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ORIGINAL RESEARCH

Impact of inflammation on cognitive function in patients with highly inflammatory rheumatoid arthritis

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ABSTRACT

Objective To evaluate cognitive function in patients with rheumatoid arthritis (RA) and inflammatory activity.

Patients and methods We performed a cross-sectional study of a cohort of patients with RA initiating their first biological treatment due to moderate-to-high inflammation and a healthy control group (no inflammatory diseases) matched for age, sex and educational level. All participants underwent a comprehensive neuropsychological assessment, with cognitive impairment defined as a Montreal Cognitive Assessment (MoCA) score<26. Additional assessments included various cognitive tests (STROOP, forward and backward digit spans), anxiety and depression scales (Hospital Anxiety and Depression Scale), quality of life measures (Quality of Life-Rheumatoid Arthritis) and average inflammatory activity according to the 28-joint Disease Activity Score (DAS28)-C-reactive protein (CRP) into high activity (DAS28≥3.2) and low activity (DAS28<3.2) groups, also CRP levels and interleukin 6 (IL-6) levels were measured using an ELISA.

Results The study population comprised 140 participants, 70 patients with RA and 70 controls. Patients more frequently experienced cognitive impairment than controls (60% vs 40%; p=0.019) and had lower mean (SD) values in the MoCA (23.6 (3.9) vs 25.1 (3.4); p=0.019. As for subtests of the MoCA, involvement was more marked in patients than in controls for the visuospatial-executive (p=0.030), memory (p=0.026) and abstraction (p=0.039) domains. Additionally, patients scored lower on executive function, as assessed by the backward digit span test (4.0 (1.7) vs 4.7 (1.9); p=0.039). Cognitive impairment is associated with age and a lower educational level in the general population, and among patients with RA with educational level, obesity and average inflammatory activity (DAS28, CRP, and IL-6).

Conclusions Patients with RA with high inflammatory activity are more susceptible to cognitive impairment, which specifically affects the domains of visuospatial, memory, abstraction and executive function.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Prior research has indicated that patients with rheumatoid arthritis (RA) may experience cognitive impairment, particularly in the presence of inflammatory activity.
⇒ Inflammatory activity in RA has been associated with various systemic manifestations, including potential effects on cognitive function.
⇒ Existing studies have used neuropsychological assessments to explore cognitive function in patients with RA, but specific associations with inflammatory activity and cognitive domains require further investigation.

WHAT THIS STUDY ADDS

⇒ This study offers a comprehensive evaluation of cognitive function in patients with RA initiating biological treatment, highlighting the impact of inflammatory activity on specific cognitive domains.
⇒ By comparing patients with RA to a matched healthy control group, this study provides insights into the relative cognitive impairment experienced by patients with RA with inflammatory activity.
⇒ The study identifies specific cognitive domains affected by RA and inflammatory activity, emphasising visuospatial, memory, abstraction and executive function deficits.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease. Although the cause of RA is not completely known, it is thought to be the result of the interaction between genetic, environmental, hormonal and immunopathological factors in a multistep process.[1] It affects approximately 1% of the population, mainly women, at a ratio of 2:1 or 3:1.[2] RA is characterised by chronic synovitis of small and large joints. If

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Findings underscore the importance of early detection and monitoring of cognitive function in patients with RA, especially those with ongoing inflammatory activity.

⇒ Understanding the specific cognitive domains affected can inform tailored treatment strategies, focusing on interventions that address memory, visuospatial perception and executive function deficits.

⇒ Clinicians can use this information to educate patients with RA about potential cognitive challenges associated with their condition, offering appropriate support and resources to optimise their quality of life.

left untreated, it may lead to joint destruction and functional incapacity.[3] In a significant percentage of patients, joint manifestations are accompanied by varied systemic morbidity,[4] including mainly neurological and cognitive conditions. Cognitive impairment associated with chronic inflammatory diseases is now a key area in neuroscience.[5] Despite advances in knowledge of the underlying mechanisms of RA, a considerable gap remains concerning our understanding of how systemic inflammation can affect cognitive function in patients with the disease.

A high percentage of patients with RA develop cognitive impairment during the course of their illness, although this can vary depending on the assessment methods used.[6 7] While various hypotheses have been put forward on the specific mechanisms underlying cognitive impairment in patients with RA, one of the most accepted is that of inflammatory activity, both in its direct form and via modifiable risk factors, for example, smoking, obesity and dyslipidaemia.[4 8 9] Inflammation is also known to affect the brain in adults with cognitive impairment and dementia.[5] In addition, it can cause vascular disease leading to cerebral hypoperfusion and affecting cognitive function. Previous studies have reported that frontal hypoperfusion is associated with cognitive impairment in patients with systemic lupus erythematosus and that a certain degree of frontal and parietal hypoperfusion is observed in patients with RA.[10] Moreover, this decrease has been associated with elevated levels of some inflammatory cytokines, such as tumor necrosis factor (TNF).[11]

The association between RA and cognitive impairment is thought to arise from the interaction between various factors. Several studies have evaluated the association between cognitive impairment and cardiovascular risk, age, educational level, disease duration and psychiatric manifestations.[12 13] Depression and anxiety are common comorbid conditions and can affect up to two-thirds of patients with RA, depending on the evaluation method used.[14] Specifically, the prevalence levels according to the Hospital Anxiety and Depression Scale (HADS) with thresholds of 8 and 11 were 34.2% in patients with RA.[15]

