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Psychiatric disturbances in radiologically isolated syndrome

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ABSTRACT

Background: Radiologically isolated syndrome (RIS) is characterized by incidental lesions suggestive of multiple sclerosis (MS) on MRI without typical symptoms of MS. Clinically isolated syndrome (CIS) is characterized by a first episode of neurologic symptoms caused by demyelination in the central nervous system. To date, psychiatric disorders have not been systematically addressed in RIS subjects. We assessed emotional disturbances, personality features and health-related quality of life (HRQoL) in a cohort of RIS patients as compared with clinically isolated syndrome (CIS).
Methods: Twenty-eight RIS patients, 25 clinically isolated syndrome (CIS) patients, and 22 healthy subjects were enrolled in the study. Participants were administered a mood scale (Hamilton Depression Rating Scale), behavioural measures (Personality Assessment Inventory), and fatigue measures (Fatigue Impact Scale for Daily Use). HRQoL was quantified using the EuroQol-5.
Results: 14 (50%) of RIS patients had clinically significant depression, with over one-third of these having moderate depression, scores virtually identical to those observed in CIS patients. 11 of 28 (39.3%) subjects with RIS had anxious depression, a figure three times higher than that found in CIS patients. RIS patients' HAMD-17 total score showed a very strong correlation with severity of fatigue. In addition, RIS patients reported lower HRQoL ($p = 0.036$) and a significantly higher symptoms load for somatisation compared to both CIS and control groups ($p < 0.002$).
Conclusion: RIS patients had high rates of depression, particularly anxious depression and somatization. Future studies are warranted to clarify whether these psychiatric disturbances are causally associated with a distinct white matter psychopathologic process.

1. Introduction

Clinically isolated syndrome (CIS) is characterized by a first episode of neurologic symptoms that lasts at least 24 h and is caused by inflammation and demyelination in one or more sites in the central nervous system (CNS). Radiologically isolated syndrome (RIS) has recently been defined as the incidental brain magnetic resonance imaging (MRI) finding of white matter lesions demonstrating dissemination in space in subjects with a normal neurologic examination and without historical accounts of typical multiple sclerosis (MS) symptoms (Okuda et al., 2009). There is a growing amount of evidence demonstrating that approximately one-third of RIS patient are at higher risk for future symptomatic demyelinating event. (Lebrun et al., 2008, 2009; Maia et al., 2012; Okuda et al., 2009; Okuda et al., 2014; Siva et al., 2009) Recent data from the largest existing multinational cohort of RIS patients suggest that younger age at RIS diagnosis, sex (men), and cervical or thoracic spinal cord lesions are the most relevant predictors for the

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development of a first clinical event (Okuda et al., 2011; Okuda et al., 2014). Of these predictors, involvement of the spinal cord has been identified as especially important, and it is widely regarded as the strongest predictor for future demyelinating event. (Okuda et al., 2014) Other predictors such as the presence of inflammatory markers (oligoclonal bands and/or a pathological IgG index), contrast enhancement and infratentorial involvement (cerebellum and brainstem), were not identified as significant risk factors for first clinical event in the latest multi-national cohort of RIS subjects (Okuda et al., 2014).

Despite substantial advances in our understanding of those RIS patients who are at higher risk for initial symptom development, there are still many gaps in the clinical characterization of RIS patients. A higher frequency of cognitive impairment with the same neuropsychological profile as patients with established relapsing-remitting MS has been found in two recent studies (Amato et al., 2012; Lebrun et al., 2010). Furthermore, evidence for widespread neuroaxonal injury, even in normal-appearing brain regions, and comparable to that in clinical MS, has recently been reported in RIS patients (Stromillo et al., 2013). Based on these results, RIS patients could have additional nonmotor features similar to MS patients. For instance, psychological disorders and symptoms of depression or anxiety are known to be common among MS patients (Mitchell et al., 2005). Despite determining the pathophysiology of depression presents a perpetual challenge, based on results from several previous MRI studies, which have demonstrated that brain injury accounts for a meaningful percent of the variance in MS-related depression, (Berg et al., 2000; Feinstein et al., 2010, 2004; Gold et al., 2014; Zorzon et al., 2002) we hypothesize that RIS patients could also present a significant rate of psychiatric disturbances, causally associated with structural brain abnormalities. To date, psychiatric disorders have not been systematically addressed in RIS subjects.

From this perspective, the present study was designed to specifically assess mood disorders, symptoms of affective instability, personality traits, and health-related quality of life (HRQoL) in a cohort of RIS patients. The present design was different from previous RIS research because instead of comparing the results to those of patients with relapsing-remitting MS, they were for the first time compared with those of clinically isolated syndrome (CIS) patients, who potentially might have a closer biologic and clinical similarity with RIS subjects.

