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ORIGINAL ARTICLE

Disease activity is associated with cognitive impairment in patients with rheumatoid arthritis

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Abstract

Objective To investigate the association between disease activity and cognitive impairment in patients with rheumatoid arthritis (RA).

Methods A total of 464 patients from the rheumatoid arthritis registry of two academic centers, Siriraj and Phramongkutklao hospitals, were included. Demographic, clinical, and laboratory data related to disease activity and functional status were collected. Cognitive function was assessed using the Thai version of the Montreal Cognitive Assessment (MoCA-T). Subjects were classified as cognitively impaired if they scored less than 25.

Results Most subjects (85%) were female with a mean age ± SD of 59.2 ± 11.4 years old and a median (range) educational level of 9 (4–14) years. They were long-standing RA patients (median disease duration (range) of 9.9 (5.1–16.6) years) and had moderate cumulative disease activity (mean DAS28 ± SD of 3.5 ± 0.81) and mild functional impairment (median HAQ (range) 0.5 (0.13–1.10)). Seventy percent of the patients were classified as having cognitive impairment. The patients with cognitive impairment significantly impaired in all domains, especially in visuospatial/executive, language, and abstraction. In multiple logistic regression analyses, old age (RR 3.45, 95% CI 2–6, $p < 0.001$), low education (RR 10.8, 95% CI 5.3–22.1, $p < 0.001$), and high cumulative disease activity (RR 2.2, 95% CI 1.07–4.7, $p = 0.033$) were independently associated with cognitive impairment.

Conclusion High cumulative RA disease activity is associated with cognitive impairment. Therefore, treat-to-target aimed at low disease activity or remission may be beneficial for preventing cognitive decline in RA patients.

Keywords Cognitive impairment · DAS28 · Disease activity · HAQ · MoCA · Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory joint disease and is characterized by persistent synovitis, systemic inflammation, and the presence of autoantibodies. It affects between 0.5 and 1% of the population [1–3] and 0.12% of the Thai population [4]. Chronic inflammation in RA leads to chronic pain, joint deformities, functional disability, and shortened life expectancy. Additionally, it has been shown in a previous study that 32% of patients had at least one comorbidity at the onset of the disease, and the cumulative prevalence increased to 81% during 15 years of follow-up [5].

Cognitive impairment is one of the most common comorbidities found in RA, ranging between 38 and 71% [6, 7]. The pathogenic mechanisms of cognitive decline in RA are unknown. A number of mechanisms have been proposed for the pathogenesis of cognitive impairment in RA, including a chronic systemic inflammatory process involving all organs

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that can involve the neural tissue [8], the side effects of medications, especially glucocorticoid [9] and methotrexate [10], and accelerated atherosclerosis associated with chronic systemic inflammation and autoantibodies [11, 12]. Therefore, RA has a negative impact on quality of life, including physical, psychological, and social functions.

Intact cognitive function is important for executing several basic tasks in people with chronic diseases, including RA. Patients with cognitive impairment have increased functional difficulties, less medication adherence, and poorer quality of life [6, 13, 14]. A standard neuropsychological evaluation would be beneficial for patients with suspected cognitive impairment. However, this method is limited in daily practice owing to high costs and it is time-consuming. Therefore, a feasible, valid, and reliable cognitive screening test is required in clinical settings. In 1996, Nasreddine ZS et al. developed the Montreal Cognitive Assessment (MoCA) as a rapid test for detecting mild cognitive impairment [15]. The MoCA is considered to be a simple and reliable screening instrument in clinical practice. The assessment examines different cognitive domains: attention, concentration, executive functions, memory, language, visuospatial skills, abstraction, calculation, and orientation. The test takes 10–15 min to complete. The MoCA test validation study demonstrated that it is a promising tool for detecting mild cognitive impairment [15, 16]. The sensitivity and specificity of the MoCA were 90% and 87%, respectively, compared with 18% and 100% for the Mini-mental Status Test (MMST).

In Thailand, the Montreal Cognitive Assessment-Thai version (MoCA-T) was translated by Hemrungrojn S. and back-translated by a linguistic staff at the Chulalongkorn Language Institute. Content validity was also verified by two psychiatrists and one neurologist. For criterion verification, Tangwongchai et al. reported a high correlation between MoCA-T and the Thai Mental Stage Examination (TMSE) [17]. The sensitivity and specificity of MoCA-T were 100% and 98%, respectively. As it has been reported that the year of education was significantly associated with the MoCA-T score, the compensation by adding 1 point for subjects with years of education less than 6 years was considered to be appropriate in Thai subjects. The total score is 30 points and a score of less than 25 is considered cognitively impaired [18]. The objectives of this study were to investigate the prevalence of cognitive impairment and the association between disease activity and cognitive impairment in Thai patients with RA.

