%, obsessive compulsive disorder (OCD) 8.6%, and generalized anxiety disorder (GAD) 18.6%, the most common diagnoses obtained. Subjects with an anxiety disorder were more likely to be female, have a history of depression, drink to excess, report higher social stress and have contemplated suicide [8].

Table 3
Clinical and demographic characteristics in MS patients with and without current depression.

	depression	absence	
	N/mean	N/mean	
Total	11	49	
Gender			
Man	3	11	p = 0.7[a]
Female	8	36	
Age	45.1	42.5	p = 0.5[b]
Disease duration	8.6	9.8	p = 0.5[b]
EDSS	3.9	2.6	p = 0.08[b]

[a] Pearson χ^2.
[b] t-test.

A study conducted in Brazil by Mendes et al. evaluated the frequency of depressive and anxiety symptoms in patients with the relapsing–remitting form of MS; these authors found depressive symptoms in 17.9% and anxiety symptoms in 34.5% of patients using the BDI and the Hospital scale Anxiety and Depression (HADS), respectively. In this study, the researchers found a positive correlation between depressive symptoms and degree of disability. However, in this study, the authors did not use structured interviews, such as the SCID-I and the MINI, and thus did not assess comorbidity with other psychiatric disorders [9].

Epidemiological studies conducted in the general population reveal that the lifetime prevalence of major depressive episode is approximately 5.6%. The estimated lifetime prevalence of any anxiety disorder is over 15%. The lifetime prevalence of suicide ideation, plans, and attempts was 13.5%, 3.9% and 4.6% respectively [10–12].

We believe that the present study is the first conducted in Brazil that evaluates the frequency of psychiatric disorders in patients with MS, using a structured interview with diagnostic criteria consistent with DSM-IV. The results of our study show that the demographic and clinical characteristics of this sample are similar to those described in the literature, involving mainly young female patients, and the most frequent clinical form the relapsing–remitting MS. Regarding the frequency of mood disorders, major depression was the most common disorder, with 18.5% showing a current depressive episode, and 18% with at least one episode of depression. Therefore, 36.5% had depression throughout life. The analysis of ROC curves indicated that a score of greater than 10 in the BDI is a reliable indicator of depression. It is essential to emphasize that patients with an exacerbation of the disease in the last three months were excluded from the study. This exclusion may explain the lower frequency of current depression in the sample studied when compared to other studies, considering that recent

functional deterioration is associated with the manifestation of major depression in these patients [13]. In addition, during the exacerbation of disease, these patients are treated with high-dose methylprednisolone, which can potentially trigger depression, mania and psychotic symptoms [14]. However, we did not exclude patients who were using antidepressants, and 15% were using this class of drugs for treating depression.

The frequency of BD was high, being detected in 13.3% of the sample. Few studies have evaluated the presence of this disorder in clinical samples; the results of our study are similar to those described by Joffe et al. in which the authors detected BD in 13% of a sample of MS patients evaluated consecutively, suggesting greater susceptibility to BD in this population [15]. Studies in the general population indicate that the aggregate lifetime prevalence of BD-I was 0.6%, BD-II was 0.4%, subthreshold BD was 1.4%, and Bipolar Spectrum was 2.4% [16].

There was a frequency of 20% for anxiety disorders, and of these, 16.3% had GAD. The presence of TP was detected in 3.3%. Other anxiety disorders such as OCD, PTSD and FS were not detected in the sample. Furthermore, the severity of symptoms of anxiety assessed by the Beck inventory detected anxiety symptoms in 34% of patients. It is important to emphasize that many anxiety symptoms assessed by BAI are mistaken for symptoms of MS, such as numbness or tingling, imbalance, tremor, and dizziness, resulting in the discrepancy between the results of the evaluation of the MINI and the BAI. Our results are similar to those described by Beiske et al.; these authors reported anxiety symptoms in 19.3% of patients using the Hopkins Symptom Checklist (HSCL-25) [17]. Moreover, Feinstein and Korostil detected anxiety disorders throughout life in 35.7% of patients with MS using the SCID-I [7]. These differences may be explained by different study populations and different instruments used.

The risk of suicide found in this sample was high. Whereas 8.3% had a past history of attempted suicide and 8.3% had current suicide risk, all patients with current suicide risk had major depression at the time of the interview. The results of this study are similar to those found by Feinstein et al. in which the authors found a past suicide attempt in 6.4% of the patients interviewed. In this study, the authors demonstrated that depression, alcohol abuse, and social isolation are important factors related to suicidal ideation and suicide attempt [18]. The results indicate that major depression is a major risk factor for suicide and should be systematically evaluated in this population.

In this study, we found no statistically significant differences in relation to gender, age, disease duration and degree of disability when compared to the group of patients with MS with and without a current depressive episode. The study population had an average degree of disability from mild to moderate. Although not statistically significant, there seems to be no relatively large difference between the degree of disability among non−depressed and depressed patients. We believe that the relatively low degree of disability in the sample could represent skewed results. Moller et al. found no correlation between age, gender, degree of disability, and disease duration using SCID-I, scales of Montgomery & Åsberg (MADRS) and the Hamilton Depression Rating Scale (HAM-D) in a sample of 27 patients with MS [19]. Zorzon et al., using a psychiatric interview according to DSM-IV and HAM-D, detected major depression in 18.9% of 95 patients with MS. In this study, the authors found no statistically significant differences regarding age, sex, disease duration and degree of disability [20]. The results of these studies are similar to those found in our study.

