



Central nervous system involvement in rheumatoid arthritis: possible role of chronic inflammation and tnf blocker therapy

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Abstract

Rheumatoid arthritis (RA) is a chronic disease, the etiology of which has yet to be clarified, which causes activation of pro-inflammatory pathways that bring about joint and systemic inflammation. Although peripheral nervous system anomalies are observed widely in RA, very few case reports on changes in the central nervous system (CNS) have been published. In recent years, the pathophysiology of CNS involvement that can occur in RA has attracted a great deal of attention. Emphasis has focused on the possibility that CNS involvement occurs due to blood–brain barrier (BBB) damage associated with chronic inflammation. The present study was performed to investigate the possible effects of BBB dysfunction and tumor necrosis factor (TNF) blocker therapy on BBB function, which may cause CNS damage in patients with RA. 58 RA patients [47 (81.0%) females, 11 (19.0%) males] and 34 healthy controls [24 (70.6%) females, 10 (29.4%) males] were included in the study. All RA patients were on synthetic DMARD therapy at the beginning. Thirty patients continued DMARD therapy, and 28 patients with high disease activity were started on TNF blocker therapy. All demographic characteristics of the patients were recorded. Disease activity was evaluated using the Disease Activity Score 28-joint count C reactive protein. The Mini-Mental State Examination was used to evaluate cognitive function, and the Fazekas scale was used to assess cranial lesions visualized by magnetic resonance imaging (MRI). Patients' peripheral blood S100 β , glial fibrillary acidic protein (GFAP), claudin, interleukin (IL)-17, and IL-1 β levels were measured at the beginning of the study and after 6 months. Demographic characteristics (including sex, age, and body mass index) were similar in the RA and control groups. S100 β and GFAP levels were significantly higher in the patient group than in the control group. In the group that was started on TNF blocker therapy, S100 β and GFAP levels were significantly decreased 6 months after commencement of treatment. No difference was observed between the RA and control groups in terms of hyperintense lesions seen on cranial MRI. The S100 β levels increased with lesions in the deep white matter seen on cranial MRI in patients with RA. In conclusion, next to decreasing disease activity and joint erosions by suppressing inflammation, anti-TNF therapy in RA can also suppress potential CNS involvement linked to BBB (blood–brain barrier) dysfunction. Further studies with broader participation and longer patient follow-up are needed to reinforce this hypothesis.

Keywords Rheumatoid arthritis · S100 beta · Blood-brain-barrier

Introduction

Rheumatoid arthritis (RA) is a chronic disease, the etiology of which has yet to be determined, which causes activation of proinflammatory pathways, resulting in joint and systemic inflammation [1].

Although peripheral nervous system anomalies are observed widely in RA, very few case reports regarding changes in the central nervous system (CNS) associated with the disease have been published. Meningitis, encephalitis, focal neurological symptoms, multiple brain infarcts, and white matter anomalies have been reported [2–6].

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Brain damage may occur due to disruption of the blood–brain barrier (BBB) associated with chronic inflammation. The permeability of the BBB was shown to be increased in cases of chronic systemic inflammation [7–12]. To assess the damage occurring in the BBB, the levels of glial- and neuronal-derived proteins, i.e., S100 β , neuron-specific enolase (NSE), and glial fibrillary acidic protein (GFAP), which can be detected in the peripheral blood, have been measured quantitatively [13–15]. A few studies have shown that the levels of these molecules are increased in the peripheral blood, synovial fluid, or cerebrospinal fluid in RA.

One of the prominent cytokines in RA's pathophysiology is the TNF-alpha. TNF-alpha is one of the molecules that lead to BBB destruction causing tight junctions in the BBB to open [16]. New therapies target cytokines associated with the disease such as TNF-alpha, immune cells and B-cells. In RA, biologicals reduce joint inflammation, limit erosive changes, reduce disability and improve the quality of life [17]. It is unclear how RA affected the blood–brain barrier due to chronic inflammation, and if there is an effect, it changes with the drugs used in RA.

