



## Impact of Rheumatoid Arthritis on Memory: An Observational Case-control study

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### ABSTRACT

Rheumatoid arthritis (RA) is the most common chronic inflammatory polyarthritis with a significant impact on the quality of life. It is usually not associated with the central nervous system and brain changes. So Neuropsychological impairment is not commonly associated with RA. However, recent studies have indicated that a link may exist between RA and cognitive impairment, but the prevalence rate was uncertain. This study aimed to evaluate the impact of rheumatoid arthritis (RA) on memory. This case-control study included 130 consecutive RA patients compared with 130 healthy controls matched in age and sex. Demographic and clinical characteristics were recorded. Six-item Cognitive Impairment Test (6CIT) - Kingshill Version 2000 was used to assess the memory. RA patients had more memory impairment than controls [(47(69.1%) versus 21(30.9%) [OR (95% CI) =2.939(1.632-5.294, p<0.001]. Age and prednisolone use were significantly and positively correlated with cognitive impairment (partial correlation ( r = 0.346, p<0.001; r=0.224, p=0.012 respectively) while educational level was significantly and negatively correlated with CIT ( r=-0.489, p<0.001). In conclusion, RA patients had a high risk of cognitive impairment. Increased age, being employed, use of oral glucocorticoids, low education. And low family income was a significant predictor of cognitive impairment. This suggest early diagnosis and treatment of RA may prevent cognitive impairment.

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### INTRODUCTION

Rheumatoid arthritis has a significant permanent functional impairment and disability (Erickson

*et al.*, 2017; Shah *et al.*, 2017). Typically, the neuropsychological disorder does not require RA. Recent studies have shown that there may be a correlation between RA and cognitive impairment and that even mild cognitive impairment can interfere with daily working conditions for people with RA (Julian *et al.*, 2012). While certain studies found a link between RA and cognitive impairment (Gorelick, 2010), others found no such correlation (Boyd *et al.*, 2010). A large retrospective population-based study found that those who have a history of RA were considerably more likely to have experienced cognitive impairment over a 21-year period than those with other joint diseases (Wallin *et al.*, 2012). Several mechanisms for RA memory impairment have been proposed, including a chronic systemic inflammatory process

involving all organs. Neural tissue (Kurne *et al.*, 2009; Evren C, 2017). Nevertheless, side effects associated with chronic systemic inflammation and autoantibodies can be accelerated (Pamuk *et al.*, 2013) as well as the effects associated with neural tissue, in particular, glucocorticoid (Coluccia *et al.*, 2008) and methotrexate (Pamuk *et al.*, 2013). Intact cognitive function in persons with chronic conditions, like RA, is essential to perform certain basic functions. Cognitive affected patients have increased behavioral issues, decreased adherence to medications and reduced quality of life (Appenzeller *et al.*, 2004; Shin *et al.*, 2012). This study was designed to investigate memory impairment in RA and to assess possible predictors.

## PATIENTS AND METHODS

### Study design

This is a case-control study done in Medical City Hospital from October 2017 till June 2018. Ethical approval was taken from the Medical Department, College of Medicine, University of Baghdad. Participant's consent was taken for inclusion in the study.

### Participants

#### Patients group

#### Inclusion criteria

1. Patients with RA and their age >16 years (Aletaha *et al.*, 2010).

#### Exclusion criteria

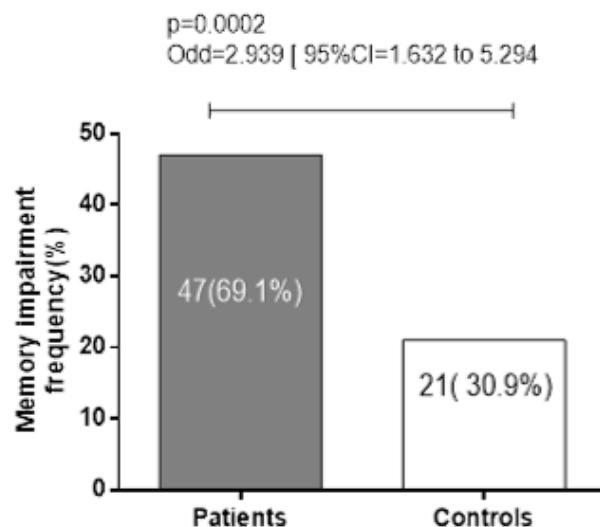
1. overlapping other inflammatory arthritis like systemic lupus erythematosus, systemic sclerosis, ankylosing spondylitis
2. infection
3. Tumors
4. kidney and liver diseases
5. neuropsychiatric problems
6. medications known to affect cognitive function

#### Control group

Inclusion criteria, healthy controls with similar age and sex.