This study was limited by the size of the sample and because it was conducted in a reference center for the treatment of patients with MS; therefore, all patients enrolled were receiving treatment for this condition. The results of our study allow us to conclude that the frequency of mental disorders, particularly mood and anxiety disorders is high in patients with MS.

4. Conclusion

The presence of mood disorders and anxiety disorders should be investigated systematically in this population because major depression and anxiety symptoms are common in patients with MS. Clinicians should actively treat these condition due to psychological distress, and increased risk of suicide.

Conflict of interest

There is no conflict of interest to declare.

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Bipolar disorder and multiple sclerosis: comorbidity and risk factors

Transtorno bipolar e esclerose múltipla: comorbidade e fatores de risco

Dear Editor,

Multiple sclerosis (MS) is a demyelinating central nervous system (CNS) disease that affects mainly young adults. The disease course is unpredictable, and clinical manifestations include motor deficits, sensory changes, bladder and bowel dysfunction, uni- optical neuritis, diplopia, and cerebellar signs. Rarely, MS may initially present itself as a manic syndrome, similar to that observed in bipolar disorder (BD).[1] We report a patient diagnosed with BD who was later diagnosed with MS. The possibility of mania as a symptom or comorbidity of MS was examined in this case report to assess possible risk factors.

Case report

The patient, JPS, is a 50-year-old divorced female. In 1999, she developed euphoria, irritability, impulsivity, and grandiose delusions. For example, she started taking various classes to achieve grandiose goals, pursuing unrealistic business ideas, acquired several debts that she could not repay, requested dismissal from her employment because she believed she would become a millionaire, exhibited inappropriate seductive behavior, and placed an advertisement in a newspaper offering call girl services that resulted in the termination of her marriage. At that time, her relatives noticed that she was experiencing psychomotor agitation, aggressiveness, auditory hallucinations and delirious ideas; she was admitted to a psychiatric clinic for treatment, and her psychotic symptoms subsequently went into remission with the use of haloperidol plus promethazine. After six months, she presented with daily sadness, anhedonia, psychomotor retardation and fatigue; these symptoms were resolved with 20mg/day of fluoxetine. In 2000, she developed a subacute motor deficit on her left side and gait impairment, both of which partially improved spontaneously. At that time, her CT scan was normal. In 2001, she developed urinary incontinence and was referred for neurological assessment. A clinical examination revealed left hemiparesis, spasticity, and tendon reflexes that were brisk on the left side, and normal on the right side. Her cutaneous-plantar reflex was equivocal on the left side and resulted in toe flexion on the right side, and her gait was hemiparetic on the left side. The remainder of the neurological examination was normal. Magnetic resonance imaging (MRI) of her brain showed demyelinating periventricular lesions (Figure 1). An MRI scan of her cervical cord also showed demyelinating lesions. Autoantibody (anti-Ro, anti-LA, anti-Sm, ANA, anti-DNA and anticardiolipin) and serology (syphilis, hepatitis B and C, HIV and HTLV) tests were negative. Analysis of the cerebrospinal fluid (CSF) detected the presence of oligoclonal bands. Visual evoked potentials showed increased latencies and reduced amplitudes. Based on these findings, the patient was diagnosed with MS, and treatment was initiated with interferon beta-1A. During the nine years of

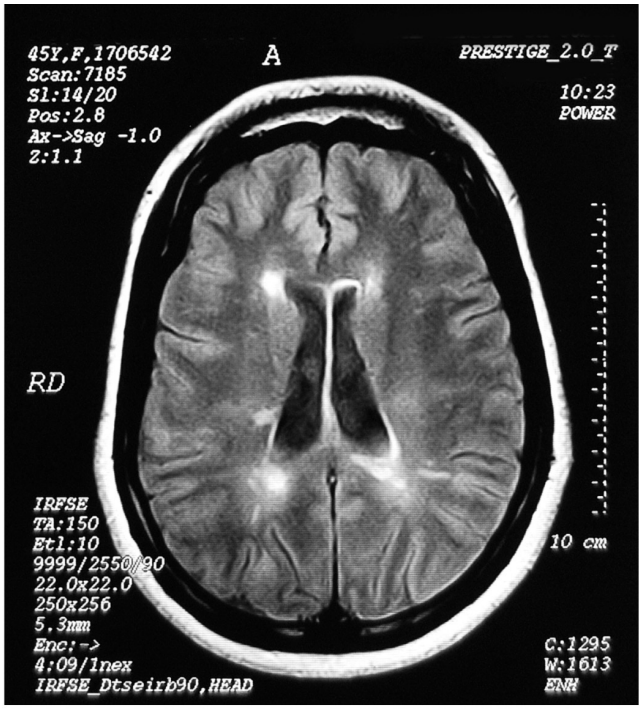

Figure 1 - Brain MRI axial section, showing demyelinating periventricular lesions in a patient presenting bipolar disorder and multiple sclerosis.

follow-up, the patient did not present any episodes suggestive of a mood disorder despite treatment with interferon beta, but she experienced worsening symptoms of her neurological disease. Neuroimaging studies revealed subsequent appearance of new lesions, mainly in the corpus callosum and in the callous-septal interface. Treatment with interferon was discontinued due to the severity of her disability.