Apart from imaging methods and electrophysiological evaluations in traumatic or atraumatic central nervous system diseases, it is also important that a laboratory evaluation parameter also points to possible central nervous system damage. 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 [28–35]. S100B is a calcium-binding protein physiologically produced and released predominantly by astrocytes.

Several studies have documented elevated serum and cerebrospinal fluid levels of S100 β , and its overexpression was shown to increase vulnerability to neurodegeneration [30], cerebral hypoxic–ischemic injury [31], traumatic brain injury [35], CNS infection [33, 34], and severe extracerebral infectious diseases [33]. As the possibility of BBB permeability disturbance due to vasculitis associated with RA cannot be excluded, the quantification of brain-derived proteins, such as glial- and neuronal-derived proteins (e.g., S100 β and NSE), may provide sensitive and direct biomarkers of brain damage in RA as well as related neurological and neuropsychological outcomes.

One of the most prominent cytokines involved in the pathophysiology of RA is tumor necrosis factor-alpha (TNF- α), which leads to BBB destruction via opening of tight junctions in the BBB [16]. New therapies target cytokines associated with the disease, such as TNF- α , immune cells and B-cells. In RA, several biologicals have been shown to reduce joint inflammation, limit erosive changes, reduce disability, and improve the quality of life [17]. The way in

which RA affects the BBB due to chronic inflammation, and whether any such effect is altered by the drugs used in treatment of RA, remain unclear.

The present study was performed to investigate the possible effects of BBB dysfunction and TNF blocker therapy on BBB function, which may cause CNS damage in patients with RA.

Methods

This study was conducted between July 2015 and March 2016 with approval of the local Ethics Committee and suitable with the Declaration of Helsinki. All individuals provided written informed acceptance.

Participants, demographic and clinical characteristics

This study was designed as an observational, prospective, follow-up study.

58 RA patients diagnosed according to the ACR/EULAR 2010 RA classification criteria and 34 control patients were included in the study. The control group composed of patients who were only admitted to the emergency service once for a headache, whose neurological examinations were normal and who had had a cranial MRI scan. Neurological examination of all healthy controls was normal. All 58 RA patients were on synthetic DMARD therapy in the beginning. The disease duration of RA patients ranged from 1 to 20 years. While 30 patients continued DMARD therapy, 28 patients with high disease activity were started on TNF blocker therapy. TNF blockers were randomly selected from the planned outbreak of biological agent therapy. Those included in the control group were matched to the patients by age and gender. All data of the patients were reevaluated 6 months after a change of treatment. The patients' age, sex, disease onset age, BMI, comorbidities, smoking status and the drugs they used were recorded.

Inclusion criteria: patient group—patients between 18 and 75 years of age with RA diagnosis according to ACR/EULAR 2010 criteria, receiving synthetic DMARD treatment, TNF blocker treatment being naive patient. Control group—being between the ages of 18–75, being completely healthy from the neurological point of view.

Exclusion criteria: being under 18 years of age; having a rheumatological disease other than RA, such as SLE; having DM and malignant HT; having any neurological or psychiatric illness; being unable to cooperate in the evaluation of cognitive functions; having undergone a neurosurgical cranial operation; being pregnant or being in the lactation period; using medication that can lead to neurotoxicity;

having a chronic infection; RA patients with a neurologic deficit in their examination.

The disease activity of the RA patients was assessed using DAS28. Disease Activity Score (DAS 28) remission criteria, involving C reactive protein (CRP), swollen and tender joint counts and patient's global health assessment were used to determine whether the disease in remission. A score of DAS28 between 2.6 and 3.2 indicates low disease activity, 3.2–5.1 moderate and > 5.1 high disease activity [18].

