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ORIGINAL ARTICLE

Assessment of biocorrelates for brain involvement in female patients with rheumatoid arthritis

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Abstract Central nervous system (CNS) abnormalities are rare in patients with rheumatoid arthritis (RA). Direct studies done to investigate brain involvement in RA are few or even absent. We hypothesized that CNS is not excluded from the inflammatory disease process in RA. Thus we systematically investigated markers of brain involvement in 55 females with RA. We examined patients' cognition using battery of sensitive psychometric testing [Mini-Mental State Examination, Stanford–Binet test (fourth edition) and Wechsler Memory Scale—Revised] and by recording P300 component of event-related potentials, a neurophysiological analogue. We also measured the serum levels of S100B and neuron-specific enolase (NSE), markers of glial and neuronal cells. Compared to control subjects, lower scores in cognitive testing were reported in 71% of the patients ($n = 39$) and abnormal P300 latency and amplitude ($P < 0.001$, 0.050). Patients had higher levels of S100B ($P < 0.029$) and higher levels of S100B were correlated with lower total scores of cognitive functions ($P < 0.01$), P300 latency ($P < 0.05$), and NSE concentrations ($P < 0.01$). However, cognitive scores did not correlate with disease activity or severity. Although depression scores were significant in patients with RA ($P < 0.001$), but they did not correlate with cognitive scores. Seven patients had white matter hyperintensities in MRI brain suggesting vasculitis, ischemic brain lesions and dots of demyelination, and all had higher levels of S100B. Results of this study directly indicate that the disease process (inflammation and demyelination) is associated with cognitive deficits observed with RA.

Keywords Cognition · Neuron-specific enolase · Rheumatoid arthritis · S100B · Vasculitis

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Introduction

Rheumatoid arthritis (RA) is an inflammatory multisystem connective tissue disorder affecting joints with approximated prevalence in white populations of northern European and North American of 0.5–1%, and a mean annual incidence of 0.02–0.05% [1]. Whereas reports from Africa note a rising incidence, for example in Egyptian population, the prevalence of RA is approximately 0.3% [2].

Peripheral nervous system abnormalities are common with RA [3–5]; however, reports about central nervous system (CNS) and brain changes are sporadically reported [6–23]. Vasculitis is defined as vessel wall inflammation with or without necrosis. Although secondary CNS vasculitis is a well-documented pathology in connective tissue diseases

as systemic lupus erythematosis (SLE) and polyarteritis nodosa [24, 25], however, manifest cerebral vasculitis is a rare and a serious complication of RA. Diverse CNS clinical and neuroimaging manifestations were reported in the literature as case reports and include seizures, meningitis, encephalopathy, and focal neurological symptoms; multiple brain microinfarcts, high-signal intensities, white matter abnormalities, and abnormal leptomeningeal enhancement on magnetic resonance imaging of the brain (MRI); and stenosis or string-of-beads stenosis of the carotid and vertebrobasilar arteries on magnetic resonance angiography (MRA) [6–23]. In addition, several histolopathological patterns of vasculitis were reported with RA including non-necrotizing lymphocytic vasculitis, leukocytoclastic vasculitis with immune complex deposition, necrotizing vasculitis, vasculitis associated with cryoglobulinemia, and vasculitis associated with hypergammaglobulinemia. The exact mechanisms of the development of RA-associated cerebral vasculitis have not been identified. It seems to be mediated by IgG rheumatoid factor (RF), immune complexes, and complement activation (particularly C3 and C4). Recently, it was shown that C-reactive protein (CRP) can in part activate the complement system and deposits of Ig and complement may activate local inflammation and possibly cerebral vasculitis [26]. Antibodies to endothelial cells, tumor necrosis factor (TNF), perinuclear antineutrophil cytoplasmic antibodies, and antiphospholipid antibodies have also been incriminated in vasculitis associated with RA [27].

During the last years, the possibility of evaluating brain damage/activity through quantification of glial and neuronal-derived proteins [such as S100B and neuron-specific enolase (NSE)] in peripheral samples has gained appropriate attention in clinical and experimental settings [28–36]. S100B is a calcium-binding protein physiologically produced and released predominantly by astrocytes [28]. NSE is a cytoplasmatic glycolytic pathway enzyme, being the $\gamma\gamma$ isoform mainly neuronal [35, 36]. Several studies have shown higher serum and cerebrospinal fluid levels of S100B and NSE and also their overexpression increases the vulnerability to neurodegeneration [30], cerebral hypoxic–ischemic injury [31], traumatic brain injury [35], CNS infections [33, 34], and severe extracerebral infectious diseases [33]. NSE is found in neurons and neuroendocrine tissue, and it is elevated in the blood circulation after increased death rate of these cells [35, 36]. As disturbance of blood–brain barrier permeability due to the possibility of vasculitis associated with RA cannot be excluded, accordingly, the quantification of brain-derived proteins as glial and neuronal derived proteins (e.g., S100B and NSE proteins) may serve as sensitive and direct biomarkers of brain damage in RA as well as its related neurological and neuropsychological outcome.