Materials and methods

Study population

The population in this study included the patients from two university-based hospitals. The Siriraj Rheumatoid Arthritis (SiRA) registry is a prospective cohort established in 2011 by the outpatient service of the Division of Rheumatology, Department of Medicine, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand [19]. The Thai Army Rheumatoid Arthritis Cohort (TARAC) is an observational, real-world cohort of patients with RA recruited at the Rheumatology Clinic, Phramongkutklao Hospital, since 1990 [20]. All the patients in these cohorts who had visited the clinic between September 2016 and March 2018 were invited to enroll in this study.

All the patients who were of Thai nationality, aged 18 years old or older, diagnosed with RA according to the American College of Rheumatology 1987 revised criteria for the classification of RA [21] or the 2010 rheumatoid arthritis classification criteria [22], literate, and who had had at least one follow-up visit were included in this study. They were excluded if they were diagnosed with overlap syndrome with other rheumatic or autoimmune diseases, had visual problems, had a history of any significant neuropsychiatric illness, such as dementia, neurodegenerative disorder, head trauma, cerebral infection, or cerebrovascular accident, or had used antipsychotics or cerebral depressants within the preceding 6 months. Informed consent was obtained from all participants.

Clinical and laboratory assessment

Demographic, clinical, and laboratory data related to functional status, disease activity, and medications were collected at baseline and every 3–6 months. Functional status was assessed using the Thai version of the Health Assessment Questionnaire (HAQ) [23]. Data related to disease activity included patient global assessment of disease activity (0–10 cm Visual Analogue Scale or VAS), physician global assessment of disease activity (0–10 cm VAS), the number of tender joints (TJC) (28 joints), the number of swollen joints (SJC) (28 joints), and the erythrocyte sedimentation rate (ESR). The Disease Activity Score 28 (DAS28) was calculated [24]. Cumulative disease activity of DAS28 was calculated by the sum of serial measurements of DAS28 divided by the total number of clinic visits from the first to last measurements. Rheumatoid factor (RF), anticitrullinated antibodies (ACPA), and radiographs of the hands and feet were collected at the baseline visit. The health-related quality of life was assessed using the Thai version of the EQ-5D-5L [25].

Cognitive, depression, and anxiety assessments

Cognitive, depression, and anxiety assessments of each patient were collected once during September 2016 and December 2017. After providing a written informed consent, the patients were registered for the following baseline variables: age and level of education. Cognitive assessment was obtained using the MoCA-T. The test was administered in

Thai by two trained outcome assessors. The subjects were classified as cognitively impaired if they scored less than 25 [18], a cutoff point validated in the Thai population.

The Thai version of the Hospital Anxiety and Depression Scale (Thai HADS) [26] was used to assess the mood by measuring anxiety (7 items) and depression (7 items). Each question was answered on a four-point verbal rating. The Thai HADS is a 21-point scale (with 0 being the best and 21 the worst), with a cutoff point of 8 or greater considered as denoting anxiety or depression.

Statistical analysis

A descriptive statistics analysis was used to describe the sample characteristics and clinical variables. The demographic and baseline characteristics were described as a mean and standard deviation (SD) or median and range for continuous data and number and percentage for categorical data. Comparisons of demographic and characteristics between the patients with or without cognitive impairment were performed using a chi-square test or Fisher's exact test as appropriate for categorical data and the Student t test or Kruskal–Wallis test as appropriate for continuous data. A univariate analysis was used to identify the potential factors related to the presence of cognitive impairment. The factors that were identified to be different between the patients who had or did not have cognitive impairment with a p value < 0.2 in the univariate analysis or factors that have been reported in previous studies to be associated with cognitive impairment in RA were then included in a multivariate analysis. A backward stepwise logistic regression analysis was performed to identify the independent factors associated with cognitive impairment. A p value < 0.05 was considered statistically significant. All analyses were performed using the Statistical Package for the Social Sciences (SPSS) 20.0.

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to the principles outlined in the Guideline for Good Clinical Practice International Conference on Harmonization (ICH) Tripartite Guideline (January 1997). The study protocol was approved by local ethics committees, the Siriraj Institutional Review Board and the Institutional Review Board of the Royal Thai Army Medical Department.

Results

A total of 464 patients with RA were included in this analysis. Most of them (85%) were female with a mean age ± SD of 59.2 ± 11.4 years. They had long-standing RA with a median (interquartile range or IQR) disease duration and a follow-up duration of 9.9 (5.1–16.6) and 5.2 (2.2–5.9) years, respectively. The median (IQR) educational level was 9 (4–14) years. Almost half were unemployed (47.6%). They had moderate cumulative disease activity (mean DAS28 ± SD, 3.5 ± 0.8) and mild functional impairment (median HAQ (IQR) 0.5 (0.13–1.10)). Most of them had severe disease based on the presence of RF (75%) and ACPA (72%) and hand or feet erosion at baseline (84%). In terms of comorbidities, hypertension was the most common underlying disease (41%), followed by dyslipidemia (39%), diabetes mellitus (10%), coronary artery disease (2.6%), and cerebrovascular disease (1.7%). Depression and anxiety were identified in only 8.4% and 9.3%, respectively. The mean utility measured by EQ-5D-5L ± SD was 0.87 ± 0.13.