The association between RA and depression should be evaluated using appropriate instruments (eg, the HADS),[16] since it can lead to abnormalities of concentration and executive function.[12] Together with the abovementioned factors, treatment of RA is associated with cognitive function. In this sense, a study on patients with RA found that anxiety and depressive disorders were less frequently identified in those receiving anti-TNF-alpha drugs compared with those who were not receiving these treatments.[17] Methotrexate proved to be very effective in some studies, although it was subsequently associated with cognitive impairment due to neurotoxicity in the long term, specifically in the form of memory disorders.[18] Moreover, evidence suggests that prolonged exposure to glucocorticoids can lead to cognitive impairment due to their cumulative and enduring effects on the function and structure of the hippocampus.[19]

One of the main limitations of previous studies is the infrequent inclusion of domains in cognitive assessment. Current recommendations are for validated assessment tools in order to standardise results, for example the Montreal Cognitive Assessment (MoCA), the TrailMaking Test and the Victoria Stroop Test.[13] It is also necessary to ensure more accurate management of the confounders that may be associated with cognitive impairment in patients with RA, for example, type of treatment, comorbid conditions, pain, psychological factors and sociodemographic factors.[20] Similarly, studies performed to date have included different grades of inflammatory activity at a specific point in time, including inactive disease, thus hampering interpretation of the association between cognitive impairment and inflammation in patients with RA. Therefore, the objectives of the present study were as follows: (1) to report the percentage of patients with RA with high cumulative inflammatory activity during the course of the disease who develop cognitive impairment; (2) to analyse the profile of cognitive involvement, mood and quality of life; and (3) to identify epidemiological, clinical-laboratory, disease activity and therapy-related factors associated with cognitive impairment in patients with RA.

MATERIAL AND METHODS

Study design

We performed a controlled cross-sectional observational study in a prospective cohort of patients with RA between 2001 and 2021. The study was performed in the Department of Rheumatology of Hospital Regional Universitario de Málaga (HRUM), with the assistance of the Department of Neuroscience of HRUM.

Patients

Patients with RA who fulfilled the inclusion criteria were consecutively recruited at the Rheumatology Clinic of HRUM between June 2022 and June 2023. The inclusion criteria were as follows: diagnosis of RA according to the 2010 criteria of American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR),[21] age≥16 years, ability to complete the study questionnaires, no previous biological therapy and moderate-high inflammatory activity according to the

28-joint Disease Activity Score with erythrocyte sedimentation rate (DAS28-ESR) despite treatment with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs). We excluded patients with rheumatic diseases other than RA or a previous neurological disease not associated with the course of RA.

Controls

The controls were healthy volunteers aged≥16 years with no inflammatory disease who were matched by age, sex and educational level with the cases. The controls were recruited consecutively from the same social environment as the cases and had to fulfil the same exclusion criteria.

Study protocol

All the patients and controls were recruited at the HRUM clinic between June 2022 and June 2023 and took the same neuropsychological test series. All patients with moderate-high inflammatory activity were included on their first day of biological therapy, before receiving the first dose. Clinical data were collected, and the physical examination was performed by two rheumatologists, whereas the design and correction of the evaluation of the neuropsychological tests was performed jointly between a neuropsychologist and a neurologist. Cognitive tests were selected based on whether they had been previously validated for various cognitive areas and used in patients with RA. We specifically sought neurological tests that did not require specific manual dexterity and that had no time restriction for completion in order to make them accessible for patients with joint deformities.

Outcome measures and working definitions

The primary outcome measure was *cognitive impairment*, defined as a score of <26 points on the validated MoCA,[22] in which all patients with under 12 years of education receive an extra point.

The secondary outcome measure was each of the items achieved and not achieved in the MoCA, with its numerical value, as follows: visuospatial-executive, identification, memory, attention, language, abstraction, delayed recall and orientation. Specifically, executive function, including working memory, selective attention and inhibition, was evaluated using the reverse digit span, STROOP-C, and STROOP-WC tasks, respectively. The evaluation also included forward digit span to evaluate attention and STROOP-W to evaluate processing speed[23]; HADS, in which a score of >11 points for the anxiety subscale and the depression subscale was considered abnormal[10]; and the RA-specific Quality of Life-Rheumatoid Arthritis Scale-II questionnaire (QOL-RA II) (numerical value of 0–10 for each item).[24]

The other variables included were epidemiological variables such as sex (male or female), race (Caucasian or non-Caucasian), date of birth and educational level (no schooling, primary, secondary, university). We also considered comorbid conditions associated with cardiovascular risk, namely, smoking (active smoker, non-smoker, ex-smoker), alcohol consumption (yes/no), arterial hypertension defined as arterial blood pressure≥140/90,[25] obesity (body mass index ≥30),[26] diabetes mellitus,[27] dyslipidaemia (defined as total cholesterol>200 mg/dL, low-density lipoproteins (LDL) >115 mg/dL, triglycerides>200 mg/dL),[28] and a history of cardiovascular disease.