Aim of work

Data from studies upon the evidence of brain involvement in RA are few or even controversial. This work aimed to investigate markers associated with brain injury in a group of patients with RA. These markers included: (1) cognitive functions, which were assessed using a battery of sensitive psychometric testing, (2) P300 component of event-related potentials (ERPs), a neurophysiological analogue of cognitive function, and (3) measurement of serum concentrations of S100B and NSE, sensitive glial and neuronal markers of brain damage. Correlations were done between pain and depression, between scores of depression and cognitive testing, and between S100B protein levels, different cognitive domains, P300 variables, and NSE levels. To our knowledge, this is the first study which objectively investigated glial and neuronal cell biomarkers in patients with RA.

Methods

This cross-sectional study included 55 females established the revised criteria of American College of Rheumatology for RA [37]. They had different classes and stages of the disease. As we recruited only three males with RA throughout the period of the study, we excluded them from the statistical analysis. Patients were recruited during the course of their regular appointments in the Rheumatology Clinic, Assiut University Hospital, Assiut, Egypt. This study was accepted by the regional ethical committee. Detailed information on the study was given to all participants, and all gave their written consent to attend this study. Forty age- and sex- matched healthy subjects recruited from the general population served as control subjects for comparison. Control subjects were also matched for socioeconomic and educational levels. Excluded were: (1) patients with systemic diseases known to involve CNS (as renal and liver diseases, SLE, and AIDS); (2) chronic medical illness that precipitates atherosclerosis as diabetes mellitus, hypertension, or others; (3) history of psychosis or other neurological diseases; (4) history of severe sensory impairment (as blindness and deafness) that may disrupt patient cooperation; (5) motor impairment that would interfere with cognitive testing; (6) cancer discovered in the previous 5 years; (7) patients with history of severe head trauma or neurosurgical operation at any time before presentation; and (8) use of drugs (other RA treatments) known to cause neurotoxicity.

Demographic, clinical, and laboratory characteristics

All participants underwent complete rheumatologic, medical, neurologic, psychiatric, and audiologic evaluations.

Clinical variables of disease activity include the count of swollen and tender joints and by a modification of the composite index of disease activity [38]. Disease severity was assessed by the ARA X-ray staging, as well as by RA seropositivity and presence of extraarticular manifestations [39]. Radiological grading was performed and staged according to Larsen index (0–4) where grade 0 is normal and grade 4 is mutilating abnormality [40]. Routine hematological tests were done and included erythrocytic sedimentation rate (ESR), CRP, complete blood count (CBC), blood sugar (fasting and postprandial), renal and liver functions, lipogram [serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c)], and uric acid. Routine serology included RF which was determined by latex agglutination test, RF titer of 1:80 was considered significant.

Cognitive assessment

Cognitive functions were assessed independently for each participant by two experienced psychologists and under supervision of psychiatrist, using a set of standardized Arabic translated versions of neuropsychological tests which are sensitive for mild cognitive impairment and covering different cognitive domains. They included: Mini-Mental State Examination (MMSE) [41, 42] and Stanford–Binet subsets testing (SBST, fourth edition) [43, 44] and subsets from Wechsler Memory Scale—Revised (WMS-R) [45]. From SBST, we selected vocabulary and comprehension for assessment of verbal reasoning, pattern analysis for assessment of visual reasoning, quantitation for quantitative reasoning, and bead memory and memory for sentences for short-term memory. From WMS-R, we tested digit forward, digit backward, mental control, associate learning, logical memory, and visual reproduction.

