Risk of premature cerebrovascular disease in patients with ankylosing spondylitis

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ABSTRACT

Objectives: Patients with ankylosing spondylitis (AS) are at an elevated risk for the development of coronary artery disease, but the risk cerebrovascular disease among these patients remains incompletely understood. We investigated the cerebrovascular risk profiles of patients with a cerebrovascular disease and AS and compared these profiles to those of cerebrovascular disease patients without AS. Methods: We retrospectively analysed 34 patients with ischemic cerebrovascular disease also diagnosed with AS and 597 controls without AS with respect to patient age, gender, cerebrovascular risk factors, and laboratory test results.

Results: AS patients were significantly younger than control patients in this study (56.2±13.5 years vs. 63.0±13.4 years, respectively; p=0.004). Logistic regression analysis did not indicate significant relationships between gender, cerebrovascular risk factors, and biochemical risk factors in AS patients, nor were any significant relationships found between erythrocyte sedimentation rate or C-reactive protein and biochemical risk factors. A low frequency of large-artery atherosclerosis and high frequency of small-vessel occlusion according to Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification were found in AS patients with stroke.

Conclusions: Among the population included in this study, patients with AS sought treatment for cerebrovascular disease were at a younger age compared to control patients without AS. Thus, our results indicate that AS patients have an increased risk for the premature onset of cerebrovascular disease. And the premature atherosclerosis may associate with the patients with AS. Furthermore, the high frequency of the small-vessel stroke subtype in AS patients indicates that small--vessel inflammation may be involved in the pathogenesis of vascular diseases in AS patients. Further prospective study with more samples will be needed to confirm this hypothesis.

Keywords: Cerebrovascular disease; anklyosing spondylitis; inflammatory factors; risk factors.

INTRODUCTION

Ankylosing spondylitis (AS) is a systemic inflammatory rheumatic disease that affects the axial skeleton, causing characteristic inflammatory back pain, and can lead to spinal immobility[1]. AS predominantly affects young adults, with a peak age of onset between 20 and 30yearsold, and AS is more prevalent in males[1].

Atherosclerosis is a chronic progressive disease and one of the main causes of vascular diseases[2]. Against a background of chronic inflammatory disease, such as in cases of AS, the development of atherosclerosis may be accelerated[3-5], and an association between premature atherosclerosis and chronic inflammatory disease has been demonstrated[6,7]. With regard to AS specifically, previous studies reported significant differences in morbidity, mortality, and risk factors such as diabetes mellitus, hypertension, and altered lipid profiles between cardiovascular disease patients with and without AS[8-10]. Moreover, additional studies have indicated that patients with AS likely have an elevated risk of developing coronary artery disease (CAD)[11-13].

Cardiovascular diseases share the same etiology related to atherosclerosis. However, the etiology of cerebrovascular disease is heterogeneous and may be related to atherosclerosis, vasculitis, and/or embolism. Some rheumatic diseases, such as polymyalgia rheumatica, were associated with higher risk of stroke[14-16]. It remains to be determined whether this is also true in cerebrovascular disease patients with AS. A few studies in the field of clinical neurology have compared the features of cerebrovascular disease between patients with

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AS and those without AS[14-16]. At present, there are no published studies comparing the cerebrovascular risk profiles of cerebrovascular disease patients with and without AS receiving treatment in the same hospital, likely due to the rarity of such cases.

In the present study, we investigated the cerebrovascular risk profiles of patients with a cerebrovascular disease and AS and compared these profiles to those of cerebrovascular disease patients without AS.

METHODS

This project was reviewed and approved by the Research Ethics Committee of Chinese PLA General Hospital. The need for informed consent was waived because the data used consisted of de-identified secondary data released for research purposes and were analysed anonymously.

In this cross-sectional study, we reviewed the records of 34 consecutive patients with ischemic cerebrovascular disease who met the 1984 modified New York diagnostic criteria for AS and who were treated at our hospital between January 1, 2004 and January 31, 2014. The diagnoses of cerebrovascular diseases were confirmed by magnetic resonance imaging results. Control subjects were recruited at the same hospital, and the control group consisted of consecutive ischemic cerebrovascular disease patients seen between January 1, 2013 and January 31, 2014 and diagnosed based on MRI. Patients were excluded based on the following criteria: hereditary dyslipidemia, other autoimmune disease, active infection at the time of assessment, liver or renal disease, malignancy, pregnancy, or lactation.