As for the characteristics of the disease, we collected the date of onset of symptoms from the history, the date of diagnosis according to the 2010 criteria of ACR/EULAR, disease duration and cut-off date when the patients were interviewed. We also collected factors related to severity, such as rheumatoid factor (IU/mL), anti-citrullinated peptide antibody (IU/mL), ESR (mm/hour), C-reactive protein (CRP, mg/dL), levels of interleukin 6 (IL-6, pg/mL) by ELISA, the Visual Analogue Scale (VAS) score of both the physician and the patient, and disease activity according to the DAS28 (continuous, range 0–9.4), which defined disease activity as high-moderate (≥3.2) and low-remission (<3.2), as well as the Spanish version of the Health Assessment Questionnaire (HAQ) at the cut-off date[29] and erosive disease according to the presence of X-ray erosions on the hands and/or feet. We recorded inflammatory activity during the course of the disease from inclusion in the cohort to the cut-off date as an average of the DAS28-CRP and CRP values. Finally, we included variables for treatment with concomitant csDMARDs: methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, corticosteroids and mean dose of corticosteroids.

Statistical analysis

We performed a descriptive analysis of the epidemiological variables and clinical characteristics, as well as the scores obtained with the different questionnaires applied. Quantitative variables are expressed as mean±SD or median IQR according to the normality of their distribution (Kolmogorov-Smirnov test); qualitative variables are expressed as an absolute number and percentage. We performed a bivariate analysis between patients and controls and between patients with and without cognitive impairment. We also evaluated the characteristics of healthy participants without cognitive impairment. In order to analyse the differences between both groups of patients, normally distributed quantitative variables were compared using the t-test, and non-normally distributed variables were compared using the Mann-Whitney test. Qualitative variables were compared using the χ^2 or Fisher's exact test (where applicable). Finally, three multivariate logistic regression models were constructed (dependent variable: cognitive impairment (yes/no)) in order to identify factors associated with cognitive impairment in the sample as a whole (patients and controls together) and only in patients with RA, with two alternative models for patients. The models were constructed by including variables such as age, sex, educational level and cardiovascular risk models. In the case of models based

on the sample of patients with RA, we also considered average inflammatory activity throughout the course of the disease. Given the collinearity between IL-6 and CRP levels, we developed two alternative models where these parameters were interchanged. Collinearity of the variables was assessed using the Pearson correlation coefficient. The statistical analyses were performed using IBM SPSS Statistics for Windows, V.28 (IBM, Armonk, New York, USA).

RESULTS

Baseline characteristics

We included a total of 140 participants, 70 patients with RA and 70 healthy controls. Most patients were women (81.4%), and the mean age was 56 years. Table 1 shows the epidemiological and clinical characteristics of both groups. The distribution by age, sex and Caucasian race was similar in both groups. Educational level was similar (p=0.980): half of the participants were educated to secondary level, followed by primary education and university, with similar percentages in both groups. As for comorbid conditions, no differences were found for most cardiovascular risk factors, except for a greater percentage of smokers and ex-smokers in patients with RA than in controls (p=0.037).

Patients with RA had established disease with a median duration of 126 months. They were mostly seropositive (80%), and half had erosions. The average DAS28 indicated moderate-to-high disease activity in 49/70 patients (72%), and the score at the cut-off was moderate-to-high in all cases. Similarly, differences were observed between the groups for acute phase reactant values and plasma levels of IL-6.

All the patients were taking a csDMARD, and 74% were taking prednisone (median, 5.0 (0.0–7.5)). No patients had received biological DMARDs (bDMARDs). A total of 54 patients were on monotherapy with csDMARD (29 methotrexate, 11 leflunomide, 8 sulfasalazine and 6 hydroxychloroquine), and 16 were on combination therapy (11 methotrexate+sulfasalazine and 5 methotrexate+hydroxychloroquine).

Evaluation of cognitive function

Table 2 summarises the characteristics associated with cognitive function in patients and controls. Patients with RA had lower average scores in the MoCA (p=0.019), and cognitive impairment was recorded in a higher percentage than among the controls (60% vs 40%; p=0.018). The most frequently affected cognitive domains of the MoCA among patients with RA were visuospatial-executive (p=0.030), memory (p=0.026) and abstraction (p=0.038). As for the backward digit span, which is applied to assess executive function, patients' results were significantly lower than those of controls (mean, 4.0 (1.7) vs 4.7 (1.9); p=0.039).

Furthermore, evaluation of mood and quality of life revealed that patients with RA had higher scores than controls in HADS (depression) (p<0.001) and HADS (anxiety) (p<0.001) and that their quality of life was poorer in all the questions of the QOL-RA questionnaire. In addition, a higher percentage of patients with RA than controls had depression (12.9% vs 2.9%; p=0.028) and anxiety (21.4% vs 5.7%; p=0.007) based on a HADS score>11 points.

Factors associated with cognitive impairment in patients with RA

Table 3 shows the clinical, epidemiological and therapy-related characteristics of patients with RA and with and without cognitive impairment according to the MoCA. Compared with the other participants, patients with cognitive impairment were older (p=0.037), had a lower educational level (p=0.004), and more frequently had comorbid conditions such as obesity (p=0.031), dyslipidaemia (p=0.048) and arterial hypertension (p=0.054).

As for the characteristics of RA, patients with cognitive impairment had more pronounced inflammatory activity maintained over time according to the average DAS28 value (p=0.021) and average CRP value (p=0.023) during follow-up than participants who maintained their cognitive function. They also had a higher IL-6 level at the cut-off (p=0.034). Similarly, patients with cognitive impairment more frequently had symptoms of depression (p=0.009) and tended to have poorer physical function according to the HAQ (p=0.053).