Discussion

The association between mood disorders and MS has been described by several studies. There is evidence that this population is more susceptible to BD. An epidemiological study conducted by Schiffer et al. showed that BD is twice as common in patients with MS than in the general population.[2] Joffe et al. showed that 13% of an outpatient sample of patients with MS were diagnosed with BD.[3] In these two studies, patients with a history of hypomania/mania episodes due to corticosteroid use were excluded. Using MRI, Lyoo et al. systematically evaluated 2,783 individuals who had been referred for psychiatric hospitalization and found changes in white matter that were compatible with the neuroradiological criteria of MS in 23 patients (0.83%).[4] The mechanisms underlying these associations are unknown and have been poorly investigated to date. Family studies investigating the involvement of HLA (human leukocyte antigen) genes have demonstrated a common genetic susceptibility among patients with BD and MS.[5]

We described a patient diagnosed with BD according to the DSM-IV-TR who was later diagnosed with MS according to the MacDonald criteria. Because a detailed neurological examination was not available at the onset of this case, it is impossible to assert that the patient's mania was a symptom of MS. However, the absence of a personal or family history of BD and the late onset of symptoms raises this possibility.

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Disclosures

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Qual a verdadeira associação entre disfunção cognitiva e o uso da *cannabis*?

What is the really association between cognitive disfunction and cannabis*?*

Prezado Editor,

Foi com grande interesse que lemos o artigo de revisão "Anormalidades cognitivas no uso da *cannabis*" publicado no primeiro suplemento da Revista Brasileira de Psiquiatria de 2010.[1] O artigo trata de forma bem objetiva a possibilidade de prejuízos cognitivos irreversíveis com o uso da *cannabis*. Por ser a droga ilícita mais usada no mundo, o estudo de tais déficits é de extrema importância.[1]

De forma sumária, os autores sugerem que o uso crônico da *cannabis* causa alterações que podem ser persistentes, mesmo após a cessação do uso, em diversas funções cognitivas. Estes efeitos seriam ainda piores em usuários pesados e com início do uso na adolescência.[1]

A partir destes dados, temos algumas ressalvas a fazer. Uma variável que não é avaliada em nenhum estudo e que pode confundir os achados trata-se das disfunções cognitivas pregressas ao uso da droga, resultando na busca e experimento da mesma. Algumas disfunções cognitivas como, por exemplo, dificuldades na tomada de decisões, poderiam propiciar o primeiro contato com a droga, e não o próprio uso causar o prejuízo da mesma. Estas considerações poderiam justificar o elevado uso de drogas lícitas e ilícitas em diversos transtornos psiquiátricos como, por exemplo, o transtorno bipolar do humor, esquizofrenia e o transtorno de personalidade antissocial.[2-4] Nestes transtornos, alterações neuroanatômicas e neurofuncionais conhecidas, com suas consequentes disfunções cognitivas, poderiam justificar o elevado uso de substâncias psicoativas por parte dos pacientes.[2,3]

Resultados preliminares de uma coorte realizada por nós mostram que disfunções neuropsicológicas pregressas estão associadas à busca pela *cannabis*. Estudamos um grupo de 124 adolescentes (entre 13 e 14 anos) sem transtornos psiquiátricos (avaliados pelo MINIPLUS) e sem história de uso de drogas ilícitas. Além de avaliarmos dados sociodemográficos e inteligência (avaliada pelo teste de Escalas Progressivas de Raven), aplicamos a *Barratt Impulsiveness Scale* (BIS-11), uma escala de autopreenchimento que avalia a impulsividade do indivíduo como um todo, além de três categorias distintas: impulsividade motora, impulsividade

Depression and Multiple Sclerosis: A cross-sectional study

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Abstract: The aim of this study was to evaluate the frequency of major depression in an outpatient sample of patients with multiple sclerosis (MS) and to investigate whether there was any association with sociodemographic and clinical parameters. Methods: A Cross-sectional study, patients evaluated consecutively, for the clinical, demographic, prevalence of depression was used structured interview (MINI). The severity of depressive symptoms was assessed using the Beck Depression Inventory (BDI). In total, 73 patients with MS were enrolled in this study. The prevalence of major depression was 35.6% in MS patients . There was positive correlation between depression and degree of disability. Conclusion: The prevalence of major depression is high in MS and is associated with related disability.

Key-words: multiple sclerosis, major depression, depressive symptoms.

Introduction

The presence of psychiatric symptoms has been known since the first detailed clinical description of “sclérose en plaques” by Jean-Martin Charcot at the Hospital Pitié-Salpêtrière, Paris in the nineteenth century. These symptoms included pathological crying and laughing, euphoria, mania, hallucinations and depression.[1] The first systematic studies on the prevalence of depression began in 1927 by Cottrell and Wilson, these authors observed symptoms of depression in around 10% of MS patients.[2]

In the present study we evaluated the frequency of major depression in an outpatient sample of patients with multiple sclerosis investigate whether there was any association with sociodemographic and clinical parameter.

