ORIGINAL ARTICLES

Clinical characteristics of ischemic stroke in patients with positive ANCA

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Abstract

Objective: To explore the clinical characteristics and recurrence rate of ischemic stroke in patients with antineutrophil cytoplasmic antibody (ANCA) , to improve the early diagnosis of these patients, so as to take effective measures to control the progress of the disease and reduce the mortality. *Methods:* A retrospective analysis of the ischemic stroke patients with ANCA positive and negative status from the neurology department, Baoding No. 1 Central Hospital, Hebei, China. *Results:* The prevalence of ANCA in 1,297 ischemic stroke patient was 10.10%. The rate of recurrence of ischemic stroke in ANCA positive group was significantly higher than that in ANCA negative group (70.99% vs 35.08%, p < 0.05). The proportion of small-artery occlusion in ANCA positive group was also significantly higher than that in ANCA negative group (33.59% vs 21.96%, p=0.003). The proportion of respiratory tract infection in ANCA positive group (54.96%) was higher than that in ANCA negative group (p < 0.05). The proportion of pulmonary interstitial lesions detected by chest CT in the ANCA positive group was also significantly higher (33.59%) than the ANCA negative group (P < 0.05).
Conclusion: ANCA positive etiology accounts for about 10% of ischemic stroke. There is higher rate of recurrent stroke and small artery occlusion. .

Keywords: ANCA, recurrence of ischemic stroke, respiratory tract infection, pulmonary interstitial lesions

INTRODUCTION

ANCA, an important member of autoantibody family, is an immunoglobulin secreted by B lymphocytes in response to various components of neutrophil cytoplasm.[1] After the immune response between ANCA and the target antigen, the neutrophil structure is damaged, and a variety of biologically active substances are released, leading to degeneration and necrosis of endothelial cells, muscle cells and surrounding tissues of the blood vessel wall, resulting in vasculitis.[2] Vasculitis is not only the basic lesion of vascular disease, but also the pathological basis of the progression of the disease. Early detection of ANCA is of great significance for early prevention and treatment of vasculitis related chronic diseases.[3-5]

ANCA-associated vasculitis (AAV) can involve a wide range of disease of peripheral nerves, when it involves the nervous system. Its pathogenesis may be related to the decrease of T cell immune function, the increase of humoral immune response, the decrease of red cell immune function, the involvement of cytokines in inflammation and brain injury.[6-8] The neurological lesions of AAV are often neglected in clinical practice, which leads to missed diagnosis and loss of opportunity for early treatment. Although there have been previous reports of clinical manifestation of AAV in ischemic stroke[9-10], there are few comprehensive clinical studies on neurological characterization of AAV. Therefore, we undertake this retrospective study in our Department of Neurology, to determine the clinical characteristics of ANCA positive ischemic stroke patients to facilitate early intervention.

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METHODS

The study population consisted of 1,297 patients with ischemic stroke in the Department of Neurology from January 2018 to January 2020. The study was approved by the Ethics Committee of Baoding NO.1 central hospitals, and informed consent was acquired from the patients or caregivers.

All cases of ischemic stroke fulfilled the diagnostic criteria revised by the Fourth National Cerebrovascular Academic Conference[11], and were confirmed by head computed tomography (CT) and magnetic resonance imaging (MRI) examination. The diagnostic criteria for recurrent ischemic stroke were: 1. There was a clear past history of ischemic stroke, with recent aggravation of the original symptoms and signs, and the time from the first cerebral infarction was more than one month; or 2. New symptoms and signs of neurological impairment were found; and 3. The above conditions were confirmed by head CT and MRI.

The main complaint, past medical history, physical examination, laboratory and imaging examinations in the ANCA positive group were retrospectively analyzed and compared with ANCA negative group. ANCA testing was done by standard indirect immunofluorescence assay on ethanol fixed neutrophils.

The common risk factors of ischemic stroke are hypertension, diabetes, hyperlipidemia were noted. There was no significant difference in the proportion of hypertension, diabetes and hyperlipidemia between ANCA positive group and ANCA negative group in patients with ischemic stroke. There is comparability between the two groups.