#### Data collection and entry

Data collection was done using questionnaires and interviews. Demographic and clinical features data included age, sex, body mass index, social class, disease duration, quality of life and medications used



**Figure 1: Prevalence of memory impairment in RA patients and controls**

and disease activity measured using Clinical Disease Activity Index (CDAI) (Aletaha *et al.*, 2005). Cognitive function was assessed by the Six-item Cognitive Impairment Test (6CIT) - Kingshill Version 2000 (Brooke and Bullock, 1999). The 6CIT uses an inverse score and questions are weighted to produce a total out of 28. Scores of 0-7 were considered normal and eight or more were significant cognitive impairment.

### Statistical analysis

Continuous data were presented as Mean  $\pm$  SD while categorical data as numbers and percentages. A chi-square test was used to measure the difference between categorical data. Univariate linear regression analysis then multiple linear regression analysis was used to assess the correlation between cognitive impairment test score with various variables in patients. SPSS v22 and Graph pad Prism v7 software for Windows were used. p-value < 0.05 was considered statistically significant.

## RESULTS AND DISCUSSION

A total of 130 patients and 130 healthy controls participated in the study. The mean age of patients was  $48.9 \pm 12.1$  years and for controls was  $48.5 \pm 12.1$  years ( $p=0.794$ ). Females were 100 (76.9%) for patients and 100 (76.9%) for controls ( $p=1.00$ ). Other sociodemographic and clinical characteristics were shown in Table 1.

Prevalence of memory impairment was more in RA patients (47(69.1%) than controls 21(30.9%) [OR (95%CI)=2.939(1.632-5.294,  $p<0.001$ )] Figure 1.

Age and prednisolone use were significantly and

**Table 1: Baseline characteristic of patients and controls**

Variables	Patients (n=130)	Control (n=130)	p-value
Age (years), mean $\pm$ SD	48.9 $\pm$ 12.1	48.5 $\pm$ 12.1	0.794
BMI (kg/m <sup>2</sup> ), mean $\pm$ SD	28.6 $\pm$ 4.1	28.3 $\pm$ 3.6	0.484
Gender, n (%)			
Females	100 (76.9%)	100 (76.9%)	1.0
Marital status, n (%)			
Single	15 (11.5%)	11 (8.5%)	0.329
Married	85 (65.4%)	83 (63.8%)	
Widow	28 (21.5%)	29 (22.3%)	
Divorced	2 (1.5%)	7 (5.4%)	
Employment, n (%)			
Unemployed	56 (43.1%)	58 (44.6%)	0.803
Employed	74 (56.9%)	72 (55.4%)	
Income (thousand ID), mean $\pm$ SD	7.2 $\pm$ 4.7	7.0 $\pm$ 4.6	0.790
Education level, n (%)			
Illiterate	16 (12.3%)	16 (12.3%)	0.074
Primary	47 (36.2%)	47 (36.2%)	
Secondary	47 (36.2%)	32 (24.6%)	
College	20 (15.4%)	35 (26.9%)	
Disease duration (years), mean $\pm$ SD	8.1 $\pm$ 6.7		
CDAI, mean $\pm$ SD	19.7 $\pm$ 8.8		
Positive RF, n. (%)	87 (66.9%)		
Positive ACPA, n. (%)	52 (40%)		
ESR, mean $\pm$ SD	43.1 $\pm$ 22.3		
MTX, n.(%)	85 (65.4%)		
Prednisolone, n. (%)	79 (60.8%)		
Biological agents, n.(%)	89 (68.5%)		

SD:standard deviation. BMI: body mass index.( kg/m<sup>2</sup>): kilogram per square meter.ID: Iraqi dinar. P-value>0.05is significant. n: number. (%) :percentage CDAI: clinical disease activity index. RF: rheumatoid factor. ACPA:anticitrullinated peptide antibody. ESR: erythrocyte sedimentation rate. MTX:methotrexate

positively correlated with memory impairment ( $r = 0.346$ ,  $p < 0.001$ ;  $r = 0.224$ ,  $p = 0.012$  respectively) while the educational level was significantly and negatively correlated with CIT ( $r = -0.489$ ,  $p < 0.001$ ) as shown in Table 2.