Figure 1 shows a heat map representing the correlation coefficients of the quantitative MoCA instrument with clinical variables, other cognitive test findings, and psychological variables in patients with RA. MoCA revealed weak negative correlations with age, DAS28-CRP, HAQ, CRP, IL-6, depression and anxiety (p<0.05), whereas moderate positive correlations were observed with the results of cognitive tests, including the forward and backward digit spans and the results of the STROOP test (p<0.01). Furthermore, we observed significant correlations between the backward digit span, average DAS28-CRP (r=–0.334; p=0.010), CRP levels (r=–0.392; p=0.002), and IL-6 levels (r=–0.307; p=0.017).

When we compared general characteristics between healthy controls with and without cognitive impairment (online supplemental table), we found that controls with cognitive impairment were older (p=0.045), were less frequently educated to secondary and university level (p<0.001), and had a higher mean score in HADS (depression) (p=0.013) and HADS (anxiety) (p=0.015) than controls without cognitive impairment.

Table 4 shows the results of a multivariate logistic regression analysis exploring cognitive impairment in the study population as a whole. Table 5 focuses on the factors associated with cognitive impairment in patients with RA. As seen in table 4, this model highlights that patients with RA are at a considerably greater risk of cognitive impairment (OR=3.043; p=0.008) according to the MoCA score and, although to a lesser extent, age (OR=1.043; p=0.016), whereas those with a secondary or university

Table 1 Clinical and epidemiological characteristics of 70 patients with RA and 70 healthy controls

Variable	RA n=70	Controls n=70	P value
Epidemiological characteristics			
Female sex, n (%)	57 (81.4)	57 (81.4)	1.000
Age in years, mean (SD)	56.2 (12.3)	56.4 (11.3)	0.947
Caucasian race, n (%)	70 (100)	71 (100)	1.000
Educational level:			0.980
Primary, n (%)	20 (28.6)	19 (27.1)	
Non-university higher, n (%)	34 (48.6)	35 (50.0)	
University, n (%)	16 (22.9)	16 (22.9)	
Clinical characteristics			
Dyslipidaemia, n (%)	16 (22.9)	13 (18.6)	0.532
Arterial hypertension, n (%)	20 (28.6)	18 (25.7)	0.704
Smoking			0.037
Non-smoker, n (%)	31 (44.3)	46 (65.7)	
Ex-smoker, n (%)	21 (30.0)	12 (17.1)	
Smoker, n (%)	18 (25.7)	12 (17.1)	
Obesity, n (%)	20 (28.6)	14 (20.0)	0.237
Diabetes mellitus, n (%)	8 (11.4)	5 (7.1)	0.382
Disease duration, median (IQR), months	126.4 (34.6–184.8)	–	–
Diagnostic delay, median (IQR) months	10.5 (3.9–11.52)	–	–
Erosions, n (%)	35 (50.0)	–	–
RF positive (>10 U/mL,), n (%)	60 (85.7)	0 (0.0)	<0.001
ACPA positive (>20 U/mL), n (%)	56 (80.0)	0 (0.0)	<0.001
ACPA elevated>340 U/mL, n (%)	21 (30.0)	0 (0.0)	<0.001
DAS28-CRP, mean (SD)	4.9 (1.15)	–	–
Average DAS28-CRP, mean (SD)	3.7 (0.9)	–	–
PGA, median (IQR)	70 (60–90)	–	–
VAS pain, median (IQR)	70 (60–90)	–	–
Physician's Global Assessment, median (IQR)	70 (60–80)	–	–
HAQ, mean (SD)	1.4 (0.7)	–	–
Average HAQ, mean (SD)	1.0 (0.5)	–	–
CRP, mg/dL, mean (SD)	14.7 (10.7)	4.0 (3.5)	<0.001
Average CRP, mg/dL, mean (SD)	10.8 (9.5)	4.0 (3.5)	<0.001
IL-6, pg/mL, median (IQR)	5.4 (2.2–13.3)	1.5 (0.9–2.5)	<0.001
IL-1β, pg/mL, median (IQR)	8.2 (2.9–13.2)	6.2 (2.3–12.3)	0.402
Erythrocyte sedimentation rate, mm/h, mean (SD)	27.2 (18.0)	12.0 (7.7)	<0.001
Treatment			
Synthetic DMARDs, n (%)	70 (100.0)	–	–
Methotrexate, n (%)	45 (64.3)	–	–
Hydroxychloroquine, n (%)	11 (15.7)	–	–
Leflunomide, n (%)	11 (15.7)	–	–
Sulfasalazine, n (%)	19 (27.1)	–	–
Corticosteroids, median (IQR)	5.0 (0.0–7.5)	0.0 (0.0–0.0)	–
Corticosteroids, n (%)	52 (74.3)	0 (0.0)	–

ACPA, anti-citrullinated peptide antibody; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HAQ, Health Assessment Questionnaire; IL, interleukin; PGA, Patient Global Assessment; RA, rheumatoid arthritis; RF, rheumatoid factor; VAS, Visual Analogue Scale.