According to TOAST criteria[12], patients with ischemic stroke were divided into the following subtypes: Large-artery atherosclerosis (LAA); Cardiogenic embolism (CE); Small-artery occlusion (SAO); Stroke of other determined etiology (SOE) and Stroke of undetermined etiology (SUE). Because there were very few patients with SOE subtype, patients with SOE subtype and SUE subtype are combined into one group and defined as other determined and undetermined etiologies. The Other subtypes will not be discussed in this study.

Statistical analysis

Statistical analysis was conducted using SPSS Version 19.0 software (IBM Corp., Armonk, NY,USA). p<0.05 was considered as statistically significant. Comparison of counting data between groups using χ2 test.

RESULTS

The patients consisted of 796 males and 501 females, with an average age of 62.25 ± 12.08 year (range 26-92).

Detection of ANCA in patients with ischemic stroke

In the 1,297 patients with ischemic stroke, the proportion of positive ANCA patients was 10.10% (131/1297). Of the ANCA positive patients, there were 78 males and 53 females, males: females = 1.47:1, with an average age of 63.91±12.36 year (age range 26-89).

In the 1,297 patients with ischemic stroke, 1,166 were ANCA negative. Of these ANCA negative group, there were 718 males and 448 females, males : females = 1.60:1, with an average age of 61.54 ± 13.18 year (range 31-92).

Relationship between ANCA status and recurrence of ischemic stroke

Among the 131 ANCA positive patients, 93 patients have recurrent ischemic stroke, accounting for 70.99%. Among the 1,166 ANCA negative patients, 409 patients have recurrent ischemic stroke, accounting for 35.08%. There was significant difference between the ANCA positive group and the negative group with higher stroke recurrence among the ANCA positive patients, χ2=64.03, p<0.05 (Table 1).

Relationship between ANCA status and TOAST classification of ischemic stroke

According to the TOAST classification of the 1,297 patients with ischemic stroke, there were

Table 1: Analysis of ischemic stroke in ANCA positive group and negative group

Occurrence of ischemic stroke	ANCA positive group	ANCA negative group	X^2	P
At onset only	29.01%(38/131)	64.92%(757/1166)		
Recurrence	70.99%(93/131)	35.08%(409/1166)	64.03	<0.05

44 cases of SAO subtypes in the ANCA positive group, accounting for 33.59% (44/131). There were 256 cases of SAO subtypes in the ANCA negative group, accounting for 21.96% (256 / 1166). There was significantly higher proportion of SAO among the ANCA positive as compared to ANCA negative group, $\chi2$=8.96, p<0.05 (Table 2).

Comparison of past clinical manifestations between ANCA positive group and ANCA negative group

Based on the investigation and analysis of the chief complaint, medical history and physical examination of the patients, we found that there were 72 cases of respiratory tract infection in the ANCA positive group in the past year (72/131, 54.96%). Among the 1,166 cases in the ANCA negative group, respiratory tract infection occurred in 436 cases (37.39%). There was thus significantly incidence of past respiratory infection among the ANCA positive group versus the ANCA negative group, $\chi^2 = 15.26$, $p < 0.05$ (Table 3).

Analysis of imaging data of ANCA positive group and negative group

The imaging data of cranial magnetic resonance imaging (MRI) and chest CT of the stroke patients was analysed. There was significantly higher proportion of pulmonary interstitial lesions in ANCA positive group (44/131. 33.59%), when compared to ANCA negative group (294/1166, 25.21%; $\chi^2 = 4.29$, $p < 0.05$) (Table 4).

DISCUSSION

AAV is an autoimmune disease involving various systems. The clinical manifestations of the AAV are diverse and often nonspecific, which often leads to misdiagnosis. Some studies have shown that AAV patients are more commonly seen in the respiratory and nephrology services with respiratory and urinary symptoms. The number of AAV patients with neurological symptoms is thought to be less common often with delay in diagnosis[13], which may affect its prognosis. It is therefore necessary to understand better the clinical spectrum of the neurological involvement of AAV, so as to facilitate its early diagnosis and treatment.