Evaluation of cognitive functions

The cognitive functions of the patients were evaluated at months 0 and 6 with the Mini-Mental State Examination. Mini-mental test; which is used for global mental status; consists of two parts. The first part covers orientation, memory and attention; the maximum score is 21. The second part tests ability to name, follow verbal and written commands, write a sentence spontaneously, the maximum score is nine. The cut-off score for normal cognitive functions was ≥ 27 [19, 20] Those included in the control group were called at the beginning of the study and at the 6th month, invited to the hospital, and the miniment test was evaluated.

Radiological assessment

RA patients had contrast-enhanced cranial MRI scans on month 0 (before starting TNF blocker therapy and in the group receiving DMARD therapy). Both groups—the one started on TNF blocker therapy and the one continuing DMARD therapy—had follow-up cranial MRI scans at the end of the 6th month, which were assessed. The patients' cranial MRI scans were evaluated by an experienced neurologist. The Fazekas scale was used to assess the white matter lesions that are indicators of small vessel disease and neurodegeneration. Based on this scale, the lesions detected in the periventricular white matter and deep white matter in T2-weighted or FLAIR sections were scored between 0 and 3. Fazekas scale on the basis of visual assessment both periventricular (0 = absent, 1 = caps or pencil lining, 2 = smooth halo, 3 = irregular periventricular hyperintensities extending into deep white matter) and subcortical areas (0 = absent, 1 = punctuate foci, 2 = beginning confluence

of foci, 3 = large confluent areas). The total Fazekas score was calculated by adding the periventricular and subcortical scores [21, 22]. In the control group, cranial MR was pulled and evaluated using the same method.

Statistical analysis

The data obtained as a result of the study were analyzed with the SPSS (Statistical Program for Social Sciences) for Windows 16.0 statistics software package. In the comparison of group averages, the One Way ANOVA test was used for data with normal distribution and the Wilcoxon Rank test, Mann–Whitney *U* test and Kruskal–Wallis test were used for data that was not normally distributed. Intergroup comparisons of categorical variables were evaluated with the Chi-square test (where the expected value was found to be under 5 in 2×2 tables, Fisher's exact test was used) and the data were expressed as number and percentage. In the evaluation of interparameter relationships, Spearman's correlation analysis was used. The results were evaluated within a confidence interval of 95%, and significance was evaluated at a level of 0.05.

Results

58 RA patients [47 (81.0%) females, 11 (19.0%) males] and 34 healthy controls [24 (70.6%) females, 10 (29.4%) males] were included in the study. 30 of the RA patients continued DMARD therapy, and 28 patients were switched to TNF blocker therapy. Demographic characteristics were similar between the two groups, and no statistically significant difference was found between the patient group and the control group in terms of sex, age, and BMI ($p > 0.05$) (Table 1).

The average age of disease onset in RA patients was 9.28 ± 9.19 , their initial average ESR 26.86 ± 10.44 and their average CRP level 13.60 ± 9.77 . The initial DAS28-CRP average was 3.23 ± 0.84 . RF positivity was determined as 76.2% and anti-CCP positivity as 56.2% in the RA group.

S100 beta, GFAP, Claudin, IL-1 beta and IL-17 mean values in both groups (RA and control group) and the differences between the groups are shown in Table 2.

Table 1 Distribution of demographic characteristics of individuals in the patient and control groups

Characteristics	Patient group mean \pm SD	Control group mean \pm SD	<i>p</i>
Age	53.09 \pm 10.08	51.59 \pm 5.96	0.159
BMI (kg/m ²)	28.64 \pm 3.71	27.31 \pm 1.86	0.053
Sex			
Female	%81 (<i>n</i> = 47)	%70.6 (<i>n</i> = 24)	0.185
Male	%19 (<i>n</i> = 11)	%29.4 (<i>n</i> = 10)	

SD standard deviation, *BMI* Body Mass Index, *1* Student *t* test, *2* Chi-square test

Table 2 Comparison of the S100 beta, GFAP, Claudin, IL-1 beta and IL-17 means of the groups

