Cognitive function of patients with rheumatoid arthritis is associated with disease activity but not carotid atherosclerotic changes

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Abstract

Objective

Although the relationship between atherosclerosis and cognitive impairment has been studied and replicated, whether cognitive deficits in RA can be attributed to atherosclerotic changes is not well understood. This study investigated cognitive function in patients with RA and evaluated whether cognitive function was affected by carotid arterial atherosclerosis.

Methods

We examined 70 RA patients and 40 healthy controls. RA activity was assessed by disease activity score with 28 joint-erythrocyte sedimentation rate (DAS28-ESR). Cognitive function was assessed by the Korean version of the Consortium to Establish a Registry for Alzheimer’s disease (CERAD-K) neuropsychological battery. Carotid arteries were scanned for the presence of plaques and to assess intima-media thickness (IMT). We assessed potential risk factors of cognitive impairment in RA patients using regression analyses.

Results

There was a significant difference between RA patients and healthy controls in the verbal fluency (p=0.004) and Boston naming test (p=0.035). Carotid ultrasound revealed significantly more plaque in RA patients than in healthy controls (p=0.017). RA patients with memory impairment had significantly higher DAS28-ESR scores (p<0.001), age (p=0.009), and mean cIMT (p=0.027) than RA patients without memory impairment. In multivariable regression analysis, CERAD-K total score showed a significant negative correlation with age (β=-0.415, p<0.001) or DAS28-ESR (β=-4.685, p<0.001), but no correlation was found between CERAD-K total score and presence of plaque or cIMT.

Conclusion

Our results indicate that disease activity of RA and aging contribute to cognitive dysfunction, but there was no association between cognitive function and carotid atherosclerotic changes in RA patients.

Key words

cognitive dysfunction, rheumatoid arthritis
Introduction

Cognitive impairment (CI) is a term that includes both dementia and mild cognitive impairment (1). The proposed diagnostic statistical manual version V (DSM-V) defines dementia as cognitive decline that is significant enough to interfere with independence in activities of daily living, but is not due to delirium or another mental disorder. Mild cognitive impairment (MCI) is distinguished from dementia in that cognitive impairment is not severe enough to interfere with independence in daily life (1). Risk factors for cognitive decline include increasing age, ε4 allele of the lipoprotein E gene, cardiovascular risk factors (e.g., diabetes, smoking, hypertension, hypercholesterolaemia, metabolic syndrome, obesity), depression, low social support, and low education level (2).

Whether rheumatoid arthritis (RA) is a risk factor for CI is not clear. CI is usually accompanied by RA. However, several studies have suggested that RA has a link with CI; CI was found in 30-71% in patients with RA (3-5). Neuroimaging findings such as brain hypoperfusion or increased white matter alterations, medication including methotrexate or steroids, increasing age, education, income, and cardiovascular disease (CVD) risk factors have been reported to be associated with an increased risk of CI in patients with RA (6-8). Recent systemic review of multiple databases ascertained the prevalence of CI in patients with RA and reported that age, education, disease activity, and depression were associated with CI (9). CVD risk factors showed significant associations with CI in some studies of RA patients, but this finding has not been consistent across studies. Although the relationships between CVD risk factors or atherosclerosis and CI has been studied and replicated (10-12), whether cognitive deficits in RA can be attributed to atherosclerotic changes is not well understood. The aim of this study was to examine if CI in RA patients is associated with atherosclerotic changes. We investigated cognitive function using the Korean version of the Consortium to Establish a Registry for Alzheimer’s disease (CERAD-K) neuropsychological battery and atherosclerotic changes using carotid ultrasound and then evaluated whether cognitive function was affected by carotid arterial atherosclerosis. In addition, we examined which demographic and clinical factors are associated with CI in patients with RA.

Methods

Study design and subjects

RA patients, diagnosed at one of two rheumatology divisions, were enrolled from December 2015 to December 2016. A diagnosis of RA was based on the American College of Rheumatology (ACR) criteria (13). All subjects were older than 18 years, and subjects with any neurological or psychiatric diseases that could affect cognition and those who abused alcohol were excluded. Other exclusion criteria were diabetes, hypertension, renal failure, chronic hepatopathy, and hypothyroidism. Disease Activity Score with 28 joints erythrocyte sedimentation rate (DAS28-ESR) was assessed in RA patients (14). The control group was recruited from the health screening centre of the hospital where control subjects underwent their regular physical checkups. The Institutional Review Board of the Korean Institute of Medicine approved this study in December 2015 (2015-212), and all patients gave written informed consent before participating.