Table 2 Cognitive test results, anxiety and depression in patients with RA vs controls

Variable	RA n=70	Controls n=70	P value
MoCA score, mean (SD)	23.6 (3.9)	25.1 (3.4)	0.019
Cognitive impairment (<26 MoCA), n (%)	42 (60.0)	28 (40.0)	0.018
Visuospatial, median (IQR)	4.0 (2.7–5.0)	4.0 (3.0–5.0)	0.030
Visuospatial achieved (5 p), n (%)	23 (32.9)	31 (44.3)	0.165
Identification, median (IQR)	3.0 (3.0–3.0)	3.0 (3.0–3.0)	0.669
Identification achieved (3 p), n (%)	66 (94.3)	67 (95.7)	0.698
Memory achieved, n (%)	56 (80.0)	65 (92.9)	0.026
Attention, median (IQR)	4.0 (3.0–5.0)	4.0 (3.0–6.0)	0.127
Attention achieved (6 p), n (%)	20 (28.6)	24 (34.3)	0.466
Language, median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–3.0)	0.244
Language achieved (3 p), n (%)	20 (28.6)	31 (44.3)	0.053
Abstraction, median (IQR)	1.5 (1.0–2.0)	2.0 (1.0–2.0)	0.038
Abstraction achieved (2 p), n (%)	39 (55.7)	47 (67.1)	0.165
Delayed recall, median (IQR)	2.0 (1.0–3.0)	2.0 (1.0–5.0)	0.526
Delayed recall achieved (5 p), n (%)	14 (20.0)	19 (27.1)	0.319
Orientation, median (IQR)	6.0 (6.0–6.0)	6.0 (6.0–6.0)	1.000
Orientation achieved (6 p), n (%)	70 (100.0)	70 (100.0)	1.000
Forward digit span, mean (SD)	5.9 (2.0)	6.4 (1.9)	0.165
Backward digit span, mean (SD)	4.0 (1.7)	4.7 (1.9)	0.039
STROOP test			
STROOP-W, mean (SD)	93.5 (28.3)	97.3 (25.5)	0.455
STROOP-C, mean (SD)	74.7 (22.5)	74.8 (22.3)	0.987
STROOP-WC, mean (SD)	47.1 (19.0)	45.2 (17.5)	0.584
HADS (depression), mean (SD)	5.5 (3.3)	3.0 (2.4)	<0.001
Depression (HADS>11), n (%)	9 (12.9)	2 (2.9)	0.028
HADS (anxiety), mean (SD)	7.7 (4.2)	4.9 (3.6)	<0.001
Anxiety (HADS>11), n (%)	15 (21.4)	4 (5.7)	0.007
QOL-RA-1, median (IQR)	5.0 (3.0–6.0)	8.0 (7.0–9.0)	<0.001
QOL-RA-2, median (IQR)	6.0 (4.0–8.0)	8.0 (7.0–9.0)	<0.001
QOL-RA-3, median (IQR)	4.0 (3.0–6.0)	9.0 (7.0–9.0)	<0.001
QOL-RA-4, median (IQR)	4.0 (3.0–6.0)	8.0 (7.0–9.0)	<0.001
QOL-RA-5, median (IQR)	5.0 (3.0–6.0)	8.0 (7.0–9.0)	<0.001
QOL-RA-6, median (IQR)	4.0 (3.0–6.0)	9.0 (7.0–9.0)	<0.001
QOL-RA-7, median (IQR)	6.0 (3.0–7.5)	9.0 (8.0–10.0)	<0.001
QOL-RA-8, median (IQR)	5.0 (3.0–7.0)	9.0 (8.0–9.0)	<0.001

HADS, Hospital Anxiety and Depression Scale; MoCA, Montreal Cognitive Assessment; QOL-RA, Quality of Life-Rheumatoid Arthritis; STROOP-C, selective attention; STROOP-W, processing speed; STROOP-WC, inhibition.

level education had a lower risk (OR=0.178; p<0.001). However, when the analysis was restricted to the sample of patients with RA (table 5), the factors associated with the greatest risk were obesity (OR=5.998; p=0.034) and inflammation throughout the course of the disease according to the average DAS28 (OR=2.370; p=0.037) and average CRP (OR=1.111; p=0.045). Given the importance of IL-6 in pathogenesis and its collinearity with CRP levels, we constructed an alternative model in which both parameters were exchanged. The model yielded similar results (table 6).

DISCUSSION

RA is an inflammatory disease that mainly affects the joints, although it can have consequences for several body systems.[30] In this study, we investigated associations between cognitive impairment in RA and inflammation,

Table 3 Clinical characteristics of patients with RA with and without cognitive impairment according to the MoCA questionnaire