Hormones	RA mean ± SD (n = 58)	Control mean ± SD (n = 34)	p
S100 beta	21.97 ± 28.77	8.04 ± 16.29	0.001*
GFAP	6.12 ± 6.42	2.46 ± 1.68	0.000*
Claudin	18.29 ± 22.51	10.87 ± 5.14	0.824
IL1 beta	4.66 ± 2.55	5.08 ± 3.45	0.859
IL-17	5.12 ± 14.53	1.96 ± 0.95	0.003*

1 = Mann–Whitney U test

SD standard deviation

*p < 0.05

Bold values indicate a significant difference between the two groups

Table 3 Comparison of baseline cranial MRI lesions in patients with RA and controls

	Patient group n (%)	Control group n (%)	^a X ²	p
LF periventricular				
0	53 (%91.4)	31 (%91.2)	0.180	0.914
1	4 (%6.9)	2 (%5.9)		
2	1 (%1.7)	1 (%2.9)		
Deep white				
0	39 (%67.2)	25 (%73.5)	1.262	0.532
1	14 (%24.1)	5 (%14.7)		
2	5 (%8.6)	4 (%11.8)		
Chronic lacuna				
Not present	57 (%98.3)	33 (%97.1)	0.699	0.605
Present	1(%1.7)	1 (%2.9)		
Acute lacuna				
Not present	58 (%100)	34 (%100)	–	–
Present	0	0		

^aChi-square test periventricular (0 = absent, 1 = caps or pencil lining, 2 = smooth halo, 3 = irregular deep white (0 = absent, 1 = punctuate foci, 2 = beginning confluence of foci, 3 = large confluent areas)

The scoring of the cranial MRI lesions of both groups according to the Fazekas scale is given in Table 3. A hyperintense lesion was detected in the periventricular white matter of five patients, and the deep white matter of 19 patients out of the 58 patients found in the patient group. A hyperintense lesion was detected in the periventricular white matter of three patients, and the deep white matter of nine patients out of the 34 patients found in the control group. No statistically significant relationship was found between the patient group and the control group in terms of the number of hyperintense lesions observed in the white matter (p > 0.05). While a chronic lacuna was detected in 1 patient in each group, the presence of an acute lacuna was not detected.

The initial and 6th-month levels of S100 beta, GFAP, Claudin, IL-17 and IL-1 beta in the group that continued DMARD therapy and the group that switched to TNF blocker therapy in RA patients are given in Table 4.

The S100 beta, GFAP and Claudin levels of hyperintense lesions in the periventricular white matter and deep white matter of the brains of RA patients according to their Fazekas scores are shown in Table 5. No relationship was determined between the hyperintense lesions observed in the periventricular region in the cranial MRI and each of the three proteins. The S100 beta level was observed to significantly increase as the number of hyperintense lesions seen in the deep white matter increased (p < 0.05).

Discussion

In this study, we found significantly elevated peripheral blood levels of the brain-specific proteins, S100β and GFAP, indicative of BBB dysfunction, in patients with RA relative to controls. In the RA group that was started on TNF blocker therapy, S100β and GFAP levels were significantly decreased 6 months after commencement of therapy compared with levels at the beginning of treatment. Cranial

Table 4 The S100 beta, GFAP, Claudin, IL-1 beta and IL-17 levels of patients in the DMARD and anti-TNF groups on baseline and 6th month

Parameters	DMARD group			Anti-TNF group		
	Baseline measurement mean ± SD	Month 6 measurement mean ± SD	p	Baseline measurement mean ± SD	Month 6 measurement mean ± SD	p
S100beta	23.46 ± 70.14	18.89 ± 23.65	0.269	20.37 ± 27.67	9.40 ± 9.38	0.045*
GFAP	5.99 ± 7.04	6.80 ± 7.31	0.489	6.25 ± 5.81	2.83 ± 2.00	0.000*
Claudin	20.12 ± 26.37	18.87 ± 19.68	0.967	16.32 ± 17.91	15.03 ± 13.47	0.964
IL-1 BETA	5.66 ± 2.40	4.71 ± 2.59	0.106	3.59 ± 2.30	4.98 ± 1.71	0.042*
IL-17	2.65 ± 2.73	2.78 ± 2.62	0.611	7.78 ± 20.58	10.71 ± 43.13	0.044*