Material and methods

A cross-sectional study with a sample of consecutive multiple sclerosis patients was performed at the outpatient clinic of Neuroimmunology, Rio de Janeiro State University (UERJ), Rio de Janeiro, Brazil. All patients with the diagnosis of multiple sclerosis according to the criteria of *McDonald et al*. were invited to participate. Exclusion criteria were patients with exacerbation of the disease in the last three months, age under 18 and over 65, elevated degree of disability EDSS (Expanded Status Scale Kurtze Disability)> 7.5, schooling less than four years, and patients with other neurological diseases that could potentially interfere with clinical assessment, such as epilepsy, history of traumatic brain injury (TBI) or stroke.

A complete medical history was obtained. The degree of MS-related disability was evaluated assessed with the Expanded Disability Status Scale (EDSS). Psychiatric evaluation comprising the Mini International Neuropsychiatric Interview (M.I.N.I.) was performed at the same time point of neurological evaluation. The M.I.N.I. is a short-structured interview designed to explore the criteria for psychiatric diagnoses of DSM-IV Axis (American Psychiatric Association, 1994),[3] including major depression. The severity of depressive symptoms was quantified using the Beck Depression Inventory (BDI).

Data analysis

Descriptive statistics used means and proportions when appropriate. Pearson $\chi 2$ was performed for categorical univariate analysis. T student and Mann-Whitney Test were used to compare continuous variables. Pearson's or Spearman's correlations were calculated, as appropriate. $P < 0.05$ was considered to be statistically significant. SPSS version 18 (SPSS Inc.,Chicago, IL, USA) was used to conduct all the analyses.

Results

Seventy-three patients with MS entered in the study. The majority was female 51 (69,1%), the age ranged from 18 to 65 years, with a mean of 41.1 (SD = 11.91) years old. Disease duration ranged from 1-28 years, with a mean

of 9.46 (SD = 6.54) years. The degree of disability ranged from 0-7.5, with a mean of 2.9 (SD = 2.21).

Regarding MS treatment, 54 (74%) patients were using interferon beta 1A; eight (11%) were using glatiramer acetate; and eleven (15,1%) were not using any immunomodulatory or immunosuppressive drugs.

Major depression was diagnosed in 26 (35,6%) patients according to the M.I.N.I. Among these patients, 14 (19,2%) had current depression; and 12 (16,4%) had recurrent depression. BDI scores ranged from 1-45 points, with a mean of 8.91 (SD = 7.94). The severity of depressive symptoms measured by the BDI showed that 22 (31,4%) patients had depressive symptoms ranging from mild to severe.

When comparing patients with and without major depression, there were no significant differences regarding sex, age or disease duration (Table 1). The average EDSS was significantly higher in MS patients with major depression There was a positive correlation between the degree of disability assessed by EDSS and severity of symptoms evaluated by BDI.

Discussion

The results indicate that the frequency of major depression is high in patients with MS. Furthermore, the degree of disability is a factor associated with depression in this population.

The lifetime risk of major depressive disorders in MS patients ranges from 20% to more than 50%.[4] These numbers are much higher in MS patients than

among the general population, and are similar or slightly higher than among other populations with chronic diseases, such as cardiovascular diseases and chronic obstructive pulmonary disease.[5] Some but not all studies have observed association between depression and the severity of MS as reflected by degree of disability. [6]

Based on findings from patients with clinically isolated syndrome, depression seems to be less common during early MS compared to later stages. As the disease progresses to clinically definite MS, depression rates increase. Higher depression rates among patients with relapsing–remitting MS compared to progressive MS suggest a possible role for inflammatory processes in the pathogenesis of depression.[7,8]

The pathogenesis of depression in patients with MS is largely unknown. Several medical and psychiatric comorbidities may contribute to the robust association between depression and MS. Chronic pain occurs in 50% of patients with MS. Fatigue may occur alone or in combination with depression. Cognitive dysfunction occurs in 40-60% of individuals with MS. Anxiety, alcohol abuse, and the use of medications, such as corticosteroids and beta-interferon, are common among individuals with MS.[9]

Neuroimaging data indicate an association between low mood and structural and functional brain abnormalities in MS, suggesting that depression may arise from the demyelination process. [9]

Immunological mechanisms have also been linked to the etiopathogenesis of depression in MS. For instance, Foley et al. prospectively evaluated patients

with MS and depression for two years. Reduction in CD8 lymphocyte counts and increased CD4 / CD8 ratio occurred during major depressive episodes in patients compared to control group.[10] Mohr et al. investigated the production of the pro-inflammatory cytokine gamma interferon (IFN-γ) in MS patients and detected higher IFN-γ levels in depressed patients. Treatment of depression with antidepressants reduced the production of IFN-γ.[11]

Few studies have investigated depressive disorders in MS using standardized interviews. Sadovnick et al. sequentially evaluated 221 patients in Canada using a structured interview and observed that the prevalence of depressive episodes was approximately 50.3%.[12]Feinstein in Canada observed that 17% of their 100 consecutive MS outpatients met the criteria for a diagnosis of major depression when assessed with the Structured Clinical Interview for DSM-IV (SCIDI).[13] Patten et al. interviewed 136 subjects with MS in Canada using the Composite International Diagnostic Interview (CIDI). They found that 22.8% of the subjects had lifetime major depressive episodes, and depressed subjects were more likely to be female, to be under the age of 35, and to report recent life events and chronic stressors.[14]

This study was limited by the size of the sample. As it was conducted in a reference center for the treatment of patients with MS, the results may not reflect the prevalence of psychiatric disorders in MS patients from the community. Most patients were receiving treatment. On the other hand, the use of a structured clinical interview may be regarded as strength of the study.