Variable	RA with cognitive impairment n=42	RA without cognitive impairment n=28	P value
Epidemiological characteristics			
Female sex, n (%)	35 (83.3)	22 (78.6)	0.616
Age in years, mean (SD)	58.7 (12.4)	52.5 (11.1)	0.037
Caucasian race, n (%)	42 (100.0)	28 (100.0)	1.000
Educational level:			0.004
Primary, n (%)	15 (35.7)	5 (17.9)	
Non-university higher, n (%)	23 (54.8)	11 (39.3)	
University, n (%)	4 (9.5)	12 (42.9)	
Clinical characteristics			
Dyslipidaemia, n (%)	13 (31.0)	3 (10.7)	0.048
Arterial hypertension, n (%)	14 (33.3)	4 (14.3)	0.054
Smoking			0.357
Non-smoker, n (%)	16 (38.1)	15 (53.6)	
Ex-smoker, n (%)	15 (35.7)	6 (21.4)	
Smoker, n (%)	11 (26.2)	7 (25.0)	
Obesity (BMI≥30), n (%)	16 (38.1)	4 (14.3)	0.031
BMI, mean (SD)	28.2 (4.4)	26.0 (4.1)	0.047
Diabetes mellitus, n (%)	5 (11.9)	3 (10.7)	0.878
Disease duration, median (IQR), months	83.6 (29.0–193.2)	71.6 (39.3–177.3)	0.874
Diagnostic delay, median (IQR) months	6.9 (4.0–13.0)	6.0 (3.8–9.9)	0.574
Erosions, n (%)	21 (50.0)	13 (46.4)	0.760
RF positive (>10 U/mL), n (%)	36 (85.7)	24 (85.7)	1.000
ACPA positive (>20 U/mL), n (%)	33 (78.6)	23 (82.1)	0.714
ACPA elevated>340 U/mL, n (%)	14 (33.3)	7 (25.0)	0.465
DAS28-CRP, mean (SD)	5.0 (1.0)	4.5 (1.2)	0.066
Average DAS28-CRP, mean (SD)	3.9 (0.9)	3.3 (0.9)	0.021
PGA, median (IQR)	70.0 (60.0–90.0)	70.0 (50.0–87.5)	0.247
VAS pain, median (IQR)	80.0 (60.0–90.0)	70.0 (50.0–80.0)	0.284
Physician's Global Assessment, median (IQR)	70.0 (67.5–80.0)	70.0 (52.5–80.0)	0.252
HAQ, mean (SD)	1.4 (0.7)	1.1 (0.5)	0.053
Average HAQ, mean (SD)	1.1 (0.6)	0.9 (0.4)	0.076
CRP, mg/L, mean (SD)	18.0 (10.0)	9.9 (7.7)	0.023
Average CRP, mg/dL, mean (SD)	12.8 (11.3)	7.8 (4.5)	0.014
IL-6, pg/mL, median (IQR)	7.5 (3.1–18.1)	2.5 (1.3–11.3)	0.034
IL-1β, pg/mL, median (IQR)	9.0 (3.6–15.0)	6.3 (2.2–11.4)	0.070
Erythrocyte sedimentation rate, mean (SD)	28.3 (16.0)	25.5 (20.0)	0.530
HADS (depression), mean (SD)	5.9 (3.6)	4.6 (2.7)	0.162
Depression (HADS>11), n (%)	9 (21.4)	0 (0.0)	0.009
HADS (anxiety), mean (SD)	8.1 (4.4)	6.9 (3.7)	0.267
Anxiety (HADS>11), n (%)	11 (26.2)	4 (14.3)	0.187
Treatment			
Synthetic DMARDs, n (%)	41 (97.6)	25 (89.3)	0.172
Methotrexate, n (%)	29 (69.0)	16 (57.1)	0.309

Continued

Table 3 Continued

Variable	RA with cognitive impairment n=42	RA without cognitive impairment n=28	P value
Hydroxychloroquine, n (%)	8 (19.0)	3 (10.7)	0.348
Leflunomide, n (%)	6 (14.3)	5 (17.9)	0.688
Sulfasalazine, n (%)	9 (21.4)	10 (35.7)	0.188
Corticosteroids, median (IQR)	5.0 (2.5–7.5)	5.0 (0.0–5.0)	0.157
Corticosteroids, n (%)	34 (81.0)	18 (64.3)	0.118

ACPA, anti-citrullinated peptide antibody; BMI, body mass index; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; DMARD, disease-modifying antirheumatic drug; HADS, Hospital Anxiety and Depression Scale; HAQ, Health Assessment Questionnaire; IL, interleukin; PGA, Patient Global Assessment; RA, rheumatoid arthritis; RF, rheumatoid factor; VAS, Visual Analogue Scale.

psychosocial factors and quality of life. Thus, our results point to significant differences between patients with RA and controls that are more evident in cognitive function, mood and quality of life.

We found that cognitive impairment (evaluated using the MoCA) was present in 60% of patients with RA. This percentage was higher than in the controls, especially in the visuospatial-executive, memory and abstraction domains. Our findings are consistent with those reported elsewhere in RA, which reveal cognitive impairment in 30%–70% of cases, depending on the assessment tool used.[2 13 31] One possible explanation for cognitive impairment in patients with RA could be a complex interaction between several factors. It has been suggested that chronic inflammation and autoimmune processes associated with RA could contribute to cognitive impairment via various mechanisms, including neuroinflammation and endothelial dysfunction. Moreover, common RA symptoms, such as chronic pain and fatigue may also have a negative impact on cognitive function.[32–34]

As for the cognitive functions and domains evaluated in our study, the most severely affected were the visuospatial, memory, abstraction and executive function domains. Our finding of more pronounced impairment in the backward digit span test in patients with RA than in controls supports the involvement of executive function, more