2. Methods

2.1. Study design and subjects

CIS patients were recruited consecutively from September 2013 to June 2014 at four MS clinics in Madrid (Spain). RIS patients were searched from already existing MS databases of those MS clinics. Age at RIS diagnosis should be between 18 and 55 years and the inclusion criteria were based on the diagnostic criteria for RIS by Okuda et al. (2009) at brain MRI, i.e., 1) the presence of white matter abnormalities suggestive of a demyelinating process (ovoid, well-circumscribed and measuring >3 mm^2) that satisfied Barkhof's criteria (at least 3 of 4 criteria) for dissemination in space; (Barkhof et al., 1997; Tintoré et al., 2000) 2) not better accounted for by other disease processes, such as, in particular, vascular disease; and 3) no apparent impact on everyday functioning.

The inclusion criteria for CIS patients were as follows: 1) age between 18 and 55; 2) total follow-up time of at least 3 months from the occurrence of the first inflammatory demyelinating event; and 3) presence of ≥1 asymptomatic T2 lesion(s) in at least two or more brain locations considered characteristic for MS (juxtacortical, periventricular, infratentorial, and spinal cord) at the initial MRI (Swanton et al., 2006).

We excluded RIS or CIS patients with history of alcohol or drug abuse, major acute co-morbidities or any major serious chronic illness one year before inclusion (patients with a stable chronic medical conditions were included).

A control group consisting of 22 healthy subjects, with no history of known neurological disorders, alcohol or drug abuse, was recruited either from relatives of patients who came to the neurological clinics for reasons other than MS (e.g. headache, dizziness) or among relatives or friends from health professionals at the University Hospital "12 de Octubre" of Madrid (Spain). None of the controls recruited were consanguineous of the RIS or CIS patients involved in the present study.

2.2. Measurement instruments

Depression severity was measured by the original 17-item version of the Hamilton Depression Rating Scale (HAMD-17), (Hamilton, 1960) which has been the most frequently used scale to subdivide depressed patients into severity groups (Zimmerman et al., 2013). Recommended ranges of scores are as follows: no depression (0–7); mild depression (8–16); moderate depression (17–23); and severe depression (≥24) (Zimmerman et al., 2013). Eight items are scored on a 5-point scale, ranging from 0 = not present to 4 = severe and nine items are scored from 0 to 2 (Zimmerman et al., 2013). Higher scores indicate more severe symptoms (Zimmerman et al., 2013).

Anxiety features were assessed by the HAMD-17 anxiety/somatization factor, which is derived from a factor analysis of the HAMD-17 scale and includes six items from the HAMD-17: psychic anxiety (Item 10), somatic anxiety (Item 11), gastrointestinal somatic symptoms (Item 12), general somatic symptoms (Item 13), hypochondriasis (Item 15), and insight (Item 17) (Mowbray, 1972). Higher scores indicate more severe anxiety symptoms (Mowbray, 1972). It has been shown that HAMD-17 anxiety/somatisation factor score >7 can reliably identify anxious depression, which may have important qualitative differences from depression with low levels of anxiety (Fava et al., 2008).

Psychological functioning was measured by the Personality Assessment Inventory (PAI) (Morey, 1996). The PAI is a widely used multidimensional 344-item self-report measure of personality and psychopathology, which consists of 22 nonoverlapping scales: 4 validity scales (which measure the respondent's approach to the test, including exaggeration or defensiveness); 11 clinical scales which assess factors related to psychiatric diagnostic categories; 5 treatment consideration scales, which includes phenomena related to clinical disorders not captured in psychiatric diagnoses (e.g., suicidal ideation, stress); and 2 interpersonal scales, which provide indicators of interpersonal dimensions of personality functioning (Morey, 1996).

The Fatigue Impact Scale for Daily Use (D-FIS) was administered to measure subjective experience of fatigue (Benito-León et al., 2007; Martínez-Martín et al., 2006). The D-FIS is an eight-item self-report questionnaire, with five options of response per item (from 0/no problem, to 4/extreme problem) (Benito-León et al.; Martínez-Martín et al., 2006). It has been recently applied in MS patients and has proved to be a feasible and valid instrument for measuring MS related fatigue (Benito-León et al., 2007).

HRQoL was measured with the Spanish version of EuroQol-5 dimension (EQ-5D), a standardised instrument developed by the EurolQol group, a consortium of investigators in Europe (EuroQol, 1990). EQ-5D consists of two parts: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS) (EuroQol, 1990). The EQ-5D descriptive system comprises five dimensions: mobility, self-