Event-related potentials testing

Before examining ERPs, all participants underwent basic audiological testing (Amplaid Model 720; Milan, Italy). Testing for ERPs was done in the audiology unit on a separate day after completion of neuropsychological testing (Interacoustics model AC40, v.1.28; Assens, Denmark). ERPs are series of scalp waves that are extracted from the electroencephalogram (EEG) by time domain analysis and averaging of EEG activity following multiple stimulus repetitions. They were elicited with an auditory discrimination task paradigm by presenting a series of binaural 1,000 Hz (standard) versus 2,000 Hz (target) tones at 70 dB with a 10-ms rise/fall and 40-ms plateau time. The obtained ERPs were subdivided into: (a) early or sensory-evoked components (e.g., P100, N100, P200, and N200), which emerge within the first 100–200 ms after stimulus onset and basically reflect stimulus detection and auditory-evoked brainstem potentials, and (b) late or cognitive-related components (e.g., P300) [46]. Latencies and amplitudes (peak to peak) of P300 component of ERPs were measured. P300 is believed to index stimulus significance and the amount of attention allocated to the eliciting stimulus event, being maximal to task relevant or attended stimuli and being absent or small to task irrelevant or unattended stimuli.

Radiological assessment

All patients did MRI and MRA of the brain using the 1.5 GE Signa Horizon scanners (GE Medical Systems, Waukesha, WI). Spin-echo echoplanar imaging, fast spin-echo, fluid-attenuated inversion recovery (FLAIR), gradient echo, and multiplanar gradient echo sequences were obtained. Two-dimensional time-of-flight MRA of the intracranial cerebral circulation and internal carotid arteries were also done.

Psychological evaluation

Standardized psychiatric interview was done by applying the Diagnostic and Statistical Manual of Mental Health Disorders, fourth edition (DSM-IV) criteria for the diagnosis of depression [47]. A differentiation between clinical depression and depressive symptoms was made throughout this work. The Arabic version [48] of the Beck Depression Inventory (BDI-II) [49] was used for assessment of the severity of depressive symptoms. BDI-II is the revised version of Beck Depression Inventory (BDI) [50]. The items reflecting somatic disease or what is known as "criterion contamination" which is the overlap between depressive symptoms and the manifestations and consequences of RA were eliminated in BDI-II (as fatigue; work disability, weight loss, loss of energy, sleep loss, appetite loss, changes in body image, and somatic preoccupation). BDI-II items are in alignment with DSM-IV criteria. BDI-II consists of 21 items, each corresponds to a symptom of depression and is summed to give a single score for the BDI-II. According to that scale, the patient may have no or minimal depressive symptoms (scoring, 0–13), mild symptoms (scoring, 14–19), moderate symptoms (scoring, 20–28), and severe symptoms (scoring, 29–63).

Measuring biomarkers of brain injury

S100B protein was measured in the serum using Human S100B enzyme-linked immunosorbent assay kits (ELISA) kits (BioVendor Research and Diagnostic Products, Cat. no.: RD192090100R, Candler, NC 28715 USA, infoUSA@biovendor.com) [28]. NSE level was evaluated in serum

samples by UBI MAGIWEL NSE ELISA kits (UBI United Biotech Inc., Cat. No.: CM-901, Mountain view, CA 94041, www.unitedbiotech.com) [51]. For NSE and S100B proteins, reactions and quantification were performed in duplicate as described by the manufacturer.

Statistical analysis

Calculations were done using statistical package SPSS for windows, version 10.0 (SPSS Inc., Chicago III). Descriptive statistics were presented as mean ± standard deviation for parametric variables and absolute and percentage frequency for categories. Unpaired two-sided Student's t test was used for comparison. Correlations were assessed using Pearson's test. Linear regression analyses were performed as follows: as a first step, we carried out bivariate correlations between the dependent variable (S100B protein) and each of the independent variables (i.e., scores of cognitive performance, disease duration, index of disease activity, RF, and depression; r and P values). Independent variables that had no significant correlations were then excluded. The model was adjusted for age as confounder and additional adjustment was done for both age and duration of illness. A two-sided $P < 0.05$ was considered statistically significant.

Table 1 Demographic, clinical, and laboratory data of the studied rheumatoid arthritis patients

Demographic data	Total (n=55)
Age, years	45.64±10.91
Duration of illness, years	9.99±3.7
Number of swollen joints	5.94±3.51
Number of tender joints	5.25±2.97
Index of disease activity	2.5±0.5
Morning stiffness (min)	88.18±52.0
ESR (mm/h)	53.27±20.34
CRP	30.25±11.30
X-ray grading (G0–4)	
G1	10 (18.2)
G2	35 (63.3)
G3	8 (14.5)
G4	2 (3.6)
Number of patients with positive rheumatoid factor	24 (43.64)
Rheumatoid factor level (mean±SD)	208.00±164.42
Subcutaneous nodules	7 (12.73)
MTX and NSAIDs	18 (32.72)
Steroids	11 (20)
NSAIDs	19 (34.45)
Colchicines	1 (1.81)
MTX and hydroquinone	6 (10.91)

