Clinical and subclinical neuropsychiatric abnormalities in rheumatoid arthritis patients

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Background
Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease with probable autoimmune aetiology. RA has many secondary complications and a variety of neuropsychological consequences.

Aim
The aim of this study was to estimate the frequencies of neuropsychiatric disorders in RA patients and their relationship with the duration and activity of disease.

Patients and methods
Seventy-four consecutive female RA patients were recruited and compared with 25 age-matched and education status-matched female healthy volunteers. All eligible participants underwent clinical, laboratory and electrophysiological examinations (motor and sensory nerve conduction study, F-wave of four limbs, P300 event-related potential and electroencephalography). The Structured Clinical Interview for *Diagnostic and statistical manual of mental disorders*, 3rd ed., Revised (DSM-III-R) Axis I Disorders (SCID-I) for diagnosis of psychiatric illness and the Wechsler Adult Intelligence Scale, 3rd ed. (WAIS-III) with assessment of total scale, verbal and performance intelligence quotients (IQ) were administered to all participants.

Results
Fourteen (18.9%) patients had evidence of symptomatic peripheral neuropathy and radiculopathy, whereas 60.8% had psychiatric disorders. Depression was the most prevalent psychiatric disorder (45%), followed by anxiety (27%) and comorbid anxiety with depression (21.6%). Low IQ scores were recorded in 54% of patients. P300 latency was significantly prolonged (P = 0.0001), and seven (9.5%) RA patients recorded abnormal P300 latency (>mean ± 2 SD) compared with control values. Abnormal electroencephalography findings were observed in 48.6%. Visual analogue scale pain score was significantly higher among patients with psychiatric disorders versus patients without psychiatric disorders (P = 0.0001). Significant negative correlation was recorded between Disease Activity Score and total IQ score (P = 0.01), whereas no significant association was seen between Disease Activity Score and the presence of neuropathy or psychiatric disorders.

Conclusion
Cognitive impairment, depression, anxiety and peripheral neuropathy are common in RA patients. Early diagnosis and management of neuropsychiatric disorders in RA patients may greatly improve the patients' health-related quality of life.

Keywords:
electroencephalography, intelligence quotients, neuropsychiatric disorders, P300, rheumatoid arthritis

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease that is commonly associated with substantial pain. The disease is associated with considerable comorbidity, which interferes with normal daily activities and contributes to a decline in the quality of life [1].

The presence of peripheral neuropathy in RA patients is frequently overlooked; however, it contributes significantly to the associated functional limitations. Hart and Golding [2] were the first to describe a definitive case series of neuropathy with rheumatoid disease. Distal sensory, mixed sensorimotor, mononeuritis multiplex and entrapment neuropathy are the most commonly reported types of neuropathy in RA [3–5].

Limited attention has been given to potential cognitive, emotional and behavioural effects in RA [6]. Depression is reported by about 43% and anxiety by 89% of RA patients [7,8]. Anxiety is believed to occur more frequently among RA patients suffering from depression than in nondepressive RA patients [9]. Most of the published studies used self-rating scales for evaluating depression and anxiety [10,11]. Only a

small number of studies used standardized psychiatric interviews to identify psychiatric disorders in RA patients [12–15]. In addition, most of the previous studies did not explore the incidence of other psychiatric conditions in RA patients.

The aim of this study was to identify the frequencies of neuropsychiatric disorders in RA patients using clinical, neuropsychiatric, laboratory, electrophysiological and psychometric tests.

Patients and methods

Ninety-two female patients with RA were consulted and recruited from the outpatient clinics of Neuropsychiatry, Internal Medicine (Rheumatology Unit), and Rheumatology and Rehabilitation Departments, Assiut University Hospital, Egypt, between June 2010 and May 2011. All of them fulfilled the revised American College of Rheumatology criteria for RA [16] and the following eligibility criteria:

(a) Fulfilment of at least four of the seven RA criteria;
(b) Having a disease duration of at least 6 months; and
(c) Ability to give written consent for participation.

Exclusion criteria were as follows:

(a) Incidence of joint infection, joint surgery or bone fracture within the last 3 months;
(b) Pregnancy;
(c) Presence of metabolic disturbance;
(d) Presence of end organ failure (cardiac, uraemic or cirrhotic);
(e) History of significant mental impairment from other systemic illnesses (hypothyroidism, malignancy);
(f) Current use of neurotoxic drugs;
(g) Presence of concomitant primary neurological or psychiatric disorders or sensory deprivation; and
(h) Refusal to participate.

