Journal of Affective Disorders 155 (2014) 255–260

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research report

The risk of Bipolar Disorders in Multiple Sclerosis

M.G. Carta [a,b,*], M.F. Moro [a,b], L. Lorefice [a,c], G. Trincas [a,b], E. Cocco [a,c], E. Del Giudice [a,b], G. Fenu [a,c], F. Colom [a,d], M.G. Marrosu [a,c]

[a] Department of Public Health and Clinical and Molecular Medicine, University of Cagliari, Italy
[b] Consultation Liaison Psychiatric Unit at the University Hospital of Cagliari, University of Cagliari and AOU Cagliari, Italy
[c] Centro Sclerosi Multipla, Cagliari, Italy
[d] Bipolar Disorders Programme, Institute of Clinical Neuroscience, Hospital Clínic, Universitat de Barcelona, IDIBAPS, CIBERSAM, Barcelona, Catalunya, Spain

ARTICLE INFO

Article history:
Received 13 September 2013
Received in revised form
10 November 2013
Accepted 12 November 2013
Available online 19 November 2013

Keywords:
Bipolar Disorders
Multiple Sclerosis
Mood Disorders
Comorbidity
Life-time prevalence
MDQ

ABSTRACT

Background: The aim was to determine the risk of Mood Disorders (MD), particularly Bipolar Disorders (BD), in Multiple Sclerosis (MS) using standardized psychiatric diagnostic tools.
Methods: Case–control study. Cases: 201 consecutive-patients with MS. Controls: 804 sex- and age-matched subjects without MS, randomly selected from a database concurrently used for an epidemiological study on the MD prevalence in the community. Psychiatric diagnoses according to DSM-IV were determined by physicians using structured interview tools (ANTAS-SCID).
Results: Compared to controls, MS patients had a higher lifetime prevalence of DSM-IV Major Depressive Disorders (MDD; $P<0.0001$), BD I ($P=0.05$), BD II ($P<0.0001$) and Cyclothymia ($P=0.0001$). As people with MS had a higher risk of depressive and bipolar spectrum disorders, ratio MDD/bipolar spectrum disorders was lower among cases ($P<0.005$) indicating a higher association with Bipolar Spectrum Disorders and MS.
Limitations: MS diagnosis was differently collected in cases and controls. Even if this might have produced false negatives in controls, it would have reinforced the null hypothesis of no increased risk for MD in MS; therefore, it does not invalidate the results of the study.
Conclusions: This study was the first to show an association between BD and MS using standardized diagnostic tools and a case–control design. The results suggest a risk of under-diagnosis of BD (particularly type II) in MS and caution in prescribing ADs to people with depressive episodes in MS without prior excluding BD. The association between auto-immune degenerative diseases (like MS) and BD may be an interesting field for the study of the pathogenic hypothesis.

1. Background

It has long been known that several medical disorders have an association with mood disorders (Joffe, 2005). These strict links have provided an opportunity to use medical illnesses to understand the pathophysiology of mood disorders (Joffe, 2005). Taking into account the hypothesis that immune activation and degeneration may influence the oxidative processes in the central nervous system (CNS), recently special attention was devoted to the association of mood disorders with immune (Bachen et al., 2009; Carta et al., 2012a, 2007; Hardoy et al., 2011) and neurological degenerative diseases (Carta et al., 2012b). In fact, increased neuronal oxidative stress (OxS) induces deleterious effects on signal transduction, structural plasticity and cellular resilience, mostly by inducing lipid peroxidation in membranes, proteins and genes (Khairova et al., 2012). It has been hypothesized that these pathological processes occur in critical brain circuits that regulate the affective functioning, the emotions, the motor behavior and pleasure involved in bipolar disorder (BD) (Machado-Vieira et al., 2007; Zarate et al., 2006). Multiple sclerosis is a chronic, inflammatory demyelinating disorder of the central nervous system, and it is also characterized by degenerative changes. The disorder is one of the most common neurological disorders among young adults: its estimated annual incidence rates ranged from $<1/100{,}000$ to $>10/100{,}000$, while its point prevalence estimates ranged widely from 20/100,000 to 200/100,000 (Kingwell et al., 2013). Although its cause is not fully understood, it appears to involve a complex interplay of genetic, environmental and immunologic factors (Ewing and Bernard, 1998). Several studies have documented high rates of depression

* Corresponding author at: Department of Public Health and Clinical and Molecular Medicine, University of Cagliari, Italy. Tel.: +39 335499994.
E-mail addresses: mgcarta@tiscali.it (M.G. Carta), mfmoro@gmail.com (M.F. Moro), lorena.lorefice@hotmail.it (L. Lorefice), giutri@email.it (G. Trincas), ecocco@unica.it (E. Cocco), emilio.delgiudice@gmail.com (E.D. Giudice), giusefenu.med@tiscali.it (G. Fenu), FCOLOM@clinic.ub.es (F. Colom), gmarrosu@unica.it (M.G. Marrosu).

0165-0327/$ - see front matter © 2013 Published by Elsevier B.V.
http://dx.doi.org/10.1016/j.jad.2013.11.008

in MS (Byatt et al., 2011), and have shown that the rates of Major Depressive Disorders (MDD) are twice more prevalent in patients with MS when compared with other chronic illnesses, including other neurological disorders (Sadovnick et al., 1996; Siegert and Abernerhy, 2005). Comorbidity between MDD and MS has been associated with a lower quality of life and increased risk of suicidal ideation (Feinstein, 2002). Psychiatric and medical comorbidity has also been associated with delays in MS diagnosis and greater disability at the time of the diagnosis (Marrie et al., 2009).