Results

Included were 55 females with RA. All reported normal levels of CBC, blood sugar, renal and liver functions, TC, TG, LDL-c, HDL-c, and uric acid. The demographic and clinical characteristics of the studied group were shown in Table 1. Only five patients aged >50 years old. Except for the presence of subcutaneous rheumatoid nodules in 12.73% (n = 7), none of the patients had obvious extra-articular manifestations. The majority of patients (>98%) were treated for at least 1 month, with a single or various combination of methotrexate (MTX), low-dose steroids, antimalaria (hydroquinone), and nonsteroidal anti-inflammatory drugs (NSAIDs).

Table 2 showed comparisons between patients and controls in scores of cognitive functions, depression, MRI findings, and concentrations of lab markers of brain damage (S100B and NSE proteins). Lower scores in cognitive testing (as verbal relations, comprehension, pattern analysis, quantitative reasoning, and memory) were reported in 71% of the patients (n = 39) together with abnormal P300 latency and amplitude (P = 0.001, P = 0.050). They also showed higher scores for S100B protein (P = 0.029) but not for s-NSE (P = 0.471). Higher levels of S100B (i.e., exceeding the upper limit for controls which was 180 pg/ml) were identified in 12 patients (21.81%, range 210–900 pg/ml). Six females (10.91%) also had higher levels of NSE (range 25–40 μg/l; i.e., exceeding the upper limit for controls which was 40 μg/l). Forty-two patients (76.36%) had depressive manifestations, mostly of mild degree (71.43%, n = 30) while 28.51% (n = 12) had moderate/severe degrees.

MRI brain showed abnormal hyperintense T2-weighted and FLAIR signals in the subcortical white matter and at the junction between the gray and white matter consistent with vasculitis, ischemic brain lesions, and dots of demyelination in only seven adult patients (≤45 years). In the remaining patients (n = 48), the high-signal, white matter lesions were not more than for control subjects. For all patients, MRA findings looked normal. All patients with MRI abnormalities (n = 7) had higher serum levels of S100B protein. Two patients with MRI abnormalities were seropositive, severely ill, had marked cognitive decline, and had higher serum levels of S100B (patients 1 and 2, Fig. 1). Except for the two patients with severe cognitive deficits, none showed manifest evidence of CNS involvement.

Levels of S100B were correlated with total scores with cognitive functions (r = −0.650, P = 0.01), P300 latency (r = 0.467, P = 0.05), and NSE (r = 0.560, P = 0.01). However, cognitive scores did not correlate with index of disease activity (r = 0.016, P = 0.949) or RF levels (r = 0.300, P = 0.412). Although depressive scores were significant in patients with RA (r = 0.750, P = 0.001), they

Table 2 Comparison between patients and controls in scores of cognitive functions, depression, MRI findings, and lab markers of brain compromise

Variable	Patients (n=55)	Controls (n=40)	P value t test
Mini-Mental State Examination	23.17±3.37	25.04±1.9	0.048
Stanford–Binet subtests			
Vocabulary	42.05±5.82	48.20±6.90	0.033
Comprehension	34.16±5.86	46.30±9.20	0.006
Pattern analysis	36.38±6.80	51.60±4.60	0.007
Quantitative test	42.29±6.24	47.50±4.27	0.050
Bead memory	28.20±8.20	58.80±9.78	0.001
Memory for sentences	36.76±7.45	63.36±7.78	0.001
Wechsler Memory Scale—Revised			
Digit forward	4.58±2.41	6.54±0.98	0.034
Digit backward	2.72±1.45	4.68±0.99	0.044
Mental control	3.57±1.07	5.09±1.56	0.050
Logical memory	10.11±2.79	14.43±2.41	0.006
Associate learning	7.45±3.44	10.00±2.11	0.010
Total scores of cognitive testing (MMSE, SBS, and WMS-R)	68.85±10.25	97.44±8.08	0.005
Depression score	20.55±10.50	8.59±8.10	0.001
Hyperintense signals in MRI brain	10.67±0.50	10.03±7.50	0.245
P_{300} latency (ms)			
RT side	349.47±32.77	328.12±23.96	0.015
LT side	344.75±32.47		0.001
P_{300} amplitude (mV)		311.94±30.75	
RT side	8.62±3.70	9.56±2.72	0.334
LT side	8.58±2.99	10.91±2.27	0.050
NSE protein (μg/l)	9.60±2.56	8.40±3.43	0.471
Number of patients with higher levels of NSE	6 (10.91%)	0	
S100B protein, pg/ml	174.05±65.69	113.67±45.07	0.029
Number of patients with higher levels of S100B	12 (21.81%)	0	