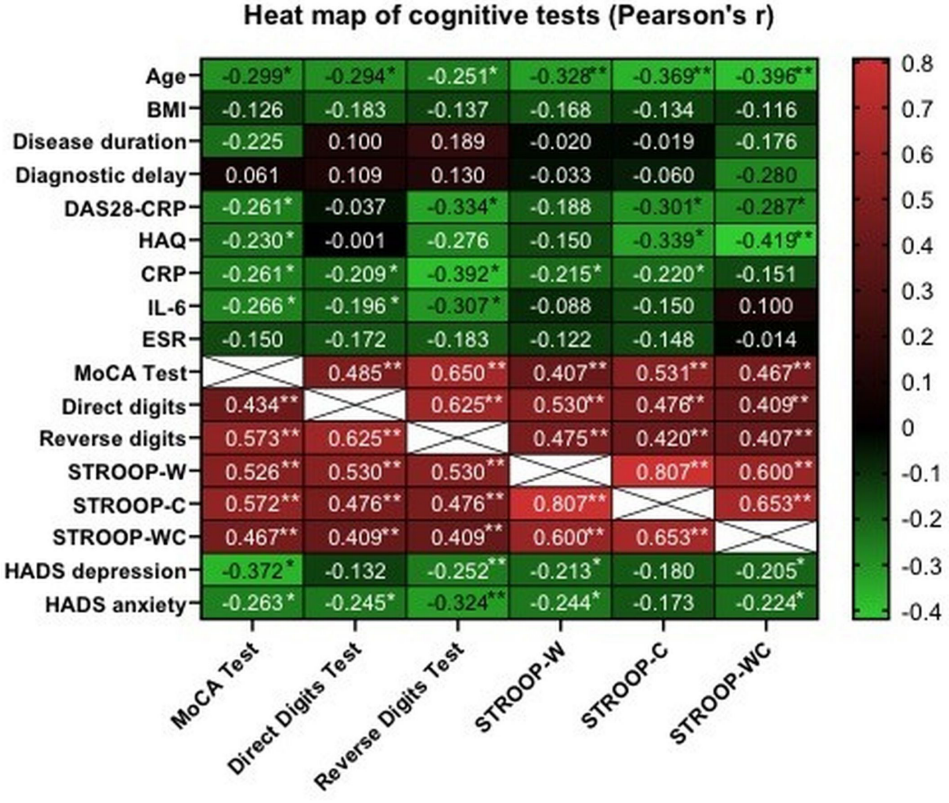

Figure 1 Correlations between the MoCA and characteristics of patients with RA. BMI, body mass index; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate; HADS, Hospital Anxiety and Depression Scale; HAQ, Health Assessment Questionnaire; IL-6, interleukin 6; MoCA, Montreal Cognitive Assessment; RA, rheumatoid arthritis; STROOP-C, selective attention; STROOP-W, processing speed; STROOP-WC, inhibition.

Table 4 Multivariate analysis of cognitive impairment in the full sample

Variable	Univariate OR (95%CI)	Multivariate OR* (95%CI)	P value
Age, years	1.044 (1.013 to 1.076)	1.043 (1.008 to 1.080)	0.016
Female sex	1.778 (0.744 to 4.249)		
Educational level*	0.201 (0.108 to 0.375)	0.178 (0.090 to 0.350)	<0.001
Obesity (BMI≥30)	1.879 (0.853 to 4.141)		
Arterial hypertension	1.336 (0.632 to 2.823)		
Dyslipidaemia	1.857 (0.803 to 4.290)		
Rheumatoid arthritis	2.250 (1.144 to 4.425)	3.043 (1.334 to 6.940)	0.008

Nagelkerke R^2 = 0.404. The variables included in the equation were age, sex, educational level, obesity, arterial hypertension and rheumatoid arthritis.
*Educational level: secondary education or university compared with primary education.
BMI, body mass index.

specifically working memory, in the cognitive compromise affecting these patients.[35] Previous studies have suggested that prefrontal cortical dysfunction and abnormalities of the frontal-parietal-temporal circuit could be involved cognitive impairment.[36] In fact, inflammatory activity in RA was associated with cognitive impairment in a multicentre study,[7] and impaired executive function in a further two studies.[31 36] The assessment of visuospatial function was not conducted independently but rather in conjunction with the executive function assessment of the MoCA. Therefore, we cannot definitively assert based on this single data point that low scores in this section are due to visuospatial impairment. However, we believe it is reasonable to suggest this possibility, given that the executive function shown to be affected in our study is working memory, which is not one of the functions evaluated in this section of the MoCA. Lee *et al*[31] and Katchamart *et al*[36] observed an association between cognitive impairment (assessed using the MoCA) and disease activity (assessed using DAS28 and CRP). Similarly, our study revealed that average inflammatory activity during the course of the disease measured using DAS28 and CRP levels was also associated with cognitive impairment in patients with RA. These results support the hypothesis that RA is a chronic systemic inflammatory disease that affects multiple systems, including neural tissue.[37] Moreover, our study also recorded other inflammatory cytokines and was based on further cognitive tests. Thus, we observed increased levels of IL-6 in patients with RA and cognitive impairment, and it has been proposed that this cytokine can act at the cognitive level and in neuroinflammation via activation of glial cells, increased permeability of the blood-brain barrier and modulation of neurotransmission.[38–40] We also found a significant correlation between levels of inflammatory factors and the results of the backward digit span test, thus supporting the association between abnormal executive function and inflammatory activity.

Cognitive impairment is associated with age and educational level not only in patients with RA, but also in the general population. Moreover, in patients with RA, an association has been observed with educational level and obesity, as well as with inflammatory activity. Older age and educational level are well-known risk factors for

Table 5 Multivariate analysis of cognitive impairment in patients with RA

Variable	Univariate OR (95%CI)	Multivariate OR* (95%CI)	P value
Age, years	1.045 (1.001 to 1.090)		
Female sex	1.364 (0.405 to 4.590)		
Educational level*	0.335 (0.156 to 0.721)	0.215 (0.081 to 0.568)	0.002
Obesity (BMI≥30)	3.692 (1.081 to 12.060)	5.998 (1.142 to 22.456)	0.034
Arterial hypertension	3.000 (0.870 to 10.343)		
Dyslipidaemia	3.630 (0.954 to 14.622)		
Depression (HADS)	1.129 (0.952 to 1.340)		
Average DAS28	2.022 (1.079 to 3.787)	2.370 (1.051 to 5.342)	0.037
Average C-reactive protein	1.080 (1.002 to 1.165)	1.111 (1.002 to 0.568)	0.045

Nagelkerke R^2 = 0.422. The variables included in the equation were age, sex, educational level, obesity, average DAS28 and C-reactive protein.
*Educational level: secondary education or university compared with primary education.
BMI, body mass index; DAS28, 28-joint Disease Activity Score; HADS, Hospital Anxiety and Depression Scale; RA, rheumatoid arthritis.