Based on the results of the current study, it was found that the prevalence of ANCA was 10.10%, which was close to our previous study of 7.69%.[14] In Zhu et al.'s[15] study, the prevalence of ANCA in patients with ischemic stroke was 14%, which was also in the same range.

Table 2: Relationship between ANCA status and TOAST classification of ischemic stroke

TOAST subtypes	ANCA positive group	ANCA negative group	X^2	*p*
LAA	45.80%(60/131)	37.48%(437/1166)	3.45	>0.05
SAO	33.59%(44/131)	21.96%(256/1166)	8.96	<0.05
CE	4.58%(6/131)	4.03%(47/1166)	0.09	>0.05

Table 3: Comparison of clinical manifestations between ANCA positive group and ANCA negative group

	ANCA positive group	ANCA negative group	X^2	*p*
Respiratory tract infection	54.96%(72/131)	37.39%(436/1166)	15.26	<0.05
Gastrointestinal symptoms	5.34%(7/131)	3.09%(36/1166)	0.12	>0.05
Urinary tract infection	6.11%(8/131)	4.46(52/1166)	0.65	>0.05

Table 4: Comparison of imaging data between ANCA positive group and ANCA negative group

	ANCA positive group	ANCA nagative group	X^2	*p*
Pulmonary nodule	29.78%(39/131)	26.59%(310/1166)	0.61	>0.05
Pulmonary interstitial lesions	33.59%(44/131)	25.21%(294/1166)	4.29	<0.05
Sinusitis/Paranasal sinusitis	9.16%(12/131)	8.50%(99/1166)	0.06	>0.05

Pulmonary interstitial disease mainly refers to pulmonary interstitial changes, pulmonary lobular subpleural interstitial changes, pulmonary interstitial fibrosis.

Our study also found that the recurrence rate of ischemic stroke in ANCA positive patients was significantly higher than that in ANCA negative patients. It may be that there was continuing change to the blood coagulation, and damage to the endothelium of the cerebral vessels. Our study showed that according to TOAST classification, the proportion of SAO subtypes in ANCA positive patients was higher than that in ANCA negative patients. This suggest that the damage to the endothelium may be predominantly in the small vessels. Perhaps the damage of vascular endothelial function and structure leads to the damage of endothelial self-regulation and the inability of vascular dilatation to maintain perfusion.[16] With the replacement of connective tissue, the vascular wall gradually thickens, eventually leading to lumen stenosis, thrombosis and occlusion.[17] Recurrent infarct is an important pathogenesis of the decline in cognitive function, paralysis, difficulty in speech and swallowing, and decreased self-care ability, with impaired function imposing increased burden to the patients and families. Early intervention is thus of great importance.

The mechanism of ANCA production is believed by most investigators to be related to infection.[18] This study found a significantly increased chronic respiratory infection in patients with ANCA positive ischemic stroke patients. The association between chronic infection of the respiratory system and ANCA positive status is thus supported by this study.

Pulmonary interstitial lesions are closely associated with AAV.[19-21] When there is pulmonary interstitial lesion, even when the ANCA is negative, the vasculitis cannot be ruled out. It has been reported that a patient with pulmonary interstitial fibrosis and ANCA-negative status was positive for ANCA after 16 months of follow-up.[22] Therefore, those with pulmonary interstitial disease should have their ANCA repeated during follow up.

In conclusion, AAV associated with central nervous system manifestation is likely to have damage to their vascular endothelium from vascular inflammation, leading to vascular wall fibrous hyperplasia, thrombus, and acute cerebrovascular disease.[13] Though treatment with hormone and immunosuppressant may result in clinical improvement, the condition carries an increased mortality.[23] Therefore, clinicians should be aware of ANCA as an important etiology cause of ischemic stroke.

DISCLOSURE

Conflict of interest: None

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