Eighteen RA patients were excluded from the study: four patients did not fulfil the revised criteria for RA diagnosis, 10 patients did not fulfil the eligibility criteria (two were pregnant, three had undergone joint surgery recently and five had associated neurological disorders) and four patients refused to participate in the study.

Seventy-four female patients with RA were found eligible and agreed to participate in the study. Their mean age was 37.78 ± 11.8 years (range 22–49 years). The duration of illness was 7.4 ± 6.1 years (range 1–16 years). Twenty-five healthy female volunteers who were matched for age, educational level and socioeconomic status were recruited as the control group. They fulfilled the above eligibility criteria, but not the RA criteria.

Methods

All recruited participants underwent bedside medical, rheumatological and neurological examination, were evaluated with the visual analogue scale (VAS) for pain, and underwent psychiatric assessment, standard neurophysiological tests and laboratory tests.

Clinical evaluation of RA patients included age of onset, duration of illness, presence of extrajoint manifestations and morning stiffness. The 'Disease Activity Score' for 28 joints (DAS 28) was used to evaluate RA activity and to classify it as being in remission (<2.6), low (2.6 to <3.2), moderate (3.2–5.1) or high (>5.1). The DAS 28 evaluation estimates the number of tender and swollen joints, the patient's global assessment of disease activity and the erythrocyte sedimentation rate [17].

VAS for pain was self-reported by each participant. It is a validated approach that consists of a 10-cm line with one end labelled 'no pain' and the other end labelled 'worst pain imaginable'. The patient marks the line at the point that best describes the pain intensity. The length of the line upto the patient's mark was measured and recorded in millimetres.

Psychiatric assessment

All participants (patients and control groups) were interviewed by designated psychiatrists using the Structured Clinical Interview for *Diagnostic and statistical manual of mental disorders*, 3rd ed., Revised (DSM-III-R) Axis I Disorders (SCID-I) [18]. The Wechsler Adult Intelligence Scale, 3rd ed. (WAIS-III) [19] with total score, verbal and performance intelligence quotients (IQ) was also administered to each participant.

Neurophysiologic assessment

Electrophysiological studies were performed on all recruited participants and included the following:

(1) Conventional motor and sensory nerve conduction studies, F-wave of four limbs and electromyography of distal and proximal muscles to confirm the presence of neuropathy. For motor conduction study, distal latency (DL), motor conduction velocity (MCV) and amplitude of compound muscle action potentials (CMAPs) were measured with standard surface-stimulating and recording techniques for ulnar, median and common peroneal nerves. For sensory conduction

study, distal latency and sensory conduction velocity were measured with a standard ring-stimulating electrode for median and ulnar nerves and surface stimulating for the sural nerve. For F-wave determination of ulnar, median and posterior tibial nerves, 10 stimuli were given, and the minimal latency value was determined for each nerve. The normal limits of MCV and DL were set at ± 2 SD from the mean values of the control group. The CMAP was considered abnormal if the amplitude (peak to peak) was below the lowest value found in controls. Entrapment neuropathy was diagnosed by the presence of focal slowing in sensory and/or MCVs across the site of entrapment by at least 20% below the lower limit of control conduction values with or without a reduction in CMAP amplitude below the lowest value of the control group. Diffuse axonal neuropathy was diagnosed by reduced amplitude of CMAP with normal shape and duration, and with normal or minimal reduction of MCV and/or sensory conduction velocity and/or DL.

(2) Conventional wakefulness electroencephalography (EEG) was carried out using an eight-channel Nihon Kohden equipment (model MEP 4217, Japan) employing scalp electrodes placed according to the international 10–20 system with bipolar and referential montages. Hyperventilation and photic stimulation were used as provocative tests.