Wilcoxon test, *p < 0.05

Bold values indicate a significant difference between the two groups

Table 5 S100 beta, GFAP and Claudin levels according to the LF periventricular white matter and deep white matter Fazekas scores in the RA group

	S100 beta	GFAP	Claudin
LF periventricular			
0	21.83 ± 29.41	6.17 ± 6.22	18.31 ± 22.58
1	29.25 ± 2238	6.071 ± 0.55	20.22 ± 27.44
2	–	3.61 ± 5.27	9.31 ± 13.72
Statistical analysis ^a	$p = 0.665 > 0.05$	$p = 0.488 > 0.05$	$p = 0.994 > 0.05$
Deep white matter			
0	16.64 ± 20.88	6.00 ± 6.37	20.44 ± 25.41
1	26.69 ± 32.37	7.71 ± 7.35	16.29 ± 17.12
2	50.29 ± 53.72	2.59 ± 1.47	7.09 ± 3.57
Statistical analysis ^a	$p = 0.035 < 0.05$	$p = 0.310 > 0.05$	$p = 0.913 > 0.05$

^aKruskall Wallis test

Bold values indicate a significant difference between the two groups

magnetic resonance imaging (MRI) findings did not differ between patients with RA and the control group. In patients with RA, S100 β levels increased with the number of lesions in the deep white matter observed on cranial MRI.

With the discovery in studies conducted in recent years, the levels of cytokines such as TNF- α , IL-6, IL-1 beta and IL-17 that play a role in systemic inflammation also rise in the central nervous system in some diseases presenting with inflammation. [23, 24]. The permeability of the BBB was shown to be increased in cases of inflammation [7–11]. The peripheral blood levels of some brain-specific proteins (S100 β , GFAP, NSE, S100A4) were shown to be high in cases in which the BBB was damaged [13–15]. Most of these studies were conducted in experimental animal models; very few studies have been conducted in humans. In one study, the S100 β levels measured in the peripheral blood of patients with RA were found to be elevated compared with controls [14]. In this study, we examined the levels of the brain-specific proteins, S100 β and GFAP; consistent with the results of the above-mentioned study, we found that levels of these proteins were significantly higher in patients with RA than in controls. We looked at IL-17 and IL-1 beta levels in patients with RA. Unlike Hamed et al., we studied IL-17 and IL-1 beta levels in our study [14]. We found that IL-17 levels were higher in the patient group than in our study. We evaluated S100 beta and GFAP levels 2 times. Another difference is that we also assessed the effect of a given treatment on brain-specific proteins. In our study, we looked at the level of claudin from the tight junction proteins, but we did not find any difference between the two groups.

Another issue that has been discussed is the presence of rheumatoid factor in RA [25]. Case reports on the CNS symptoms of RA have indicated the presence of rheumatoid factor in the cerebrospinal fluid of patients [26, 27]. Recent studies suggested that circulating immune complexes may cause certain neuroinflammatory responses in the brain

[28]. In this study, we found no significant difference in the S100 β , GFAP, or claudin level between rheumatoid factor and anti-CCP positive and negative patients with RA.

Studies using functional brain imaging indicated that TNF inhibitor therapy can reduce CNS activity associated with pain resulting from inflammation in patients with RA [29].

In one animal study, TNF- α activation was shown to sustain proinflammatory activity in the brain [30–32]. Patients with RA undergoing TNF inhibitor therapy (infliximab, etanercept, adalimumab) showed a decreased risk of developing Alzheimer's disease compared with controls [33]. Exposure to disease-modifying anti-rheumatic drugs (DMARDs) does not affect the risk of Alzheimer's disease. Detrait et al. [34] reported that the peripheral administration of TNF inhibitors to rats eliminated the amyloid-induced increase and memory loss effects of hippocampal TNF- α . In another study, TNF- α inhibition was shown to have a direct effect on central pain processing before its anti-inflammatory effects were exerted in the periphery [35].