The clinical records of patients in the AS group and the control group were analysed retrospectively, and the following data were recorded for each case: patient's age at cerebrovascular disease onset, gender, body mass index (BMI), personal history of cardiovascular disease, family history of premature ischemic heart disease, and other cerebrovascular risk factors (including hypertension, diabetes mellitus, and smoking status), stroke subtype, laboratory findings including serologic tests (e.g., homocysteine [HCY], haemoglobin A1c [HbA1c], total cholesterol [TC], low density lipoprotein [LDL], high density lipoprotein [HDL], triglycerides [TG], apolipoprotein AI[ApoAI], ApoAII, ApoB, ApoE, lipoprotein (a) [Lp(a)], erythrocyte sedimentationrate [ESR], and C-reactive protein [CRP]). The atherogenic index (TC/HDL) and ApoB/ /ApoAI ratio were also calculated.

The stroke subtypes were classified according to the original TOAST, including large-artery atherosclerosis, cardioembolism, small-vessel occlusion, stroke of other determined cause, and stroke of undetermined cause[17].

Comparisons were performed using two sample t-tests for parametric values, Wilcoxon Mann-Whitney tests for non-parametric values, and Chi-square tests for categorical values. Based on the results of univariate analysis, binary logistic regression was used to identify risk factors. Correlation analyses were performed with Pearson's or Spearman's rank order correlation coefficients, where appropriate, while a comparison for confounding factors was made using binary logistic regression analysis. For all tests, *p*-values less than 0.05 were considered significant. Data are presented as mean ± standard deviation unless otherwise noted. Statistical analysis was performed using SPSS 16.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Thirty-four AS patients and 597 control patients were included in the analysis. The patients' characteristics are shown in Table I. With an average age of 56.2±13.5 years (range, 33.4–83.4 years), AS patients were significantly younger than the control patients without AS (63.0±13.4 years; range, 18.25–90.05 years; p=0.004). However, the patient groups with and without AS did not differ in terms of gender. AS patients had a slightly, but not significantly (p = 0.347), lower BMI than control patients, and the mean BMI values for both groups were in the overweight range. The frequencies of current smoking, hypertension, and diabetes mellitus were similar among patients with and without AS (Table I).

The prevalence of LAA was significantly lower in the AS group than in the control group, whereas the prevalence of SVO was significantly higher in the AS group than in the control group. Stroke subtype of AS group was significantly different than control group (p=0.047).

With regard to biochemical cerebrovascular risk factors, AS patients had significantly higher levels of TC, HDL, and ApoAI (p<0.05). In contrast, HCY, LDL, atherogenic index, and ApoB/ApoAI did not differ significantly between patients with and without AS

TABLE I. EPIDEMIOLOGICAL, ANTHROPOMETRIC, AND CLINICAL CHARACTERISTICS, AS WELL AS CEREBROVASCULAR AND BIOCHEMICAL RISK FACTORS, IN THE AS AND THE CONTROL GROUPS

Parameter	AS group	Control group	p
N	34	597	-
Male, %	76.5%	71.0%	0.494
Age, years	56.2±13.5	63.0±13.4	0.004
BMI, kg/m2	24.8±4.1	25.3±3.4	0.347
ESR, mm/h	24.63±25.35	–	–
CRP, mg/L	2.62±3.44	–	–
Current smokers, %	35.3%	40.4%	0.552
Hypertension, %	58.8%	72.5%	0.084
Diabetes mellitus, %	29.4%	34.7%	0.108
Personal history of cardiovascular disease, %	32.4%	28.6%	0.642
HCY, µmol/L	13.79±5.72	16.71±9.79	0.112
HbA1c, %	6.67±2.64	7.92±19.07	0.749
TC, mmol/L	4.58±1.27	4.16±1.10	0.037
TG, mmol/L	1.84±1.68	1.55±1.21	0.338
HDL, mmol/L	1.20±0.39	1.07±0.30	0.022
LDL, mmol/L	2.76±1.08	2.49±0.90	0.096
TC/HDL	4.17±1.69	4.06±1.22	0.739
ApoAI, mmol/L	1.26±0.27	1.15±0.26	0.034
ApoAII, mmol/L	26.31±5.10	24.23±6.95	0.223
ApoB, mmol/L	0.86±0.28	0.83±0.23	0.479
ApoB/ApoAI	0.72±0.29	0.75±0.25	0.540
ApoE, mmol/L	3.95±1.47	4.65±2.95	0.300
Lp(a), mmol/L	27.69±34.61	23.84±19.44	0.578
Stroke subtype-LAA	28.6%	49.0%	0.047*
Stroke subtype-CE	5.7%	5.5%	
Stroke subtype-SVO	57.1%	34.3%	
Stroke subtype-Others	8.6%	11.2%	