The prevalence of depressive disorders is high in patients with MS. Depression must be investigated systematically due to the high risk of suicide in this population in addition to the negative impact on treatment and disease progression. The neurobiological mechanisms of depression in MS are unknown, but disease-related disability seems to be a risk factor.

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Table 1: Demographic and clinical characteristics between the groups of patients with multiple sclerosis with and without major depression

Characteristics	Non depressed	depressed	p value	r	p
	N / mean	N/ mean			
	N=47	N=26			
Gender					
females	32	19	p=0.65*	-0,052[&]	0,662
males	15	7			

Mean of age in years	39,40 SD=12,67	44,42 SD=9,81	P=0,09**	0,203[&]	0,042
Disease duration	9,29 SD = 6,77	9,76 SD= 6,21	p=0,624 **	0,035[&]	0,385
EDSS (mean)	1,55 SD= 0,82	2,13 SD= 0,99	P=0,004**	0,35[&]	0,001

*Pearson Chi-quadrado ** Mann-Whitney Test [&]Pearson correlation

Quality of life in multiple sclerosis: The impact of fatigue and depression

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Abstract: The impact of fatigue and depression on the quality of life (QOL), independent of the severity of neurologic disability, has not been clearly defined in patients with MS. The aim of this study was to determine the impact of fatigue and depression on QOL in a sample of MS patients in Brazil. Methods: Cross-sectional study patients evaluated consecutively for QOL was used SF-36, prevalence of fatigue was used D-FIS, severity of symptoms of depression was used Beck inventory.Results: Of the 60 patients, 35 (58.3%) reported fatigue based on the definition. The severity of depressive symptoms measured by the BDI showed that 17 patients (28.3%) had depressive symptoms ranging from mild to severe. Regarding QOL as assessed by the SF-36, a deterioration in QOL in patients with MS and fatigue compared to those without fatigue was detected. The comparison between the groups of MS patients with and without depression found a significant deterioration in QOL in patients with depression.

Conclusion: We consider it important to stress that fatigue and depression should be carefully screened for in patients with MS because they are highly associated and they determine negative impact QOL of patients with MS.

Key-words: multiple sclerosis, fatigue, depression, quality of life

1. Introduction

Multiple sclerosis (MS) is an autoimmune inflammatory disease of the central nervous system (CNS) that predominantly affects the white matter by promoting the destruction of myelin, oligodendrocytes and axons. Although its etiology is unknown, theories suggest an interaction among immunologic, genetic, environmental and infectious factors. Its frequency is higher among females by a ratio of 3:1, and the disease mostly affects individuals between the ages of 20 and 40. Clinical manifestations include sensory changes, motor deficits, sphincter complaints, optic neuritis, diplopia, cerebellar signs and cognitive dysfunction.[1,2]

MS has a major impact on the lives of patients. It substantially interferes with daily activities and social and working life; disturbs emotional well-being; and reduces quality of life (QOL).[3,4] This psychosocial impact of the disease was found to be significantly associated with the severity of disability.[4] Studies on the QOL and psychological well-being in MS patients have mainly been

conducted among patients who were at more advanced stages of disease. In these studies, the average illness duration varied from 8 to 16 years, and median scores on the Expanded Disability Status Scale (EDSS) were between 3.5 and 5.0.[5,6] However, neurologic disability has been shown to only partly explain impaired QOL. This supports the hypothesis that factors other than neurologic disability may play a role in the QOL of MS patients.[7,8]

Fatigue can be defined as a lack of physical or mental energy or a feeling of tiredness. It is one of the most common but least understood symptoms of MS.[9] Fatigue is reported by 50 to 90% of patients according to different studies, and as many as 40% of such patients regard fatigue as their most disabling symptom.[10] It can affect social relations, daily activities, and cognitive and physical domains, all of which are associated with the QOL in MS patients.[11]

Depression is more common in MS patients than in the general population.[12] Depression affects approximately 25 to 50% of patients and substantially impairs QOL.[13] The impact of fatigue and depression on the QOL, independent of the severity of neurologic disability, has not been clearly defined in patients with MS. Recognizing fatigue and depression and understanding their relationship with QOL are important as both pharmacological and nonpharmacological strategies can be effective in the treatment of such conditions, potentially improving the QOL in MS patients.

The aim of this study was to determine the impact of fatigue and depression on QOL in a sample of MS patients in Brazil.