Although all of these studies showed that CNS symptoms in RA are suppressed by inhibition of TNF- α , TNF inhibitor therapy is also known to potentially cause neurological events [35]. The incidence of CNS demyelination after the initiation of anti-TNF- α therapy is unknown. Randomized controlled studies and post-marketing studies have indicated a prevalence ranging between 0.05 and 0.2% for the first three anti-TNF- α agents used clinically (infliximab, etanercept, adalimumab). Bosch et al. [35] investigated 151 demyelinating CNS processes following anti-TNF- α therapy, including optic neuritis and multiple sclerosis (MS) or MS-like diseases. Nozaki et al. [37] reported seven cases, five of which included peripheral neuropathy. Recently, Andreadou et al. [38] reported four additional cases of CNS demyelinating disease in patients receiving anti-TNF therapy.

In this study, we compared the S100 β , GFAP, claudin, IL-1 β , and IL-17 levels before and after 6 months of TNF

inhibitor therapy in patients with RA with those of patients receiving DMARD therapy. Comparison of pre-treatment and post-treatment levels indicated significant decreases in S100 β and GFAP levels after 6 months of TNF inhibitor therapy, with no difference in the claudin level and significant increases in the IL-17 and IL-1 β levels following TNF inhibitor therapy. In the group that continued to receive DMARD therapy, however, no difference in any of these laboratory parameters between months 0 and 6 was observed. These results suggest that the permeability of the BBB decreases due to the suppression of inflammation with TNF inhibition in RA, and therefore, the levels of brain-specific proteins in the peripheral blood are reduced. In addition, increased IL-17 and IL-1 β levels following therapy may be indicators that the inflammation pathway is continuing through other mechanisms due to inhibition of TNF.

MRI provides different benefits using different techniques for the assessment of neurological involvement. Morphological changes in the brain can be assessed in T1-weighted sections, and the microstructural form of the tissue can be assessed in T2-weighted sections. T2-weighted images can be used to identify hyperintense lesions associated with inflammatory and degenerative changes in the white matter, hyperintense lesions that increase with age in normal populations, and hyperintense lesions associated with microvascular disease [39].

Hamed et al. [14] reported hyperintense lesions and small or lacunar ischemic lesions in the deep white matter, periventricular, and gray–white matter junction areas on MR-FLAIR sections in some patients with RA and no neurological deficit. In another quantitative T2-weighted MRI study, no difference was detected between the RA and control groups in terms of white matter lesions [40]. In the present study, hyperintense lesions were detected in the periventricular region in five of 58 patients with RA and in the deep white matter of 19 patients, and a chronic lacunar infarct was detected in one patient. Consistent with other studies, we found no significant difference between the RA and control groups in terms of white matter lesions in the present study. Similar to the study of Hamed et al. [14] we also found that S100 β levels increased with the number of hyperintense lesions in the deep white matter observed on cranial MRI in patients with RA.

Hamed et al. [14] found no relationships between cognitive function and S100 β levels in patients with RA. We also found no relationship between the MMSE score, which we used to evaluate cognitive function, and the S100 β or GFAP level in the present study.

This study has some limitations. It would have been improved by the inclusion of larger numbers of patients in our treatment groups. In addition, we performed cranial MRI assessment in the 6 months after commencement of therapy in patients with RA. We found no difference in hyperintense

lesions in the white matter on MRI in the 6 months compared with pre-treatment results. A longer follow-up period may have generated a different result.

Conclusion

In the present study, we showed that subclinical BBB deterioration can occur in patients with RA, that brain-specific protein levels are elevated in the peripheral blood due to BBB dysfunction, and that the levels of these proteins decrease significantly after TNF blocker therapy. Further studies with larger cohorts of patients with RA receiving TNF blocker therapy are required to determine the impact on CNS damage.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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