Based on the MoCA-T cutoff point validated in a Thai population, 323 out of the 464 (70%) were classified as having cognitive impairment. The mean ± SD of the total MoCA-T scores was 21.31 ± 4.46. The mean ± SD of cognitive subdomain scores of visuospatial/executive, naming, attention, language, abstraction, delayed recall, and orientation were 2.91 ± 1.53 out of 5, 2.73 ± 0.61 out of 3, 4.86 ± 1.23 out of 6, 1.45 ± 0.98 out of 3, 0.59 ± 0.74 out of 2, 2.94 ± 1.51 out of 5, and 5.82 ± 0.48 out of 6, respectively. Overall, the subjects with cognitive impairment scored significantly lower in all the cognitive subdomains of MoCA-T, compared with those without cognitive impairment (Table 1).

In the univariate analysis, the factors that significantly related to cognitive impairment were age, educational level, unemployment, DAS28, and HAQ. In the multiple logistic regression analysis, only the patients who were older than 60 years and had an education level of less than 6 years and high cumulative disease activity (mean DAS28 > 2.6) were statistically significantly associated with cognitive impairment with an RR (95% CI) of 3.45 (1.99–6.03), 10.8 (5.28–22.1), and 2.23 (1.07–4.37), respectively, after adjusting for smoking, alcohol use, unemployment, anxiety, depression, HAQ, and comorbidities (Table 2). This model explained 36% (the Nagelkerke R^2) the variability of the factors predicting cognitive impairment in this population.

Discussion

In this study, the prevalence of cognitive impairment in our population was 70% based on the MoCA-T, while it has been reported in previous studies to range between 31 and 71% [6, 7, 27]. These differences are mainly due to the different tools used to evaluate cognition. Some studies used the full battery neuropsychological test [14], while others used the MMSE [13, 28]. To our knowledge, as yet, there has been no study that has used the MoCA to detect cognitive impairment in RA. In our study, we used the MoCA-T because it is a highly sensitive test to detect cognitive impairment [15, 17, 18] and is lower cost and less time-consuming than a full battery neuropsychology test. Therefore, it is feasible in routine practice.

Table 1 Scores of each domain of cognitive impairment based on the MoCA-T

MoCA-T	Total score* ($N = 464$)	Patients with cognitive impairment* ($N = 323$)	Patients without cognitive impairment* ($N = 141$)	*P* value
Total score (30)	21.31 ± 4.46	19.22 ± 3.67	26.09 ± 1.28	< 0.001
Visuospatial/executive (5)	2.91 ± 1.53	2.29 ± 1.36	4.31 ± 0.76	< 0.001
Naming (3)	2.73 ± 0.61	2.63 ± 0.69	2.96 ± 0.19	< 0.001
Attention (6)	4.86 ± 1.23	4.50 ± 1.28	5.68 ± 0.52	< 0.001
Language (3)	1.45 ± 0.98	1.13 ± 0.88	2.21 ± 0.75	< 0.001
Abstraction (2)	0.59 ± 0.74	0.39 ± 0.61	1.05 ± 0.80	< 0.001
Delayed recall (5)	2.94 ± 1.51	2.51 ± 1.50	3.92 ± 1.01	< 0.001
Orientation (6)	5.82 ± 0.48	5.77 ± 0.53	5.96 ± 0.29	< 0.001

*Data are expressed as mean ± standard deviation

Despite the different cognitive tests used, we found that RA patients had substantial impairment of visuospatial, language, and abstraction subdomains. These results are similar to those in studies by Bartolini et al. [6] and Shin et al. [14], which found that impairment in visuospatial tasks is commonly found in RA patients, being reported in 71% and 29% of patients, respectively. Furthermore, impaired performances in language, especially in verbal fluency, are analogous to previous studies by Shin et al. [14], Appenzeller et al. [13], and Lee et al. [29]. Similar to our study, Lee et al. found an association between cognitive impairment and disease activity measured by DAS28 and C-reactive protein (CRP). Impairment of these domains is related to prefrontal cortex dysfunction and disturbances in the frontoparietotemporal circuit. A previous study reported that the lower scores in the assessment of attention, executive, and visuospatial functions were related with hypoperfusion and alterations in subcortical areas of the frontal and parietal lobes, which were detected by brain magnetic resonance imaging (MRI) and single-photon emission computed tomography (SPECT) [6]. Moreover, Baptista TSA et al. reported that patients with active RA with cognitive impairment had a robust increase in peripheral levels of autoantibodies against CNS proteins [28] and another study reported the immune reaction correlates with cognitive impairment in RA patients [30]. These findings are consistent with the hypothesis previously proposed that RA is a chronic systemic inflammatory disease involving all systems, which can involve the neural tissues and increase risk of atherosclerosis leading to cognitive impairment [8, 10, 11]. Additionally, RA patients who had cognitive impairment had increased levels of TNF-α, IL-2, IL-4 IL-6, and BDNF levels. These cytokines are negatively involved with cognitive functions [30].

