

Risk of Dementia in The Paients With Inflammatory Arthritis

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Introduction

Several studies have suggested that chronic systemic inflammation plays a more critical role in the development of dementia compared to short-term systemic inflammation. Research indicates that peripheral inflammation is linked to central nervous system inflammation, and inflammatory substances are associated with microglial activation. Elevated serum levels of various inflammatory cytokines, such as TNF, have been found in patients with Alzheimer's disease, and an association between increased TNF cytokines and the progression of dementia has been established. This study aims to investigate the association between inflammatory arthritis and the risk of dementia in Korea, changes in the incidence of stroke and dementia following treatment for inflammatory arthritis, and changes in medical costs associated with these conditions.

Methods

Using National Health Insurance claim data, the study analyzed the annual frequency of new registrations from 2010 onwards. The analysis excluded patients diagnosed by 2009 with ankylosing spondylitis (M45, V140), seropositive rheumatoid arthritis (M05, V223), or psoriatic and enteropathic arthropathies (arthritis related to inflammatory bowel disease) (M071-073, V237).

Results

Among patients newly registered for special benefit programs for inflammatory arthritis since 2010, the number of patients with ankylosing spondylitis was 35,686. Biologic agents were administered to 29% of these patients, with anti-TNF antagonists accounting for 97%, and the matched control group consisted of 178,430 individuals. For seropositive rheumatoid arthritis, there were 102,366 patients; 9.3% received biologic agents (57% of which were anti-TNF antagonists), with a matched control group of 511,830. Psoriatic and enteropathic arthropathy patients numbered 4,062, with 38% receiving biologics (36% anti-TNF antagonists) and a matched control group of 178,430. Epidemiologically, ankylosing spondylitis was more prevalent in males, with over half the patients under 40. Seropositive rheumatoid arthritis was significantly more common in females, with over half aged 50 or older. Cases of psoriatic and enteropathic arthropathies were fewer but have been increasing recently, with over half the patients aged 50 or older. In analyzing risk factors for dementia, including ankylosing spondylitis, advanced age, female sex, medical aid (social security type), and depression were associated with a higher incidence of dementia. Patients in the 4th income quartile had a lower incidence of dementia compared to those in the 1st quartile. Multivariate analysis incorporating dementia risk factors (hypertension, diabetes, dyslipidemia, depression) showed no significant correlation between a diagnosis of ankylosing spondylitis or the use of biologic agents and the occurrence of dementia. Similar results were observed when biologics for ankylosing spondylitis were categorized into TNF and non-TNF blockers.

For seropositive rheumatoid arthritis, risk factors for dementia included advanced age, female sex, medical aid, hypertension, and depression. Patients in the 2nd, 4th, and 5th income quartiles showed a lower incidence of dementia compared to the 1st quartile. Multivariate analysis revealed that a diagnosis of seropositive rheumatoid arthritis was associated with a higher risk of dementia (HR 1.10, 95% CI 1.02-1.20, p=0.0159). However, the group using biologic agents had a lower incidence of dementia compared to non-users (HR 0.46, 95% CI 0.33-0.65, p<0.0001). When distinguishing between TNF and non-TNF blockers, the diagnosis of seropositive rheumatoid arthritis remained associated with increased dementia risk (HR 1.10, 95% CI 1.01-1.19, p=0.0222). Notably, the group using non-TNF blockers showed a significantly lower incidence of dementia (HR 0.37, 95% CI 0.21-0.65, p=0.0005). In psoriatic and enteropathic spondylitis, depression was associated with a higher incidence of dementia. However, sex, social security type, income level, hypertension, diabetes, and dyslipidemia showed no significant association. Multivariate analysis also found no significant link between a diagnosis of these conditions or biologic use and dementia occurrence. No dementia cases were observed in the group aged 40 or younger. Categorizing biologics into TNF and non-TNF blockers yielded identical results. For ankylosing spondylitis patients, who are generally younger, subgroup analysis by age also showed no significant impact of the diagnosis on the occurrence of stroke or dementia.

Table. Risk Factors for Stroke in Patients with Seropositive Rheumatoid Arthritis (by Biologic Agent Type)

Category	Subgroup	HR	95% CI	p-value
Sex	ref: Male, Female	1.43	1.33–1.54	<.0001
Age Group	ref: ≤ 40s			
	50s	6.35	2.26–17.85	0.0005
	60s	44.08	16.47–117.98	<.0001
	70s and above	596.30	224.11–1586.57	<.0001
Social Security Type	ref: Health Insurance (Employee/Self-employed)			
	Medical Aid	1.54	1.34–1.77	<.0001
Income Level	ref: 1st Quartile			
	2nd Quartile	0.86	0.76–0.98	0.0270
	3rd Quartile	0.96	0.84–1.09	0.5290
	4th Quartile	0.81	0.72–0.91	0.0006
	5th Quartile	0.89	0.80–0.99	0.0384
Hypertension	ref: No, Yes	1.14	1.05–1.24	0.0016
Diabetes	ref: No, Yes	1.04	0.94–1.15	0.4411
Dyslipidemia	ref: No, Yes	0.91	0.83–0.99	0.0229
Depression	ref: No, Yes	1.39	1.28–1.51	<.0001
TNF Blocker	ref: Non-user, User	0.53	0.35–0.81	0.0033
Non-TNF Blocker	ref: Non-user, User	0.37	0.21–0.65	0.0005
Seropositive RA	ref: No, Yes	1.10	1.01–1.19	0.0222

Conclusions

In patients with seropositive rheumatoid arthritis (RA), the diagnosis itself was associated with an increased risk of dementia. However, the administration of biologic agents was shown to significantly reduce the incidence of dementia. In contrast, for patients with ankylosing spondylitis or psoriatic and enteropathic arthropathies, no significant association was found between the diagnosis or the use of biologic agents and the risk of dementia. These findings suggest that the impact of systemic inflammation and its treatment on cognitive decline may vary depending on the specific type of inflammatory arthritis.