2. Patients and methods.

The current study was performed at a public university-based outpatient service for neuroimmunology in Rio de Janeiro, Brazil between January 2012 and December 2013. Patients with a diagnosis of MS according to the McDonald criteria were invited to participate in this study. The exclusion criteria were patients younger than 18 years or older than 65 years, and patients with other neurological diseases that could potentially interfere with the evaluation. A complete medical history, including the course of disease, medication use, and sociodemographic data, was collected.

The degree of disability was evaluated by the Kurtzke Expanded Disability Status Scale (EDSS)[14], which ranges from 0 to 10 with increments of 0.5 (half) points; higher scores indicate a greater degree of disability. A neurological examination evaluated eight functional systems: pyramidal, cerebellar, brainstem, sensory, bladder, bowel, visual and mental.

Patients were asked about the presence of fatigue, defined as ‘an overwhelming sense of tiredness, lack of energy, or feeling of exhaustion that limits or makes difficult a sustained physical or mental activity.’ Patients who acknowledged experiencing fatigue according to this definition were considered ‘patients with fatigue’, and the remainders were ‘patients without fatigue’. Patients with fatigue were asked to complete the Fatigue Impact Scale for Daily Use (D-FIS).[15]

Instruments

QOL was assessed using the Short Form 36 Health Survey (SF-36)[16]. It is a self-report questionnaire that includes eight multi-item scales (36 items) that evaluate the extent to which an individual's health limits his/her physical, emotional, and social well-being. SF-36 covers eight domains of QOL: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems, and mental health. Scores on each subscale range from 0 to 100, with higher scores indicating a better QOL.

Fatigue was assessed using the D-FIS. This instrument is an adaptation of the Fatigue Impact Scale (FIS). The FIS is a specific instrument that was developed 'for use in medical conditions in which fatigue is a prominent chronic symptom', and has been shown to be a useful and valid measure in a variety of medical conditions, including MS. The D-FIS is an eight-item self-report questionnaire with five response options per item (from 0, indicating no problem, to 4, indicating extreme problem). The total score is derived from the sum of the ordinal scores obtained for each item. This approach was chosen by the original authors to facilitate the scoring of the scale in which higher scores reflect greater fatigue.

The severity of depressive symptoms was assessed using the Beck Depression Inventory (BDI).[17]

Patients provided written informed consent to participate in the study, which was approved by our local Research Ethics Committee. The neurologic examination for EDSS scoring and the SF-36, BDI and D-FIS assessments were performed on the same day.

Data analysis

Descriptive statistics used means and proportions when appropriate. Pearson $\chi 2$ was performed for categorical univariate analysis, and Student's t test, the Mann-Whitney Test and the Kruskal-Wallis Test were used to compare continuous variables. Pearson's or Spearman's correlations were calculated as appropriate. $P < 0.05$ was considered to be statistically significant. Subsequently, to assess factors most closely associated with QOL, multiple regression analyses were performed. SPSS version 18 (SPSS Inc., Chicago, IL, USA) was used to conduct all the analyses.

3. Results.

A total of 60 eligible patients with MS were enrolled in the study. The majority were female 46 (76.7%), and the age ranged from 19 to 65 years with a mean of 43 (SD = 11.8). Disease duration ranged from 1 to 28 years, with a mean of 9.6 (SD = 6.8). The degree of disability ranged from 0 to 7.5 with a mean of 2.9 (SD = 2.2). Of the 60 patients, 35 (58.3%) reported fatigue based on the definition given above. These 35 patients with fatigue completed the D-FIS. Their scores ranged from 6 to 25 points with a mean of 12.7 (SD = 5.0). The severity of depressive symptoms measured by the BDI showed that 17 patients (28.3%) had depressive symptoms ranging from mild to severe. Beck et al. suggested the following ranges of BDI cut-off scores for depression: 0–9 (minimal), 10–18 (mild), 19–29 (moderate), and 30–63 (severe). Patients' BDI scores ranged from 1–45 with a mean of 8.0 (SD = 7.8).

The group of MS patients without fatigue was compared to the group of MS patients with fatigue (Table 1). No differences were found between the groups with respect to age and disease duration. However, in relation to the degree of disability as measured by the EDSS, statistically significant differences were detected and EDSS scores were higher in the group with fatigue. Regarding gender, fatigue was significantly higher in females.

Regarding QOL as assessed by the SF-36, a deterioration in QOL in patients with MS and fatigue compared to those without fatigue was detected. The scores of the SF-36 for the group with fatigue were significantly lower in all areas. The results show that there is a correlation between fatigue and various aspects of QOL in patients with MS and that fatigue has a negative impact on QOL.

The severity of depressive symptoms was assessed using the BDI (Table 2). The group without depression was compared to the group with depression, with respect to demographic and clinical data. The results of this study found no statistically significant differences in age, disease duration or degree of disability. However, differences were found in relation to gender, and the presence of depression was significantly higher in females.

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Regarding QOL, the comparison between the groups of MS patients with and without depression found a significant deterioration in QOL in patients with depression. The evaluation with the SF-36 showed lower scores in various domains of QOL in the group with depression, except in the domains physical functioning and physical role functioning. The results show that there is a correlation between depressive symptoms and various aspects of QOL in patients with MS and that depression has a negative impact on QOL.