Data are expressed as mean±SD. P value, significance versus control group

NSE neuron-specific enolase

did not correlate with cognitive scores (r = 0.276, P = 0.080). Total scores with cognitive functions did not correlate neither with the dose of corticosteroids (r = 0.199, P = 0.235) nor with MTX dose (r = 0.254, P = 0.098). Bivariate analysis revealed significant associations between S100B levels and age, duration of illness, various domains of cognitive functions (as comprehension, pattern analysis, quantitative test, bead memory, memory for sentences, digit forward, digit backward, mental control, logical memory, associate memory, and total scores of cognitive testing), P300 latency and amplitude, and NSE levels (Table 3). Table 4 showed that after adjustment of age as a covariate, S100B protein levels were significantly associated with total scores of cognitive testing, P300 latency, and NSE levels. This association still remained significant after adjustment of age and duration of illness.

Although it is not our aim, 17 patients (9.35%) had mononeuritis multiplex and 24 (13.2%) had bilateral sensory neuropathy in both lower limbs (sural nerves) suggesting peripheral nervous system involvement. This indicates that central and peripheral nervous systems manifestations coexist with RA.

Discussion

Rheumatoid arthritis (RA) is a debilitating illness in which chronic pain, stiffness, and swelling of joints and physical disability can severely impede patients' functioning and emotional well-being [1, 2]. This study systematically and directly investigated patients with RA looking for evidence of brain compromise. Brain involvement with RA is