Table 6 Alternative multivariate analysis of cognitive impairment in patients with RA (including IL-6 instead of average CRP)

Variable	Univariate OR (95%CI)	Multivariate OR* (95%CI)	P value
Age, years	1.045 (1.001 to 1.090)		
Female sex	1.364 (0.405 to 4.590)		
Educational level*	0.335 (0.156 to 0.721)	0.173 (0.060 to 0.499)	0.001
Obesity (BMI≥30)	3.692 (1.081 to 12.060)	7.482 (1.297 to 23.176)	0.024
Arterial hypertension	3.000 (0.870 to 10.343)		
Dyslipidaemia	3.630 (0.954 to 14.622)		
Depression (HADS)	1.129 (0.952 to 1.340)		
Average DAS28	2.022 (1.079 to 3.787)	2.372 (1.046 to 5.376)	0.039
IL-6, pg/mL	1.025 (1.002 to 1.062)	1.079 (1.005 to 1.159)	0.036

Nagelkerke R^2 = 0.455. The variables included in the equation were age, sex, cultural level, obesity, average DAS28 and IL-6.
*Educational level: secondary education or university compared with primary education.
BMI, body mass index; CRP, C-reactive protein; DAS28, 28-joint Disease Activity Score; HADS, Hospital Anxiety and Depression Scale; IL-6, interleukin 6; RA, rheumatoid arthritis.

cognitive impairment in the general population[41 42] and in patients with RA.[36 43 44] Obesity in patients with RA can contribute to cognitive impairment owing to systemic chronic inflammation, metabolic dysfunction and cerebrovascular adverse effects. This inflammatory state leads to increased production of proinflammatory cytokines, which may have a negative effect on cerebral function. In addition, obesity is linked to vascular diseases and comorbid conditions such as type 2 diabetes, which can also play a role in cognitive impairment.[45 46] These findings highlight the importance of a multidimensional approach covering both clinical and psychosocial aspects in the assessment and management of cognitive impairment in patients with RA.

Given that the different domains of cognitive function are interconnected,[2 13] the results of the various cognitive function tests correlate with each other in patients with RA. Depression and anxiety are also common in these patients,[14 47] and both conditions can affect the assessment and management of cognitive function. Furthermore, while there are differences between patients and controls in working memory, which is a component of executive function, we found no differences in the STROOP test between the groups or in the forward digit span test. The STROOP test evaluates cognitive inhibition, or interference, within the executive function, and the forward digit span test measures selective attention. This is consistent with the absence of abnormal values in the STROOP test and in all its components. This might suggest that other factors play a role in this specific task,[48] whereas in the patients in our study, the involvement of working memory seems to be more selective.

Our study is subject to a series of limitations. First, its cross-sectional design precluded us from establishing causal associations and evaluating the patients' previous cognitive status. However, our prospective data collection and evaluation of average disease activity made it possible to identify robust associations between cognitive impairment and the characteristics of RA. Although the duration of follow-up and the number of visits varied between patients, but all available data were included to calculate these averages. Second, while some patients had deformities of the hand that could have affected their performance in the visuospatial and executive function tests, we evaluated these functions using additional tests such as the backward digit span, thus highlighting cognitive involvement with a test in which manual dexterity was not necessary. Our study is also limited by the absence of imaging tests to detect vascular damage associated with cognitive impairment, although we adjusted the analysis for cardiovascular risk factors and observed similar associations in controls with cognitive impairment. This observation reinforces the role of inflammatory activity in cognitive impairment in RA. Moreover, a significant strength of our study is that in all the patients, inflammatory activity was, on average, moderate to high. In addition, the patients had not previously received biological or targeted therapy; this probably contributed to the clear role of inflammatory factors in the brain. Although pain and fatigue may also negatively impact cognitive function,[27–29] our study did not find differences in the Patient Global Assessment or the VAS for pain between patients with RA with and without cognitive impairment. This could be attributed to the fact that our cohort of patients exhibited moderate to high inflammatory activity prior to biological therapy initiation. However, we observed an association between inflammation and cognitive impairment, further underscoring the link between these factors.

In patients with RA and average moderate-to-high inflammatory activity, two-thirds have cognitive impairment, mainly affecting the visuospatial, memory, abstraction and executive domains. Impairment is associated with age and a lower educational level in the general population, whereas in patients with RA it is directly associated with the mean level of inflammatory activity based on the DAS28, CRP and IL-6, as well as on obesity. However, educational level was shown to have a protective effect.

These findings highlight the importance of controlling inflammatory activity and comorbidity in the systemic management of RA. Our results underline the importance of earlier and more stringent control of the activity of arthritis and the need for new therapeutic strategies aimed at associated factors with the aim of mitigating the risk of cognitive impairment in patients with RA. Similarly, the connection between psychosocial factors and cognitive impairment highlights the need for a holistic approach to RA.

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