(3) Event-related potentials (P300) (ERPs) were also assessed for each patient. ERPs were elicited with an auditory discrimination task paradigm by presenting a series of binaural 1000-Hz (standard) versus 250-Hz (target) tones at 70 dB with a 10-ms rise/fall and 40-ms plateau times. Tones were presented at a rate of 1.1/s, with target tones occurring randomly with a 0.2 probability. The participants were seated with their eyes closed. They were instructed to mentally count the target tones, but not the frequent tones, and then asked to report the number of target tones counted at the end of each run. Evoked potentials were recorded from scalp electrodes placed at Cz and Pz and were referred to linked ears. Filter settings were 0.5 and 70 Hz, analysis time was 1 s, sensitivity was 20 μV and duration of stimulus was 0.1 ms. To assess performance accuracy at the end of each session, the patient's count was compared with the actual number of target tones presented. Two or three trials were performed to demonstrate the consistency of the waveform. P200 and P300 latencies were measured from stimulus artefact to the first and second major positive peaks with a range of 150–250 and 250–500 ms, respectively. Amplitudes were measured (peak to peak) from the negative component just before the maximum positive peaks (P200 and P300) [20]. Nerve conduction studies and ERPs were recorded using Nihon Kohden equipment (model 7102).

The following laboratory tests were conducted: erythrocyte sedimentation rate, which was measured by means of the Westergren method to track the disease activity of RA; rheumatoid factor (RF), which was determined by means of the latex agglutination test (RF titre of >1 : 80 was considered positive); complete blood count; peripheral blood film; prothrombin time; partial thromboplastin time; fasting blood sugar; blood urea nitrogen; serum creatinine; liver function tests for bilirubin, albumin, globulin, transaminases and alkaline phosphatase; C reactive protein (CRP); and thyroid function tests.

Ethics

This study was approved by the Ethical Committee of Assiut University Hospital. Written informed consent was obtained from all participants after they had been informed about the purpose of the study in detail.

Statistical analysis

Mean values of each parameter in patients and controls were compared using the Student *t*-test. In electrophysiological studies, abnormal values were considered when their values exceeded 2 SD above or below the mean control values. Spearman's correlations between age, duration of illness, laboratory findings and DAS 28 with IQ and P300 latencies were also performed. Two-sided *P* values less than 0.05 were considered statistically significant.

Results

Seventy-four female patients with RA were investigated; their mean disease activity (DAS 28) was 5 ± 0.8. Details of demographic, clinical (articular and extra-articular) and laboratory data as well as the mean VAS for pain are given in Table 1. All studied patients had been treated for at least 3 months, with various combinations of methotrexate, sulfasalazine, leflunomide, low-dose steroids and antimalarial (hydroxychloroquinone) and NSAIDs to avoid physical disability.

Clinical history and neurological examination revealed that 14 patients were symptomatic: eight patients had peripheral neuropathy (distal weakness, lost deep reflexes and glove and stock hypaesthesia) confirmed by neurophysiological assessment; two patients had clinical signs and symptoms compatible with lumbosacral radiculopathy and confirmed by neurophysiological assessment (prolonged F-wave

and H reflex of both lower limbs); and four patients had cervical pain, with one (1.35%) of them having quadriparesis on examination secondary to atlantoaxial sublaxation as a radiological finding (Table 2). Another four patients had evidence of peripheral neuropathy diagnosed by neurophysiological assessment without symptoms.

Table 1 Demographic, clinical and laboratory profile of rheumatoid arthritis patients

Demographics/clinical data	Mean ± SD or *n* (%)
Age (years)	37.78 ± 11.8
Sex (male/female)	0/74
Duration (years)	7.4 ± 6.1
Disease Activity Score	5.01 ± 0.84
Moderate disease activity	42 (56.8)
High disease activity	32 (43.2)
Articular manifestation	
Number of swollen joints	2.2 ± 1.8
Number of tender joints	6.79 ± 5.6
Duration of morning stiffness (min)	63.55 ± 55.7
Extra-articular manifestation other than neuropathy	
Subcutaneous nodules	13 (17.6)
Pleurisy	8 (10.8)
Pleural effusion	4 (5.4)
Pericarditis	3 (4)
Visual analogue scale	7.31 ± 1.5
Laboratory markers	
Erythrocyte sedimentation rate	
1st hour	66.3 ± 34.3
2nd hour	89.9 ± 34.7
Positive C reactive protein	70 (94.6)
Positive rheumatoid factor	52 (70.3)
Haemoglobin (g/dl)	10.9 ± 1[a]

[a]Ten patients were anaemic.