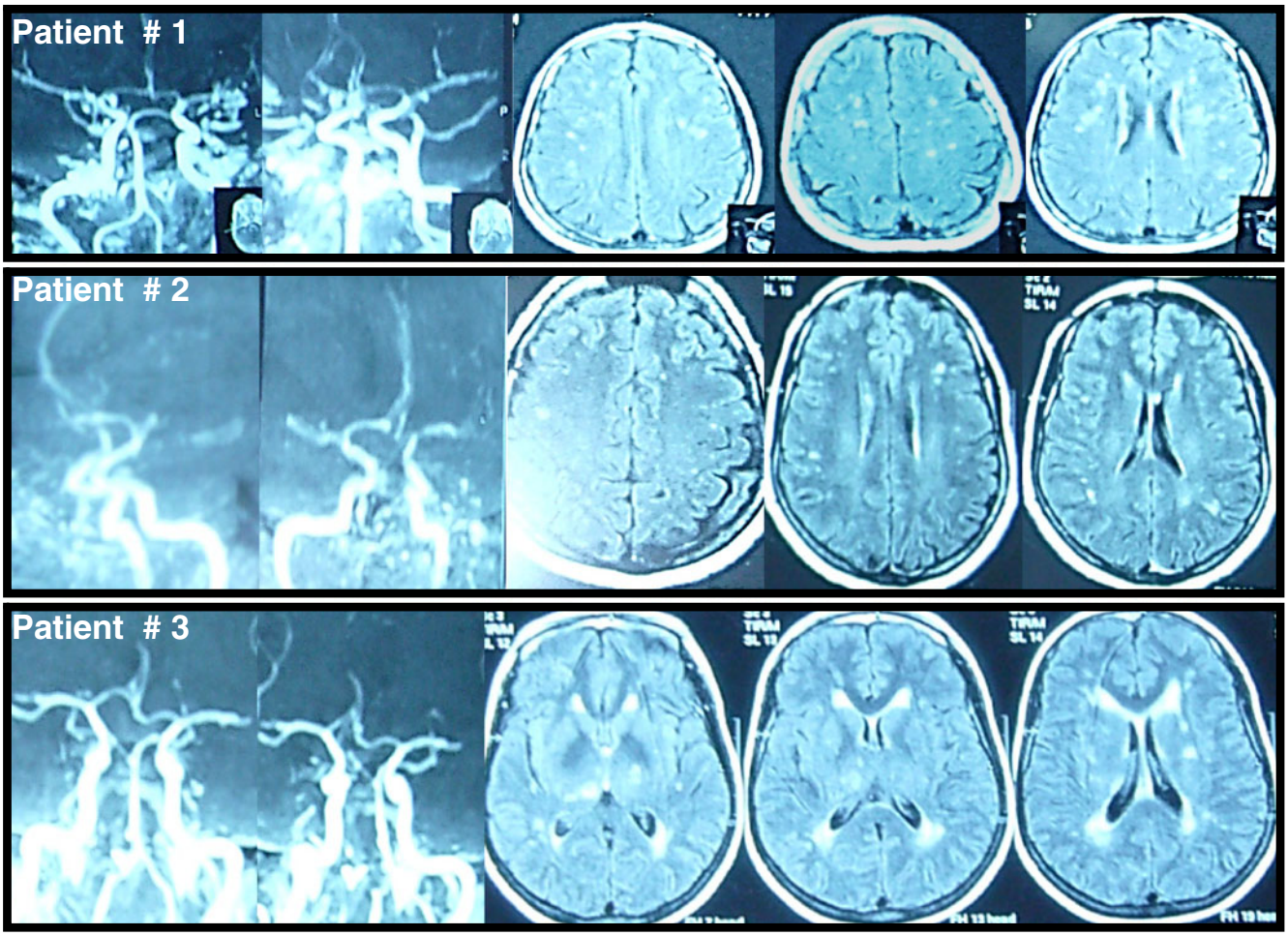

Fig. 1 MRI brain of seropositive patients with manifestations suggesting vasculitis

indicated by the presence of (1) higher concentrations of S100B protein, a marker of glial cell damage and neuroinflammation, (2) poor performance in cognitive testing, and (3) prolongation of P300 latency and reduction of P300 amplitude, a neurophysiological analogue of cognitive function. These results also indicate that measuring the concentrations of some specific brain-derived proteins (S100B and NSE proteins) in the serum of patients with RA may have a diagnostic relevance to cognitive dysfunction with brain injury induced by inflammation [30–36]. Higher concentrations of S100B protein were associated with poor performance in cognitive testing, abnormal P300, and higher levels of NSE levels, a marker of neuronal cell injury. This supports the previous findings, which stated that higher levels (micromolar) of NSE cause exacerbation of neuroinflammation, oxidative stress, and neuronal apoptosis [35].

In this study, 71% of the patients had reduction in total scores of cognitive function testing particularly in verbal relations, comprehension, pattern analysis, quantitation, short-term memory, logical memory, memory for digits, objects and sentences, mental control, and associate learning processing. Similar degrees of cognitive deficits were identified in absence of disease activity, severe illness, or depressive symptoms. Cognitive impairment with RA was further confirmed by the presence of delayed latencies (indicating demyelination) and reduced amplitudes (indicating axonapathy and degeneration) of P300, a neurophysiological cognitive component of ERPs [46]. In this study, although we reported higher depressive scores, but these were associated neither with pain or poor cognitive performance nor with elevated levels of S100B protein, thus excluding depression as a cause of cognitive deficits in our patients [52]. This is in contrast to data from different studies which reported association between cognitive deficits and depression with RA caused by long-standing illness, chronic pain [53, 54], and chronic medications (e.g., methotrexate, TNF blockers) [55–57]. In general, the prevalence of depression with RA was estimated to range from 14% to 46% [58] and specifically ~0.3% in the Egyptian population [2]. The prevalence of major depression was estimated to be 11% in the Egyptian population

Table 3 Pearson's correlation (*r* and *P* value) between S100B protein levels and clinical variables, scores of cognitive function, neurophysiological testing, depression, and neuron-specific enolase levels

Variables	S100B protein levels	
	r	*P* value
Age	0.450	0.040
Duration of illness	0.578	0.01
Index of disease activity	0.265	0.140
Rheumatoid factor	0.165	0.190
Mini-Mental State Examination	−0.434	0.004
Stanford–Binet subtests		
Vocabulary	0.370	0.060
Comprehension	−0.654	0.007
Pattern analysis	−0.790	0.010
Quantitative test	−0.520	0.026
Bead memory	−0.480	0.025
Memory for sentences	−0.450	0.036
Wechsler Memory Scale—Revised		
Digit forward	−0.670	0.005
Digit backward	−0.740	0.001
Mental control	0.920	0.0001
Logical memory	−0.870	0.0001
Associate learning	−0.470	0.045
Total scores of cognitive testing (MMSE, SBS, and WMS-R)	−0.560	0.008
P300 latency	0.480	0.025
P300 amplitude	0.440	0.048
NSE levels	0.540	0.006
Depression scores	0.274	0.600

[59]. Hence probably, such frequency rates for major depression might be increased among the patients with RA, which is also common (with a prevalence rate of ~0.3%) [2].