Neuroimaging data have revealed an association between depressive symptoms and structural and functional brain abnormalities, suggesting that the demyelination process may have a causal role in depression (Bakshi et al., 2000; Feinstein et al., 2004).

Up to now, little research was made using psychiatric clinical standardized tools for MDD instead of the screening tools for mood disorders, such as the CES Depression Scale (CES-D) (Chwastiak et al., 2002) or the Hospital Anxiety and Depression Scale (HADS) (Giordano et al., 2011) in MS patients. For these reasons, scarce data are available on psychiatric diagnoses according to the international classification of mood disorders, and most specifically from studies with large samples and control groups. Thus, the link between multiple sclerosis and specific diagnoses like bipolar I and II disorders have not been adequately investigated (Iacovides and Andreoulakis, 2011).

The objectives of this study were to determine the frequency of bipolar disorders and mood disorders in a consecutive series of MS inpatients, using standardized diagnostic tools, and to compare the risk of bipolar disorder in MS patients with the risk in controls. The data for controls were collected from a large epidemiological study (Carta et al., 2012c, 2011).

2. Methods

2.1. Study design

This was a case–control study.

2.2. Groups

The cases were 201 consecutive MS patients seen from November 2011 to January 2013 at the Multiple Sclerosis Unit, Azienda Sanitaria N.8 of Cagliari, Italy, a center of excellence that provides care to MS patients. The controls included 804 subjects with no diagnosis of MS, who were randomly selected from a database used for an epidemiological study of the health conditions in Italy (Carta et al., 2010). The selection of sex- and age-matched controls from the 3398-subject database from six Italian regions (2 from the north, 1 from the center, and 2 from the south of Italy including Sardinia) was performed using a randomized block design. A block was constructed for each case that included all eligible age-matched (± 1 year) and sex-matched controls in the database. Four individuals were extracted per block for each case, automatically excluding them from the remaining blocks.

2.3. Psychiatric diagnosis interview, tools and psychiatric assessment

The psychiatric interviews were conducted using several standardized tools. First, we used a standard form to record basic demographic data. Second was the "Advanced Neuropsychiatric Tools and Assessment Schedule" (ANTAS; Carta et al., 2010), a semi-structured clinical interview derived in part from the non-patient version (SCID-I/NP) for DSM-IV (First et al., 2002). It was used to assess the presence of full or sub-threshold psychiatric disorders. The ANTAS tool was administered by physicians. A preliminary reliability study of the diagnoses derived from ANTAS and SCID was carried out, and the results were previously published. The reliability in terms of mood and anxiety diagnoses using ANTAS vs. SCID was measured, and mean *K* was 0.85 (Carta et al., 2010). Third, the Mood Disorder Questionnaire (MDQ; Italian version; Hardoy et al., 2005) was used to assess bipolar spectrum disorders. The adopted MDQ cut off was 7 (Bipolar Cases identified by score of 7 or more; Hardoy et al., 2005).

2.4. Diagnosis of MS

The diagnosis of each MS patient was made applying the 2010 revised Mc Donald diagnostic criteria for multiple sclerosis (Polman et al., 2010).

2.5. Screening controls for MS

During the interviews, each control was asked about general wellbeing, the presence of illness, consultation with physicians, and medical tests they underwent both routinely (e.g., work or driver license eligibility tests) or to help diagnose or monitor medical issues. Diagnosis of physical illness was reported using a structured form.

2.6. Data analysis

Lifetime prevalence of DSM-IV Major Depressive Disorder, Bipolar disorder type I and II, Cyclothymic Disorder, Mood Disorder due to General Medical Condition, Substance Induced Mood Disorder and Dysthymic Disorder was calculated for the case and the control groups, as was lifetime positivity (score >6) on the MDQ as an indicator of bipolar spectrum disorder. The odds ratio association (univariate analysis) for DSM-IV diagnosis (dependent variable) was calculated using the control group as "pivot". Statistical significance was calculated using the χ^2 test in 2×2 tables. Odds ratio 95% confidence intervals (OR 95% CI) were calculated using the method of Miettinen (Miettinen, 1974). The comparisons between the scores at SF-12 in the study groups were calculated using the ANOVA one-way statistics.

2.7. Ethics

The study subjects gave their informed consent for the use of anonymous data for an aggregate study. The community study (involving controls) was approved by the ethics committee of the Italian National Health Institute (Rome), and the approved project anticipated and planned the carrying out of a series of case–controls studies. This project was additionally approved by the ethics committee of the Università Europea del Mediterraneo NGO. Data were not nominal at the source, and each subject was identified by a code number.

3. Results

The demographic characteristics of the study subjects are shown in Table 1. Age and sex were homogeneous in cases and controls thanks to the matching method. The mean time on illness for MS patients was 9.8 years. Patients with MS had a higher lifetime prevalence of manic/hypomanic episodes (with positivity as assessed on the MDQ), and a higher prevalence of lifetime DSM-IV Major Depressive Disorders, Bipolar Disorders type I and II, Cyclothymic Disorder, Mood Disorder due to General Medical Condition, Substance Induced Mood Disorders detected by the ANTAS-SCID interview (Table 2). MDQ positivity was higher in cases than in controls (41.8% vs. 3.85%, $\chi^2=22.6$, $P<0.0001$,