Table 2 Neuropsychiatric findings in rheumatoid arthritis patients

Neuropsychiatric findings	*N* (%)
Normal neurological and neurophysiological examination	56 (75.7)
Neurological examination findings	14 (18.9)
Peripheral neuropathy	8 (10.8)
Lumbosacral radiculopathy	2 (2.7)
Cervical pain	4 (5.4)
Neurophysiological findings	
Sensory and mixed sensorimotor axonal polyneuropathy	8 (10.8)
Mononeuropathy multiplex	2 (2.7)
Carpal tunnel	2 (2.7)
Radiculopathy	2 (2.7)
No psychiatric disorders	29 (39.2)
Positive psychiatric disorders	45 (60.8)
Depressive disorders either single or comorbid with anxiety	34 (45.1)
Anxiety disorders either single or comorbid with depression	20 (27)
Generalized anxiety disorder	10 (13.5)
Phobic disorders	4 (5.4)
Obsessive compulsive disorders	4 (5.4)
Panic disorders	2 (2.7)
Somatoform disorders	6 (8)
Schizophrenia	1 (1.4)

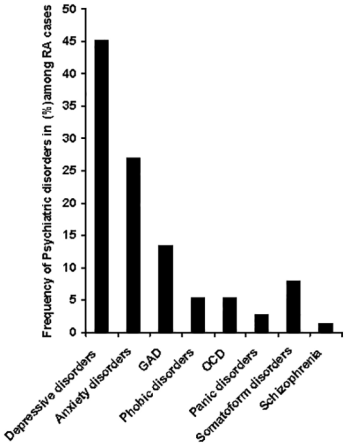
The most common neurophysiological abnormality was distal systemic sensory neuropathy (in the lower limbs) (10.8%); mixed sensorimotor axonal polyneuropathy was recorded in four (5.4%) patients, whereas mononeuropathy multiplex and carpal tunnel were recorded in two (2.7%) patients each (Table 2). Because leflunomide can produce peripheral neuropathy we classified the patients into two groups: out of 31 patients taking leflunomide, seven (22.6%) showed evidence of peripheral neuropathy; however, the proportion was very similar (P = 0.7) in the remaining 43 patients who were taking drugs other than leflunomide; in these patients, seven (16.3%) showed evidence of peripheral neuropathy.

RA patients with peripheral neuropathy were significantly older (44.1 ± 7.1 vs. 35.7 ± 12.5 years; P = 0.001) and had higher RF (116.1 ± 160.8 vs. 43.6 ± 49; P = 0.003) compared with patients without peripheral neuropathy; no significant association was found between disease activity and peripheral neuropathy (P = 0.107). The VAS rating scale for pain was nearly similar in both groups of patients.

The frequency of current psychiatric disorders in RA patients was 60.8%, compared with 12% in controls (three out of 25; anxiety, somatoform disorder and depression, respectively). This difference was statistically significant (P < 0.001). In the RA group, depressive disorders as a single entity or comorbid with anxiety were found in 34 (45%) cases. Anxiety disorders either as a single entity or comorbid with depression were found in 20 (27%) cases, and comorbid anxiety and depression were found in 16 (21.6%) cases. Generalized anxiety disorder was the most common anxiety disorder (13.5%), followed by specific phobias, obsessive compulsive disorders (5.4% for each) and panic disorder (2.7%), in RA patients (Table 2 and Fig. 1). Interestingly, comorbid neurological findings and psychiatric disorders were recorded in eight (44.4%) out of 18 RA patients.

There were no significant differences between patients with and those without psychiatric disorders in terms of age, duration, RF and clinical profile (i.e. articular or extra-articular manifestations). The mean VAS pain score was significantly higher among patients with psychiatric disorders (8.1 ± 1.4) versus patients without psychiatric disorders (6.1 ± 0.6) (P = 0.0001). There was no significant association between RA patients with psychiatric disorders and DAS (P = 0.136).

Figure 1



The frequency of different psychiatric disorders among the studied patients. GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder; RA, rheumatoid arthritis.

Table 3 Electroencephalography pattern in rheumatoid arthritis patients

EEG patterns	*N* (%)
Normal EEG pattern	38 (51.4)
Abnormal EEG pattern	36 (48.6)
Background activity	
Normal background activity	67 (90.5)
Diffuse slowing 4–7 Hz/s	7 (9.5)
Focal activity	
Focal slowing	6 (8.1)
Focal sharp or spike activities	12 (16.2)
Generalized paroxysmal activities	28 (37.8)
Paroxysm of high-voltage slow wave or sharp activities	20 (27)
Paroxysm of spike wave complexes	8 (10.8)

EEG, electroencephalography.