In this study and despite the absence of clinically manifest neurologic deficits suggesting cerebral involvement in patients with RA (with the exception of the two females with marked and manifest cognitive decline), the MRI brain abnormalities seen in some patients with RA were in the form of abnormal hyperintense FLAIR signals in the subcortical white matter, periventricular and at the junction between the gray and white matter consistent with vasculitis, small or lacunar brain ischemic lesions, or dots of demyelination. In partial accordance, many authors reported clinical and neuroimaging evidences of brain involvement in patients with RA (Table 5) which included: (1) headache, delirium, disorientation, disturbances in higher cortical functions, recurrent focal or generalized seizures, Wernicke aphasia, ideomotor, ideational, and constructional apraxia, dysarthria, hemiparesis, gait disorders, and optic atrophy; (2) multiple brain microinfarcts, ischemic brainstem lesions, multifocal high-signal intensity abnormalities of the white matter, focal high-signal intensity in the subcortical region of the frontal, temporal and occipital lobes, periventricular high-signal intensity dot-like areas in T2-, FLAIR- and diffusion-weighted imaging (DWI) MRI brain, and abnormal enhancement of the leptomeninges with meningeal gadolinium enhancement; (3) tight stenosis and string-of-beads stenosis of the carotid arteries and cerebral vasculitis of vertebrobasilar arteries on MRA; and (4) marked improvement on immunotherapy as methotrexate, methylprednisolone, cyclophosphamide, and intravenous immunoglobulins (IVIGs).

This and other studies indicate the presence of nervous system compromise with the inflammatory process of RA with resultant vasculitis, ischemic infarctions, and demyelination, in support: (1) in this study, we reported mononeuritis multiplex and bilateral sensory neuropathy in both lower limbs (sural nerves) in 9.35% and 13.2% of patients with RA suggesting vasculitis. Mononeuritis multiplex is explained as vascular affection of vasa nervorum which are small arteries that provide blood supply to peripheral nerves and seems to be mediated by IgG-RF, immune complexes, and complement activation (particularly C3 and C4); (2) long-standing RA was found to be associated with more cerebral and cerebellar atrophies consistent with cognitive

Table 4 Adjusted differences of cognitive functions, P3100 latency, P300 amplitude, and NSE per standard deviation increase in S100B protein

	Adjusted[a]		Adjusted[b]	
	β	95% confidence interval	*β*	95% confidence interval
Total scores of cognitive testing (MMSE, SBS, and WMS-R)	−1.19	−2.30 to −0.04*	−1.07	−1.02 to −1.13**
P300 latency	−1.05	−1.03 to −1.14*	−1.20	−2.50 to −0.06*
P300 amplitude	−0.06	−0.27 to −0.15	−0.09	−0.030 to −0.13
s-NSE	−1.02	−1.07 to −1.16*	−1.08	−1.03 to −1.14**

*$P<0.05$; **$P<0.05$

[a] The difference is based on the estimates of scores of cognitive function, neurophysiological test and NSE adjusted for age

[b] The difference is further adjusted for age and duration of illness

Table 5 Literature reported clinical, radiological, and pathological evidences of brain involvement in patients with rheumatoid arthritis