Laboratory evaluation

Rheumatoid factor (RF) was quantified using turbid immunochemistry (Adria 1800, Siemens) with a cut-off of 15 IU/ml for positive values. Anti-cyclin citrullinated peptide antibody (anti-CCP Ab) was quantified using enzyme-linked immunosorbent assay with a cut-off of 5 IU/ml for positive values. Plasma concentrations of high sensitivity C-reactive protein (hsCRP) were also measured by automated turbid immunochemistry (Adria 1800, Siemens). All patients had fasted for at least 12 hours before total cholesterol was measured.

CERAD-K neuropsychological battery

The subjects were asked to fill out the CERAD-K neuropsychological battery questionnaire, which is a standardised
evaluation tool for assessing cognitive functions (15). Two trained research assistants at each hospital helped patients answer questions on the questionnaire. The CERAD-K consists of nine neuropsychological tests: verbal fluency (VF) test, modified Boston naming test (BNT), Korean version of the mini-mental state examination (MMSE), word list memory (WLM), construction praxis (CP), word list recall (WLR), word list recognition (WLRc), construction recall (CR), and trail-tests A and B. The study participants were subdivided into two groups based on the presence of objective memory impairment, defined as a performance score 1.5 standard deviations below the respective age-specific, education-specific, and sex-specific normative mean for at least one of the four episodic memory tests in CERAD-K (WLR, WLM, WLRc, CR). Two CERAD-K total scores (TS), TS-I and TS-II, were calculated. TS-I was generated by simply summing the scores of six tests (VF, BNT, WLM, CP, WLR, and WLRc). TS-II was calculated by adding the CR score to TS-I (16). Demographic information such as age, sex, and education level were also recorded for each subject.

**Carotid artery ultrasonography**

Carotid intima-media thickness (CIMT) of the common carotid arteries was measured 1–2 cm proximal to the bulb as the distance between the intima-lumen interface and the media-adventitia interface. CIMT was measured bilaterally, and the average was used in statistical analyses. Plaques were identified as protrusions into the lumen of ≥1.5 mm or at least twice the thickness of the adjacent IMT.

**Statistical analysis**

Data were analysed using standard statistical software (SPSS package v. 22; Chicago, IL, USA). Continuous data are expressed as mean ± standard deviation. Categorical data are presented as frequency and percentage. Measurements were compared using Student’s t-test for continuous variables and Fisher’s exact test for discrete variables. Pearson correlation tests were performed to assess the correlations between variables. A p-value < 0.05 was considered statistically significant.

### Results

**Clinical characteristics of subjects**

A prospective analysis of 70 RA patients and 40 control subjects was performed. There were no significant differences in age, sex, or education between the RA patients and the control group. There was no significant difference between groups in CIMT, but plaque was more frequently observed in RA patients. Of the CERAD-K subtests, there were significant differences between the RA patients and healthy controls in VF, BNT, trail making B, TS-I, and TS-II (Table I). Our participants were on a variety of medications for RA. We evaluated the correlation between the medication and TS-I, and TS-II (Table II).

**Clinical variables of subgroups with and without memory impairment**

We divided RA patients into two groups: patients with and patients without memory impairment. There were no significant differences in sex, level of RF, anti-CCP Ab or total cholesterol between these two groups. Patients with memory impairment were older and had higher hsCRP, DAS28-ESR, and mean CIMT than patients without memory impairment. Plaques were more frequently...
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observed in patients with memory impairment, but this finding was not statistically significant (Table III).

Correlations between laboratory and clinical parameters and total scores of the CERAD neuropsychological assessment battery

Cognitive function, represented as TS I and TS II, showed a significant inverse association with age and DAS28-ESR in univariate and multivariate regression analyses (Table IV). However, TS I and TS II did not show any significant correlations with the level of RF, total cholesterol, CIMT, or presence of plaques.

Discussion

In the present study, we evaluated cognitive function in patients with RA. Cognitive function was reflected by the TS of the CERAD-K neuropsychological battery. Two CERAD total scores, including TS-I and TS-II, have been reported to be valid measures for detecting and monitoring the progression of MCI and dementia, regardless of the etiologic background. Also, both can discriminate MCI or very mild stage of dementia from a cognitively normal state. In a clinical setting, it is recommended that clinicians consider both TS-I and TS-II to make a better clinical decision, because some dementia or MCI patients with asymmetrically prominent right hemisphere pathology might be better monitored by TS-II than TS-I (16).