The evaluation of the correlation between fatigue and depressive symptoms showed that there is an average correlation between these two variables assessed by Pearson correlation ($r = 0.556$, $p = 0.000$).

Discussion

The present study shows that the prevalence of fatigue assessed by the D-FIS in patients with MS is high, given that 58.3% of patients had fatigue. Fatigue has a negative impact on the QOL of patients with MS. A study by Benito-Leon et al.[18] detected fatigue in 54.8% of patients with MS using the D-FIS. Wood et al.[19] detected fatigue in 53.7% of a sample of MS patients.[19] The results of this study are similar to those described by other authors and highlight the importance of recognizing this symptom in patients with MS, in view of the negative impact fatigue has on the QOL and the fact that there are effective therapeutic measures for the treatment of fatigue in patients with MS.

The presence of depressive symptoms found in this population was high, considering that 28.3% of the patients with MS had depressive symptoms ranging from mild to severe, as measured by the BDI. There is an association between fatigue and the presence of depressive symptoms; however, it should be noted that fatigue is a common symptom in patients with major depression. We have noted the negative impact that depression has on the QOL of patients with MS. The scores of various domains were significantly lower in the QOL assessed by the SF-36 in patients with MS and depression compared to those without depression. However, we found no significant relationship between the degree of disability and depressive symptoms. It should be noted that most patients with MS have moderate disability, with a mean EDSS score of 2.9. The prevalence of depressive symptoms is high in this population and that depression worsens the QOL in patients with MS, so the presence of these symptoms should be investigated systematically, considering the psychological distress and especially the risk of suicide in this population. A study conducted by Janssens et al.[20] assessed the prevalence of anxiety and depression in patients newly diagnosed with MS and their companions and found significant symptoms of anxiety and depression. In this study, the authors found significant deterioration in the QOL in patients with MS who were assessed by the SF-36.

This study was limited by the size of the sample and because it was conducted in a reference center for the treatment of patients with MS, and, therefore, all patients enrolled were already receiving treatment for their condition.

Various neurobiological mechanisms have been proposed to explain the development of depression and fatigue, and whether these factors share common pathways in MS remains controversial. A dysregulation of the hypothalamic-pituitary-adrenal HPA (evidenced by a shift in diurnal cortisol secretion patterns) has been found in MS patients with depression and fatigue.[21,22] Changes in the levels of cytokines, such as interferon alpha (IFN-α), Tumor Necrosis Factor beta (TNF-β), interleukin 1 beta (IL-1β) and interleukin-6 (IL-6), have been associated with an increase in depressive symptoms.[23] MS patients with fatigue have an mRNA expression of TNF-alpha in excess of those patients without fatigue.[24]

The relationship between fatigue and depression in MS is complex. Fatigue can occur regardless of depression or may be an integral symptom. Fatigue can also be a symptom of a secondary sleep disorder[25], which, in turn, can be directly attributed to MS, be an adverse effect of the disease-modifying treatment, or be a symptom of depression. Fatigue can also reflect various combinations of one or more of these factors.[26]

Conclusion

We consider it important to stress that fatigue and depression should be carefully screened for in patients with MS because they are highly associated and they determine negative impact QOL of patients with MS. Successful

treatment of depression can lead to a concomitant improvement of fatigue if it is a minor problem, with considerable improvement of the QOL of patients with MS.

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Table (1) Impact of fatigue on quality of life (QOL) in Brazilians patients with multiple sclerosis

	No fatigue	fatigue	p	r	p	R^2	Beta	P
N	25	35				Multiple Regression Analysis		
mean of age in years	39,4 SD=12,8	45,6 SD=10,38	0,054*	0,316	0,14			
Gender								
females	17	29	0,180**	-0,275	0,033			
males	8	6						
EDSS	2,2 SD=2,2	3,2 SD=1,9	0,0025*	0,202	0,061			
Disease duration	8,7 SD=6,4	10,3 SD=7,0	0,36*	0,105	0,14			

General health perceptions	69,08SD=17,4	53,08 SD=16,3	0,002*	-0,507	0,000	0,257	-0,507	0,000
bodily pain	86,72SD=21,2	74,11SD=24,4	0,037*	-0,403	0,001	0,162	-0,403	0,001
vitality	74,92SD=19,3	48,77SD=24,3	0,000*	-0,623	0,000	0,388	-0,630	0,000
physical functioning	99,00SD=5,00	76,54SD=36,1	0,002*	-0,493	0,000	0,243	-0,493	0,000
physical role functioning	72,00 SD=27,1	44,42SD=23,1	0,000*	-0,552	0,000	0,283	-0,532	0,000
emotional role functioning	97,32 SD=13,4	78,05 SD=37,0	0,015*	-0,474	0,000	0,224	-0,479	0,000
social role functioning	84,24 SD=24,68	76,68 SD=27,2	0,173*	-0,324	0,006	0,105	-0,324	0,011
mental health	85,60 SD=10,4	70,97SD=21,19	0,005*	-0,589	0,000	0,347	-0,589	0,000

* Two-tailed T-test ** Pearson's Chi square r= Pearson Correlation

Table (2) Impact of depression on quality of life (QOL) in Brazilians patients with multiple sclerosis