Abbreviations: AS, ankylosing spondylitis; BMI, body mass index; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LAA, large-artery atherosclerosis; CE, cardioembolism; SVO, small-vessel occlusion; HCY, homocysteine; HbA1c, hemoglobin A1c; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoAI, apolipoprotein AI; ApoAII, apolipoprotein AII; ApoB, apolipoproteinB; ApoE, apolipoproteinE; Lp(a), lipoprotein (a).
*Contingency table-based chi square test for stroke subtype shown in the table.

(Table I).

A subsequent binary logistic regression model, in which AS was the dependent variable and the variables with significant difference in univariate analysis (including age, stroke subtype, TC, HDL, and ApoAI) were entered as independent variables showed that age and stroke subtype (SVO vs. LAA) were independently associated with AS (Table II). Only age (odds ratio [OR]=1.041) was found to be significant variables.

Among the AS patients, there were no significant relationships between ESR or CRP and biochemical risk factors (Table III).

DISCUSSION

In this study, we evaluated the prevalences of the major cerebrovascular risk factors in patients with AS in comparison with those in a control group of patients without AS. Although the number of AS patients with a cerebrovascular disease included in our study was small due to the rarity of such cases, the mean age of these patients was significantly less than that of patients without AS. Thus, our results demonstrate the premature onset of cerebrovascular disease in AS patients. In a study comparing AS patients with the general popu-

TABLE II. RESULTS OF LOGISTIC REGRESSION ANALYSIS OF PATIENTS WITH AND WITHOUT AS

Model	B	SE	Wald	p	OR (95% CI)
Age	0.040	0.015	6.888	0.009	1.041 (1.010–1.072)
Stroke subtype (CE vs LAA)	-0.646	0.823	0.616	0.432	0.524 (0.105-2.629)
Stroke subtype (SVO vs LAA)	-0.887	0.437	4.126	0.042	0.412 (0.175-0.969)
Stroke subtype (Others vs LAA)	0.992	1.077	0.849	0.375	2.698 (0.327-22.266)
Constant	0.940	0.923	1.035	0.309	2.559

Abbreviations: B, regression coefficient; SE, standard error; OR, odds ratio; 95% CI, 95% confidence interval

TABLE II. ASSOCIATIONS BETWEEN INFLAMMATORY MARKERS AND BIOCHEMICAL PARAMETERS AMONG 34 PATIENTS WITH AS

	CRP		ESR	
	Correlation coefficient	p	Correlation coefficient	p
HCY	0.209	0.296	0.189	0.155
TC	0.115	0.553	-0.247	0.268
TG	-0.051	0.793	-0.314	0.155
HDL	-0.184	0.340	-0.317	0.150
LDL	0.098	0.613	-0.130	0.563
TC/HDL	0.117	0.547	-0.059	0.793
ApoAI	-0.007	0.973	-0.353	0.138
ApoB	0.327	0.111	0.216	0.375
ApoE	0.022	0.929	0.252	0.365
Lp(a)	0.189	0.389	0.574	0.116

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; HCY, homocysteine; TC, total cholesterol; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ApoAI, apolipoprotein AI; ApoB, apolipoproteinB; ApoE, apolipoproteinE; Lp(a), lipoprotein (a).

lation, AS patients were found to be at an increased risk for cerebrovascular diseases, and the excess risk is greatest in younger patients with AS[14-16]. Therefore, the results of our present study are in agreement with those of studies in AS patients with cardiovascular disease[6,10,11,13,18,19].