Table 2 Multiple logistic regression analysis to identify factors related to cognitive impairment in RA

Factors	RR	95% CI	*P* value
Age > 60 years	3.45	1.99–6.03	< 0.001
Smoking	1.89	0.72–4.92	0.199
Alcohol use	0.93	0.49–1.76	0.827
Education < 6 years	10.80	5.28–22.10	< 0.001
Unemployment	1.02	0.59–1.74	0.956
DAS28 > 2.6	2.23	1.07–4.67	0.033
HAQ > 0.5	1.03	0.63–1.68	0.922
Anxiety	2.01	0.72–5.60	0.184
Depression	1.12	0.41–3.09	0.820
Diabetes mellitus	1.11	0.46–2.67	0.812
Hypertension	0.78	0.46–1.33	0.366
Dyslipidemia	1.46	0.85–2.53	0.172
Coronary artery disease	1.41	0.25–8.08	0.700
Stroke	2.72	0.23–31.77	0.425

CI confidence intervals, *RR* relative risk, *DAS 28* Disease Activity Score 28, *HAQ* Health Assessment Questionnaire

However, the association between disease activity and cognitive impairment was not found in other studies [13, 27]. In Shin et al.'s study, the Rheumatoid Disease Activity Index (RADAI) was used to assess disease activity. RADAI may not accurately measure disease activity, as it is a patient-reported outcome and does not include objective inflammatory markers, e.g., ESR or CRP. In their multivariate analysis, there was a trend that a high CRP was associated with cognitive impairment with OR (95% CI) 1.21 (0.43–3.38), but it was not significant, partly due to the limited sample size. Furthermore, Appenzeller S et al. also found no correlation between disease activity and cognitive function. This may be due to a small sample size ($N = 80$) in this study.

Our study has some limitations. First, we had no baseline cognitive test before the onset of RA, so cognitive impairment found in some patients may not directly relate to RA disease activity if they had cognitive impairment prior to the onset of RA. Second, we had no comparison with age-matched healthy subjects; however, it has been shown in a previous study that Thai patients with RA had a higher prevalence of cognitive impairment when compared with healthy individuals [7].

Furthermore, as we wanted to focus on the relationship between disease activity and cognitive impairment, we did not include a healthy population in this study. Third, some patients had hand deformities leading to poor performance in drawing, which is used to assess visuospatial and executive function. We did not specifically record hand function; therefore, impaired visuospatial and executive functions found in this study may not directly relate to cognitive decline. Fourth, we did not collect data related to other common reported risk factors for cognitive impairment, including hypothyroidism [31], anemia [32], and vitamin B_{12} and folate deficiency [33]. These factors may contribute to the high prevalence of cognitive impairment in RA. Lastly, although we excluded patients who had used antipsychotics or cerebral depressants within the preceding 6 months, we did not record the use of muscle relaxants, which is commonly used in patients with musculoskeletal pain. This medication may affect cognitive performances to a certain extent.

Despite these limitations, this is the first study that uses longitudinal data to represent cumulative disease activity. Consequently, we can demonstrate that chronic, active inflammation in RA may lead to cognitive impairment.

In conclusion, based on a MoCA cutoff point validated in the Thai population, the prevalence of cognitive impairment, especially in visuospatial/executive, language, and abstraction, is quite common in patients with RA. This study highlights that chronic active inflammation in RA may lead to significant cognitive impairment, in addition to traditional risk factors. Therefore, treat-to-target aimed at low disease activity or remission may be beneficial for preventing or attenuating cognitive decline in RA patients, in addition to preventing joint damage and functional disability. This issue should be confirmed in future research.

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Compliance with ethical standards

This study was conducted in accordance with the ethical principles of the Declaration of Helsinki and adhered to the principles outlined in the Guideline for Good Clinical Practice International Conference on Harmonization (ICH) Tripartite Guideline (January 1997). The study protocol was approved by local ethics committees, the Siriraj Institutional Review Board and the Institutional Review Board of the Royal Thai Army Medical Department.

Disclosures None.

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