References	Evidences
Watson et al. [6]	The authors reported a patient with RA and necrotizing vasculitis of CNS and pathological involvement by vasculitis in cerebral hemispheres, pons, and spinal cord.
Beck and Corbett [7]	The authors reported a patient with RA and seizures and rheumatoid meningovasculitis in the biopsy of which improves with corticosteroids.
Paci et al. [8]	The authors reported a 50-year-old woman with RA with an expansive intracranial process, areas of hypodensity with marked contrast enhancement on CT brain, and cerebral arteritis on angiography.
Gobernado et al. [9]	The authors reported a 48-year-old woman with chronic RA with an acutely diffuse cerebral disease, cerebral edema, and hemorrhage on CT brain, extensive cerebral vasculitis on angiogram, and marked improvement on corticosteroids.
Bathon et al. [10]	The authors reported a patient with chronic RA, meningitis complicated by optic atrophy, and CNS rheumatoid nodules, pachymeningitis or leptomeningitis, and vasculitis in the autopsy.
Ishizuka et al. [11]	The authors reported three patients with chronic RA and focal neurological symptoms and multiple brain microinfarcts.
Ohno et al. [12]	The authors reported a 46-year-old woman with RA with dysarthria and left hemiparesis and ischemia of the right pons on MRI, cerebral vasculitis of vertebrobasilar arteries on MRA, and marked improvement on methotrexate.
Ando et al. [13]	The authors reported an RA patient with high-signal intensity in the subcortical region of the frontal and occipital lobes on T2-weighted MRI and autopsy specimen revealed severe systemic vasculitis.
Singleton et al. [14]	The authors reported a patient with chronic RA and striking multifocal abnormalities of the white matter seen in MRI and vasculitis and chronic ischemic changes were seen on postmortem examination.
Ohta et al. [15]	The authors reported a 64-year-old female with RA and systemic vasculitis; delirium; disturbances in higher cortical functions including Wernicke aphasia, disorientation and ideomotor, ideational, and constructional apraxia, and fresh infarctions in bilateral temporal and parietal lobes of the cerebrum in T2-weighted and diffusion-weighted MRI; and improvement on prednisone.
Chowdhry et al. [16]	The authors reported a woman with RA and headaches, focal neurological dysfunction, abnormal leptomeningeal enhancement in neuroimaging, and necrotizing granulomatous inflammation on meningeal and brain biopsy indicating arteritis without giant cells on a temporal artery biopsy.
Zheng et al. [17]	The authors reported a 71-year-old Chinese man with RA and recurrent weakness of the left extremities, dysarthria, hand tremor, leptomeningeal enhancement in frontal and parietal lobes, and several old white matter infarcts in MRI brain, numerous infiltrating macrophages and lymphocytes within the leptomeninges in meningeal biopsy, and good clinical response on immunoglobulin (IVIG) therapy.
Mrabet et al. [19]	The authors reported a 59-year-old woman with RA with gait disorders, dot-like areas of high signal in a periventricular subcortical white matter in magnetic resonance imaging of the brain, a long tight stenosis of the right internal carotid artery, and a string-of-beads stenosis of the left internal carotid artery in MRA brain with improvement on methylprednisolone and cyclophosphamide.
Matsuura et al. [20]	The authors reported a 63-year-old man with RA and headache, recurrent focal seizures of the right upper limb and generalized seizures and high-signal intensity lesions on FLAIR MRI, and associated with abnormal enhancement of the leptomeninges, high-signal intensity on DWI and improvement with prednisone.
Kurne et al. [22]	The authors reported a female patient with RA with headaches, encephalopathy, seizures and relapsing focal neurological deficits and abnormal leptomeningeal enhancement, and hyperintense FLAIR signal in the cortical subarachnoid spaces consistent with pachymeningitis. Cerebral angiography findings were consistent with vasculitis.
Caballol Pons et al. [23]	The authors reported a 71-year-old female with RA with headache, dysarthria, and a high-intensity image in FLAIR-weighted sequences in the right cerebral hemisphere with meningeal gadolinium enhancement, necrotizing and lymphocytic vasculitis in the meninges, as well as cerebral parenchyma and improvement with high dose of corticosteroids.

deficits [60]; (3) pathological examination of some patients with chronic RA revealed evidence of chronic ischemic brain changes; cerebral vasculitis; and necrotizing and lymphocytic vasculitis in the meninges, cerebral parenchyma, pons, and spinal cord; CNS rheumatoid nodules; pachymeningitis or leptomeningitis; necrotizing granulomatous inflammation of the meninges and brain (Table 5). Recent immunological studies revealed evidence of elevation of the levels of myelin basic protein antibodies in patients with RA which correlated with the degree of neurological disturbances and the duration of the disease [18]. In the study of Gerasimova and Skugar [18] on 42 females with RA, the authors identified evidences of cerebrovascular pathology, high concentrations of myelin basic protein antibodies which correlated with the degree of neurological disturbances and duration of the disease, and high concentrations of myeloperoxidase. The authors suggested that chronic RA results in cerebral functional insufficiency and disseminated cerebral micro-symptoms, focal cerebral lesion, primary lesions of small vessels in

RA, and secondary vasculitis followed by demyelinization of CNS white matter.

To summarize, the results of this study, others, and of case reports will result in novel ideas to back up the need for more comprehensive research in this area and interesting additions to the literature. The knowledge that brain might be involved in RA will have important implications for treatment of this disease and for research purposes. Future researches have to include the following: (a) longitudinal studies that prospectively assess the relation of the disease process to cognition over time, (b) randomized clinical trials that compare cognitive function in RA patients receiving memory enhancers and antidepressants versus a control group of RA patients, and (c) longitudinal studies have also to consider the possible impacts of immunosupressants on RA patients' cognitive functioning. Despite the strength of our findings, this study had some limitations: (1) the cross-sectional design is one important limitation, and (2) despite the clinical and MRI evidence of vasculitis in some patients, none showed MRA abnormalities which can be explained by technical inaccuracies.

Disclosures None.

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