	No depressed	depressed	p	r	p	R^2	beta	p
N	43	17				Multiple Regression Analysis		
mean of age in years	41,9 SD= 12,9	45,7 SD=7,8	0,187*	0,316	0,14			
Gender								
Females	30	16	0,044**	-0,275	0,033			
Males	13	1						

EDSS	2,6 SD=2,1	3,4 SD=2,1	0,176*	0,092	0,242			
Disease duration	10,5 SD=7,1	7,4 SD=5,6	0,086*	-0,213	0,102			
General health perceptions	64,44 SD=16,8	47,88 SD=17,3	0,003*	-0,333	0,005	0,111	-0,333	0,009
Bodily pain	86,65 SD=22,7	60,94 SD=22,7	0,000*	-0,431	0,000	0,185	-0,431	0,001
Vitality	68,55 SD=20,4	37,17SD= 24,5	0,000*	-0,410	0,001	0,168	-0,410	0,001
Physical functioning	91,37 SD=23,9	72,05SD=38,4	0,007*	-0,229	0,043	0,050	-0,224	0,085
Physical role functioning	61,27SD=27,9	42,35 SD=24,6	0,015*	-0,305	0,009	0,093	-0,305	0,18
Emotional role functioning	93,00SD=22,5	68,58SD=41,6	0,004*	-0,253	0,025	0,063	-0,252	0,053

Social role functioning	87,02SD=22,8	61,64 SD=26,1	0,000*	-0,356	0,003	0,126	-0,356	0,005
Mental health	83,8 SD=13,2	60,00SD=20,5	0,176*	-0,454	p=0,000	0,209	-0,454	0,000

* Two-tailed T-test ** Pearson's Chi square r= Pearson Correlation

2. CONSIDERAÇÔES FINAIS

Os resultados deste trabalho permitem concluir que a depressão maior é alta nesta população, acomete 36,5% dos pacientes com EM ao longo da vida. Um estudo populacional recente que incluiu dezoito países entre eles o Brasil, mostrou que a prevalência de depressão maior ao longo da vida na população em geral é de 18,4%,[4] portanto podemos concluir que em pacientes com EM a prevalência da depressão é o dobro da população em geral.

A prevalência de transtorno bipolar (TB) em pacientes com EM é alta, detectamos TB em 13,3% da amostra estudada. Um estudo epidemiológico, realizado em diversos países, entre eles o Brasil encontrou que a prevalência de TB e espectro bipolar foi de 4,3% no Brasil.[5] Os dados do nosso estudo permitem concluir que a prevalência de TB em pacientes com EM é quase o triplo quando comparado à população em geral.

O risco de suicídio em pacientes com EM foi alto sendo que 8,3 % haviam tentado suicídio. Estudos epidemiológicos mostram que a prevalência de tentativa de suicídio na população em geral é em torno de 4,6%. Portanto, o risco de suicídio em pacientes com EM é praticamente o dobro da população em geral.[6]

A prevalência de transtornos de ansiedade foi alta nesta população, sendo que 20% dos pacientes com EM apresentavam algum transtorno de ansiedade. Neste estudo detectamos a presença de fadiga em 58,3% dos

pacientes com EM, e observamos o impacto negativo da depressão e da fadiga sobre a QV em pacientes com EM.

Em um trabalho recente, a *American Academy of Neurology* (AAN) [7]publicou um consenso baseado em evidências, recomendando o *screening*, o diagnóstico e o tratamento de transtornos psiquiátricos em indivíduos com EM. Consideramos de extrema importância o diagnóstico dessas condições, tendo em vista o sofrimento psíquico, o impacto na QV e o risco de suicídio nesta população.

Alguns autores defendem a hipótese de que processos de inflamação e neurodegeneração na EM parecem exercer um papel relevante no surgimento de manifestações neuropsiquiátricas como a depressão maior e no desempenho em funções cognitivas. Sendo assim, tem sido proposto, que sintomas psicopatológicos na EM são potencialmente devidos a dano inflamatório focal, efeitos gerais de uma suprarregulação do sistema autoimune neurodegeneração generalizada ou combinação desses mecanismos.[8]

A inter-relação entre sistema imune e funções complexas do SNC, como a memória e processos de aprendizagem, tem sido demonstrada em estudos com animais, utilizando o modelo experimental da encefalomielite autoimune. Durante condições patológicas como a EM, células da microglia interagem com neurônios e induzem uma resposta neuroinflamatória caracterizada pela *up-regulation* de citocinas, como IL-1, IL-6 e TNF, alterando a plasticidade sináptica, a aprendizagem e a memória. O fator neurotrófico derivado do cérebro (BDNF), um membro da superfamília das neurotrofinas, é expresso na

maior parte cérebro humano desempenha um papel-chave na plasticidade cerebral, por ser responsável pela manutenção, crescimento, e pela sobrevivência de neurônios em animais e em seres humanos. [8]

Por fim, acreditamos que estudos futuros que possibilitem a investigação de uma possível associação entre transtornos de humor e biomarcadores inflamatórios e fatores neurotróficos em pacientes com EM, poderá identificar possíveis marcadores biológicos envolvidos no surgimento de alterações neuropsiquiátricas na EM.

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