RA patients exhibited decreased cognitive function relative to healthy controls in this study. Of the CERAD-K subtests, patients and controls showed significant differences in VF, BNT, trail making B, TS-I, and TS-II. The VF test measures visual naming through the identification of 15 line drawings. BNT

Table III. Clinical variables of subgroup with and without memory impairment.

<table>
<thead>
<tr>
<th></th>
<th>Patients with memory impairment (n=14)</th>
<th>Patients without memory impairment (n=56)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65.71 ± 7.71</td>
<td>58.50 ± 11.33</td>
<td>0.009</td>
</tr>
<tr>
<td>Male (%)</td>
<td>2 (0.14)</td>
<td>10 (0.18)</td>
<td>1.000</td>
</tr>
<tr>
<td>RF (IU/mL)</td>
<td>86.74 ± 161.03</td>
<td>87.86 ± 163.69</td>
<td>0.681</td>
</tr>
<tr>
<td>Anti-CCP Ab (U/ML)</td>
<td>101.42 ± 159.72</td>
<td>147.27 ± 153.25</td>
<td>0.190</td>
</tr>
<tr>
<td>hsCRP (mmol/L)</td>
<td>15.59 ± 21.89</td>
<td>3.86 ± 8.48</td>
<td>0.050</td>
</tr>
<tr>
<td>DAS28</td>
<td>4.14 ± 0.99</td>
<td>2.60 ± 0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TC</td>
<td>185.37 ± 72.12</td>
<td>182.30 ± 39.31</td>
<td>0.547</td>
</tr>
<tr>
<td>Mean CIMT</td>
<td>0.56 ± 0.10</td>
<td>0.50 ± 0.08</td>
<td>0.027</td>
</tr>
<tr>
<td>Presence of plaque</td>
<td>9 (0.64)</td>
<td>18 (0.32)</td>
<td>0.057</td>
</tr>
</tbody>
</table>

Values are presented as the mean±SD.
RF: rheumatoid factor; anti-CCP Ab: anti-cyclin citrullinated peptide antibody; hsCRP: high sensitivity C-reactive protein; TC: total cholesterol; CIMT: carotid intima-media thickness.

Table IV. Correlation coefficients between the laboratory and clinical parameters and total scores of the CERAD neuropsychological assessment battery.

<table>
<thead>
<tr>
<th>Total score I</th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (β)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Total 1 (n=70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.370</td>
<td>(-0.561, -0.180)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>1.394</td>
<td>(-4.727, 7.514)</td>
</tr>
<tr>
<td>RF (IU/mL)</td>
<td>0.004</td>
<td>(-0.011, 0.018)</td>
</tr>
<tr>
<td>Anti-CCP Ab (U/ML)</td>
<td>0.017</td>
<td>(-0.001, 0.036)</td>
</tr>
<tr>
<td>hsCRP (mmol/L)</td>
<td>-0.020</td>
<td>(-0.198, 0.159)</td>
</tr>
<tr>
<td>DAS28</td>
<td>-3.949</td>
<td>(-5.861, -2.038)</td>
</tr>
<tr>
<td>TC</td>
<td>0.016</td>
<td>(-0.033, 0.066)</td>
</tr>
<tr>
<td>Mean CIMT</td>
<td>-21.912</td>
<td>(-47.561, 3.737)</td>
</tr>
<tr>
<td>Presence of plaque</td>
<td>-1.210</td>
<td>(-5.947, 3.527)</td>
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</table>

Total score II

<table>
<thead>
<tr>
<th></th>
<th>Univariable analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Coefficient (β)</td>
<td>95% CI</td>
</tr>
<tr>
<td>Total 2 (n=70)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>-0.494</td>
<td>(-0.711, -0.277)</td>
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<tr>
<td>Male (%)</td>
<td>2.121</td>
<td>(-5.079, 9.320)</td>
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<tr>
<td>RF (IU/mL)</td>
<td>0.003</td>
<td>(-0.014, 0.020)</td>
</tr>
<tr>
<td>Anti-CCP Ab (U/ML)</td>
<td>0.017</td>
<td>(-0.005, 0.040)</td>
</tr>
<tr>
<td>hsCRP (mmol/L)</td>
<td>-0.074</td>
<td>(-0.284, 0.135)</td>
</tr>
<tr>
<td>DAS28</td>
<td>-5.402</td>
<td>(-7.552, -3.252)</td>
</tr>
<tr>
<td>TC</td>
<td>0.020</td>
<td>(-0.038, 0.078)</td>
</tr>
<tr>
<td>Mean CIMT</td>
<td>-26.082</td>
<td>(-56.257, 4.103)</td>
</tr>
<tr>
<td>Presence of plaque</td>
<td>-1.209</td>
<td>(-6.79, 4.371)</td>
</tr>
</tbody>
</table>