Table 4 Intelligence quotients and event-related potentials in rheumatoid arthritis patients

Variables	Mean ± SD		*P*-value
	RA patients (*N* = 74)	Control (*N* = 25)	
Intelligence quotients (IQ) score			
Total IQ	81 ± 11.55 (40)	104.4 ± 12.2	0.000
Verbal IQ	79.35 ± 10.5	96 ± 14.2	0.000
Performance IQ	78.84 ± 10.3	98.9 ± 14.2	0.000
Auditory event-related potentials (ERPs) latency (ms)			
N100	114.125 ± 31.1	119 ± 29.23	0.493
P100	196.4 ± 45.7	206.8 ± 38.5	0.309
N200	262.8 ± 38.9	268.3 ± 48.8	0.568
P300	354.9 ± 41.8 (7)	319.4 ± 35.5	0.0001
Amplitude (mv)			
N200	8.66 ± 6.5	8.8 ± 2	0.916
P300	9.7 ± 6.4 (3)	7.9 ± 6.5	0.228

Number in parentheses indicate number of abnormal cases; RA, rheumatoid arthritis.

Abnormal EEG findings were observed in 36 (48.6%) RA patients. The most common abnormality in RA patients was generalized paroxysmal activity (epileptiform activities) in 28 (37.8%) patients, either as paroxysms of high-voltage slow wave or sharp activities or paroxysms of spike wave complexes. Focal activities were recorded in 18 (24%) patients. Interestingly, seven (9.5%) patients showed diffuse slowing down of background activity (Table 3).

On cognitive assessment, total IQ, verbal IQ and performance IQ scores were found to be significantly lower in RA patients compared with controls (P = 0.0001), as 40 (54%) patients had a low IQ score, which ranged from borderline IQ in 30 (40.6%) patients to mild mental retardation in 10 (13.5%) patients. ERPs P300 latency in RA patients was significantly prolonged compared with control values (P = 0.0001); moreover, seven (9.5%) RA patients had a prolongation of P300 latency (>mean ± 2 SD) compared with the control group. However, no other abnormalities were recorded among the parameters of ERPs (Table 4).

Spearman's correlation showed significant negative correlation between total IQ and disease activity and RF (r = −0.278, P = 0.018, and r = −0.289, P = 0.014, respectively). No significant association was found between cognitive functions, psychiatric disorders and various combination drug therapies whether corticosteroids, immune-modulating or NSAIDs, as measured by the χ^2-test.

Discussion

The present study is one of the few that have been performed to estimate neuropsychiatric disorders among RA patients. In this study 14 (18.9%) patients were symptomatic; eight (10.8%) of them had symptomatic peripheral neuropathy and two had lumbosacral radiculopathy. Another four patients were diagnosed with peripheral neuropathy according to the electrophysiological testing without symptomatology. The most commonly detected abnormalities using electrophysiological testing were systemic sensory and mixed sensorimotor axonal polyneuropathy (10.8%), whereas mononeuropathy multiplex and carpal tunnel were recorded in 2.7% each. Our results are consistent with those of Bayrak *et al*. [21], who found neuropathy in 17% of RA patients in Turkey using nerve conduction studies. A higher frequency of occurrence of peripheral neuropathy in RA patients was reported by other studies, ranging from 37 to 50% [22–24]. In contrast, a lower frequency of neuropathy (8.57%) was reported in the study by Bharadwaj and Haroon [4]. Variations in selection criteria, duration of disease and method of diagnosis may contribute to the wide variation in prevalence.

The prevalence of entrapment neuropathy in RA patients varied widely between 4 and 54.6% [5,25]. In the current study, two (2.7%) cases were diagnosed with carpal tunnel syndrome, detected only by electrophysiological study, similar to the results obtained in other studies [22,26]. Atlantoaxial subluxation was recorded in only one (1.35%) of our patients, whereas four (4%) patients were diagnosed in the study by Al-Ghamdi and Attar [27].

Age was the most important independent predictor of peripheral neuropathy, with probability of steady increase after the age of 50 [28]. In our RA patients, neuropathy patients were older and had a longer duration of illness compared with those without, and no significant association was seen between DAS and neuropathy. These results are in accordance with previous reports [4,5,24] with no relation between disease activity and neuropathy [22,24,29].