This study evaluated the impact of RA on memory. It showed that memory impairment was more in RA patients than controls. RA increased the risk of having cognitive impairment with three folds. Also, increasing age and steroid use were significantly and positively correlated with cognitive impairment scores, while the educational level was significantly and negatively correlated with it. These findings are clinically important because early screening for cognition impairment may help early diagnosis and treatment, which will impact positively on health-related quality of life by improving adherence and response to treatment of RA.

The inflammation in the brain, high risk of cardiovascular comorbidity, immunosuppressive agents, and Glucocorticoid therapy (Hart *et al.*, 2003; Shin *et al.*, 2012) are possible causes of more memory deterioration in RA. Similar findings were reported by previous studies. (Shin *et al.*, 2012; Appenzeller *et al.*, 2004; Bartolini *et al.*, 2002), who observed more memory drop in RA.

In the current study, we found a significant direct correlation between memory impairment with age, this in line with (Bartolini *et al.*, 2002; Kim *et al.*, 2017) which concluded that aging might contribute to memory drop. Also, low education, and use of oral glucocorticoids were associated with memory impairment. These findings were in agreement with (Shin *et al.*, 2012) who demonstrated that persons with less education, and use of oral glucocorticoid were more likely to be cognitively impaired.

**Table 2: Correlation between Cognitive Impairment Test score with various variables in patients**

Variables	Cognitive Impairment Test score			
	Univariate analysis		Multivariate analysis	
	r	p-value	r	p-value
Age	0.509	<0.001 [S]	0.346	<0.001 [S]
Gender	-0.059	0.504	-	-
BMI	-0.069	0.435	-	-
Employment	0.317	<0.001 [S]	0.053	0.556
Education level	-0.659	<0.001 [S]	-0.489	<0.001 [S]
Crowding index	0.139	0.115	-	-
Disease duration	0.166	0.059	-	-
CDAI	0.088	0.322	-	-
Family income	-0.285	0.001 [S]	-0.081	0.365
RF	0.070	0.427	-	-
ACPA	0.013	0.887	-	-
ESR	0.042	0.636	-	-
MTX	0.135	0.125	-	-
PND	0.222	0.011 [S]	0.224	0.012 [S]
Biological	0.004	0.968	-	-

R<sup>2</sup> = 0.53, multiple linear regression using dummy variables was used, R, partial correlation; CDAI, clinical disease activity index; RF, rheumatoid factor; ACPA, anticitrullinated peptide antibody; ESR, erythrocyte sedimentation rate; MTX, methotrexate; PND, prednisolone. P > 0.05 was considered significant

Similar finding was demonstrated by (Wolkowitz *et al.*, 1990), who concluded that corticosteroids are related to memory problems.

In this study, there was no significant association between memory impairment and disease activity in RA patients. This was consisting of that reported by (Shin *et al.*, 2012) ,whoreported that disease severity was not a significant predictor of memory impairment in RA patients. On the other hand, this result was in contrast to (Kim *et al.*, 2017), who found disease activity of RA contribute to memory impairment. These controversial studies findings may be due to different classifications of memory impairment and diverse assessment methods used and reflect the social and habits of a different society

This study had some limitation: small sample size, lack of follow up of RA patients to demonstrate an improvement in memory function following effective treatment of RA, and the third limitation was lack of new techniques of brain imaging such as Single-photon emission computed tomography, Positron emission tomography and Magnetic resonance imaging. However, up to the best of our knowledge, this is the first study among Iraq patients with RA that assessed memory impairment with strict inclusion and exclusion criteria.

## CONCLUSIONS

In conclusion, RA patients had significantly higher memory impairment compared to control. Increasing age, low education, and using of steroids were significant predictors of memory impairment. There is no significant association between memory impairment and disease activity in RA patients. These findings suggest that memory impairment should be evaluated and assessed in RA patient. Extended evaluation of socioeconomic classes across patient's life is required and a large prospective study is needed to clarify the results.

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