Values are presented as the mean±SD.
RF: rheumatoid factor; anti-CCP Ab: anti-cyclin citrullinated peptide antibody; hsCRP: high sensitivity C-reactive protein; TC: total cholesterol; CIMT: carotid intima-media thickness.
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has been used to support the diagnosis of dementia because impairment in language function is one of the core symptoms of dementia. BNT performance is useful for predicting the subsequent development of Alzheimer’s disease (AD) in preclinical cases or prognosis in patients with AD (17). Trail making B is predominantly a mental flexibility measure in which the individual must switch their focus of attention repeatedly between two sequences (numerical and alphabetical). Mental engagement, motor dexterity, and working memory are also recruited during the test (18).

Cognitive impairment was associated with age and disease activity in our RA patients. In previous studies, variables associated with cognitive function were pain (19, 20), disease activity (6, 7), fatigue (21), medications such as steroids or methotrexate (8, 22, 23), biomarkers like IL-6, B, T cells (24, 25), and CVD risk factors. One study demonstrated that subjects with more CVD risk factors were more likely to be cognitively impaired (8). They used CVD risk scores calculated using the Framingham Risk score system, which includes measures such as hypertension, systolic blood pressure, antihypertensive medication use, total cholesterol, high-density lipoprotein cholesterol, smoking, and obesity.

The main strength of this study was the examination of CERAD-K and carotid ultrasound to evaluate whether cognitive function was affected by carotid atherosclerosis, which has not previously been assayed in RA patients. Ultrasound markers of carotid atherosclerosis, namely plaques and CIMT, are associated with CVD and various vascular events. Evidence suggests that CIMT and plaques are associated with cognitive impairment (26-28). However, we did not find any significant association between CIMT or presence of plaques and cognitive decline. A recent longitudinal, population-based study, namely the Northern Manhattan Study (11), reported that those with greater CIMT exhibited worse episodic memory, but participants with greater CIMT at baseline did not exhibit significantly greater cognitive decline. Carotid plaque burden was not significantly associated with cognition at baseline or over time in that study, which is consistent with the results of our study. They reported that APOE ε4 carriers with greater CIMT exhibited worse episodic memory, semantic memory, and proceeding speed, which suggests that the APOE ε4 allele has a mediating effect on vascular wall changes and cognition.

Cognitive function encompasses a wide range of domains, including orientation, attention, concentration, judgement, problem solving, memory, verbal function, and visual and spatial function (9). We found no significant association between carotid atherosclerosis and cognitive decline, but patients with memory impairment had higher mean CIMT. Higher CIMT could result in increased arterial stiffness, causing impaired memory because of chronic cerebral hypoperfusion. In this study, autoantibodies such as RF or anti-CCP Ab were not significantly associated with cognitive function. We found a significant inverse association between cognitive function and DAS28, but not hsCRP, which might be explained that multiple mechanisms may be involved in cognitive decline in RA patients including tender joints, swollen joints, patients’ subjective assessments, which implies both pain and inflammation, together impact on cognition.

In conclusion, we found that RA patients were more cognitively impaired than healthy controls, and disease activity and aging contributed to this impairment. We did not find any association between cognitive function and carotid atherosclerotic changes. Considering the burden of cognitive impairment in RA, further evaluation with long-term follow-up is necessary to elucidate the pathophysiology that contributes to cognitive impairment in RA patients.

Study limitations

There were several limitations to this study. We evaluated the influence of medications on cognitive function. Our participants were on a variety of medications for RA. Pharmacologic treatment in RA commonly consists of a combination of drugs rather than monotherapy, and it is difficult to isolate the singular effect of any one medication. Also the sample size was small. Therefore, the findings of this study constitute only preliminary data, and large surveys with strict selection criteria and thorough medical examinations are necessary in the future. Predominantly female sample which female was 83% of total is considered to be another limitation. Finally, we did not evaluate the neuroimaging findings. The main purpose of this study was to examine the cognitive function in RA patients, and CI and dementia still remains a clinical diagnosis that cannot be made on imaging. However, neuroimaging techniques, such as computed tomography or magnetic resonance imaging and molecular imaging techniques, such as positron emission tomography could be useful, especially in evaluating CI in RA patients to rule out other underlying neuropathologies. Structural and functional changes that may not clinically manifest but could be associated with rheumatoid vasculitis, chronic inflammation, or demyelination may represent an adjunctive mechanism contributing cognitive impairment in RA. Therefore, further research using neuroimaging techniques could provide stronger study strength.

References

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