In the present study, there were no differences in smoking status, hypertension, or diabetes mellitus between patients with and without AS. However, different results were reported by other studies of AS patients with cardiovascular disease, such as higher prevalences of smoking[20, 21], hypertension[10, 21, 22], and diabetes mellitus[10, 22].

Regarding the lipid profile, in this study, patients with AS had significantly higher levels of TC, HDL, and ApoAI. However, the logistic regression analysis did not indicate significant differences in these markers. Notably, the AS patients in our study were on average younger than the control patients, and if the mean ages of the groups had been more similar, the results regarding lipid levels may have been completely different. Moreover, similar inconsistencies have been reported for AS patients with cardiovascular disease, specifically in relation to lower levels of TG[8,21], TC[8,23,24], ApoB[8], LDL[9,24], ApoE[8], Lp(a)[8], and HDL[8,9,21]; a higher TC/HDL ratio[9,21]; and no change in serum LDL and HDL[24,25]. In addition, intensive lipid-lowering therapy with a statin achieved comparable lipid-lowering effects in patients with and without AS[23].

The controversial results related to vascular risk factors in AS patients may hint that these factors are not key indicators of premature cardiovascular or cerebrovascular disease. Traditional cardiovascular risk factors are involved in the pathogenesis of vascular diseases in AS patients, but such alterations cannot completely explain the enhanced vascular risk in AS patients[26,27].

The stroke subtype according to the TOAST criteria was a determined etiologic classification[17]. We found significant differences in the frequencies of TOAST classifications (low frequency of large-artery atherosclerosis and high frequency of small-vessel occlusion) in AS patients with stroke, but multivariate analysis showed that the small-vessel stroke subtype was independently associated with AS. This may indicate that the factors that resulted in small-vessel stroke are involved in the pathogenesis of vascular diseases in AS patients, such as small-vessel inflammation. Of cause the age either influence the consisting of stroke subtype.

The relationships between inflammatory mediators and lipid profiles have been explored, and no significant correlations were identified in our present study.

However, circulating inflammatory mediators such as interleukin-6, tumor necrosis factor-alpha, and CRP have been shown to negatively affect endothelial function, ultimately leading to endothelial dysfunction[9]. Previous studies of vascular structures in patients with AS have shown impaired endothelial function[28,29]. Moreover, other studies have reported that treatment with tumor necrosis factor-alpha inhibitors may improve reduce the inflammatory response to improve microvascular dysfunction[30] and promote endothelial function[31,32].

HCY levels did not differ between patients with and without AS. However, the disproportionate frequency of a methylenetetrahydrofolate reductase (C677T) gene polymorphism in patients with AS compared to those without AS may provide a potential prognostic factor for AS[33].

Cyclooxygenase-2 selective inhibitor has been used to treat patients with inflammatory rheumatic diseases and has been associated with an increased incidence of cardiovascular events in recent clinical trials and observational studies[34]. Therefore, such a drug may not be a suitable for treating AS patients with a vascular disease. Also, nonselective nonsteroidal anti-inflammatory drugs, such as aspirin, may achieve a better response than cyclooxygenase-2 selective inhibitor in patients with AS.

Finally, a previous study reported that AS disease activity, functional and mobility limitations, and structural damage may be the most influential risk factors for the premature onset of vascular diseases among AS patients[3].

With the combination of AS and stroke being a rare medical condition, only a few related reports have been published, and the sample sizes of these studies were small, just as in our study. Other limitations of our study include the retrospective nature and the fact that it was a single center study. A prospective, multi-center study with a larger sample size is needed to confirm our findings. Moreover, disease activity and treatment of AS should be considered in the study.

CONCLUSION

Cerebrovascular patients with AS were found to be significantly younger than matched patients without AS. Our results indicate that AS patients may be more likely to experience premature onset of cerebrovascular disease than patients without AS, and the lack of significant difference in traditional risk factors between the two groups suggests that premature atherosclerosis occurs in patients with AS. Also, the high frequency of the small-vessel stroke subtype in AS patients suggests that small-vessel inflammation may be involved in the pathogenesis of vascular diseases in AS patients. A further prospective study with more samples will be needed to confirm this hypothesis. The disease activity and treatment of AS should be included in this study.

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