The seropositivity of RF was significantly associated with the presence of peripheral neuropathy in our patients. These findings are similar to those of Biswas *et al.* [24] and Albani *et al.* [28] and not in accordance with some others [3,4,29]. Kho and Kermode [30] found that the prevalence of peripheral neuropathy in RA could be attributed to the leflunomide treatment that is commonly prescribed. In the present study there was no significant association between neuropathy and drug intake, although this may be due to the relatively small sample size that we used.

The present work identified a point prevalence of 60% for psychiatric disorders in RA patients, a figure that was higher than that reported in western RA patients using the same evaluation tools (21–26%) [31]. Depression (45%) and anxiety (27%) were the most prevalent, whereas comorbidity between both was seen in 21% of our RA patients. The above figure for depressive disorder (45%) is more than double the figure reported in western societies (13–20%) [32] and the Chinese population [33], using the same research tool. The same higher figures were seen in anxiety disorders of the present work (27%) as compared with the British population (8.8–9.5%) using the Psychiatric Assessment Schedule [13,31]. This difference could result from either a methodological difference or a real difference in the nature of the study population. However, obsessive compulsive and phobic disorders were not assessed in Psychiatric Assessment Schedule [34], whereas these were taken into consideration in our evaluation. Given that anxiety can lead to depression, early detection of psychiatric manifestations in RA patients appears to be worthwhile. As previous reports suggested, systemic inflammation might induce depressive symptoms by activating the immune brain pathway [35,36]. Although the present work did not find any association between inflammatory markers and depression or other recorded psychiatric manifestations, it was consistent with recently reported data by Sato *et al.* [37], who found no relationship between major depressive disorders and RA disease activity. However, this association has been reported before by Kojima *et al.* [38], who showed that depression scores were mildly and positively correlated with the CRP level ($r = 0.46$, $P < 0.001$).

The results of IQ and ERPs in the present study confirmed that cognitive impairment is prevalent among RA patients, as mild cognitive impairment was recorded in 54% of RA patients. This is consistent with the recorded prevalence of 66% for moderate cognitive impairment by Lisitsyna *et al.* [39] among RA patients.

In the current study the significant prolongation of P300 latency may suggest affection of neurocognitive function in our patients. This finding had been supported by the presence of seven cases with prolonged latencies in the study population. Early components of ERPs (P100, N100 and P200) have been attributed to primary and secondary steps of auditory information processing rather than distinctive cognitive processes. Thus, the fact that these were unchanged in our population indicates that the early processing of auditory information is intact in RA patients. Therefore, it appears that abnormality of the attention-binding process happens at later stages of cognitive processing. The significant association between high DAS and IQ score suggests that cognitive deterioration in these patients may be related to disease activity.

Nearly half of the studied RA patients showed EEG abnormalities. The most common EEG findings were generalized paroxysmal activities (epileptiform activities). Epileptiform activity may be a sign of cerebral (cortical neuron) dysfunction related to the disease pathogenesis and may be related to the associated sleep disturbance in RA patients secondary to pain or high prevalence of psychiatric disorders. However, the above EEG findings were mostly not directly related to isolated psychiatric symptoms as reported by Shelley *et al.* [40]. Moreover in the present study, seven cases had diffuse slow activity, which is generally considered a sign of organic brain disease. This EEG pattern is consistent to some extent with an RA case report by Sillanpää *et al.* [41]. These EEG changes that were recorded in the present study may be clinically relevant to cognitive impairment or psychiatric disorders.

The changes recorded in IQ, ERP and EEG may confirm the central nervous system involvement in RA patients. This may reflect that RA may act centrally on the brain to produce cerebral dysfunctions and changes

in the IQ. The systemic inflammation and diffuse vasculitis associated with the process of inflammation in RA might induce all these dysfunctions by activating the immune brain pathway. In fact, if the RA disease has these central effects, the psychiatric symptoms may be primary (i.e. caused by the disease agent) rather than secondary to chronic pain or reduced quality of life.

Conclusion

Neuropsychiatric manifestations are fairly common in clinical and subclinical RA patients, confirming the central and peripheral effect of RA disease on nervous system functions. Thus, the diagnosis of these comorbid disorders must be based on clinical examination and psychometric and electrophysiological tests. The use of such tools gives a true prevalence of the nervous system involvement and more accurate and early diagnosis, which leads to better clinical care before the development of debilitating nervous system changes and subsequent physical dysfunctions and impairment of the quality of life of RA patients.

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Conflicts of interest

There are no conflicts of interest.

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