Association between infection with Chlamydia pneumonia and cerebral noncardioembolic ischemic stroke

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Abstract

Introduction: Stroke is the third most common cause of mortality and the most common disability disorder among adults. We aimed to study the relationship between Chlamydia pneumonia infection and non-cardio Ambulatory ischemic stroke.

Methods: This case-control study was performed on 162 patients with non-cardio ambulatory ischemic stroke admitted to Shahid Beheshti Hospital of Kashan in 2019 as the case group and patients with neurological headache and degenerative diseases as the control group. After filling out the questionnaire for all subjects, we took blood samples. We analyzed all three anti-chlamydia pneumonia antibodies (IgM, IgG, IgA) by ELISA method after data were analyzed by Chi-square and Fisher tests.

Results: The findings of this study showed that positive IgA in the stroke group was significantly higher than in the control group (p=0.001); it was also found that the risk factors of HTN (p=0.001), HLP (p=0.001), DM (p=0.001), and age (p = 0.049) were significantly higher in the stroke patients' group than the control group. On the other hand, there was not a significant difference in serum IgG level (p = 0.349), IgM (p = 0.745), smoking (p = 0.211) and gender (p = 0.157) in understudied groups.

Conclusion: Chlamydia IgA antibodies can be a complementary tool for predicting prognosis and monitoring new therapies for ischemic stroke. This study provides a way for further studies, especially with other markers of acute and chronic systemic Chlamydia pneumonia infection. Antibiotic treatment significantly helps to reduce mortality and stroke complications.

Keywords: Non-Cardioembolic, Stroke, Atherosclerosis, Antibody, Infection, Chlamydia

Introduction

Strokes are the third leading cause of death and the most common debilitating brain and nerve disorder among adults (1). Despite a decrease in stroke prevalence in recent decades, mainly due to improvements in the treatment of high blood pressure, stroke continues to rank first among brain and neurological diseases in adults. Some studies have proven that atherosclerosis plays an essential role in the development and prognosis of this disease. The risk factors of this disease are similar to atherosclerosis, including diabetes, smoking, hypercholesterolemia, etc. (2). These risk factors cannot fully explain the pathogenesis of this disease. Many patients, especially young people, do not have these risk factors (3).

Chronic viral and bacterial infections have been shown in recent decades to contribute to the development of atherosclerosis lesions (4). Chlamydia pneumonia is one of the pathogens that has received more attention (5). Chlamydia pneumonia is a Gram-negative bacterium that causes respiratory disease in humans. Approximately 30-50% of people worldwide have antibodies against this bacterium (6). There is evidence linking Chlamydia bacteria to coronary arteries and cerebral vessel atherosclerosis. Several serological studies have demonstrated this bacterium's role in atherogenic processes of brain vessels, including phospholipid antibodies, oxidation of LDL, and smooth muscle proliferation (7).

It should be noted that Chlamydia pneumonia is often not considered the cause of respiratory infection, and common treatments for other respiratory infections are not effective against this bacterium (8). Infection with Chlamydia pneumonia has been linked to cerebrovascular events and stroke in many studies. These studies have reported conflicting results.

A study conducted for this purpose showed that the positivity of IgG against Chlamydia pneumonia has a significant relationship with stroke (9). Also, in a study similar to the previous research, it was observed that the positivity of anti-chlamydia pneumoniae IgG does not have a significant relationship with stroke. At the same time, there is a significant relationship between the positivity of anti-chlamydia pneumoniae IgA and stroke (10).

In contrast to these mentioned studies, there are also studies in which it was reported that there is no significant relationship between cerebrovascular infarcts and chlamydia pneumonia infection (11). As a result of the importance of the stated content and conflicting findings, the study was designed to investigate whether Chlamydia pneumonia infection may be associated with non-cardioembolic ischemic strokes. To improve the quality of diagnosis, treatment, and prevention of diseases.

Materials and Methods (Patients and Methods for clinical investigations)

Selection and Description of Participants

This case-control study was conducted on 162 patients admitted to Shahid Beheshti Hospital in Kashan in 2018. We divided the patients into two groups for one year, the case group with non-cardioembolic ischemic stroke(based on the clinical features confirmed by the neurologist) and the control group of patients with nervous headache, discopathy and degenerative diseases. A neurologist examined the patients in the case and control groups, and patients with acute respiratory infections and immune system diseases were excluded from the study. A checklist and a questionnaire were used to collect information from documents (files) and laboratory results.

After filling out the questionnaire for each patient, a blood sample (3 ml) was sent to one laboratory, and each of the blood samples was tested for all three types of anti-chlamydia pneumoniae antibodies (IgM, IgG, IgA) by ELISA method with the Vircell kit (13) was examined by one person. Then, the relationship between antibodies and the incidence of non-cardioembolic ischemic stroke was investigated with statistical methods.

Statistical analysis

First, we described the variables of both groups. We presented centrality and dispersion indices for quantitative variables. A Chi-square test and a Fisher test were used if necessary to analyze the data.

Results

A total of 70 men (40 cases and 30 controls) and 92 women (42 cases and 50 controls) participated in the study with (Total mean age of 61.80±15.13), and 82 people in the case group with a mean age of 71.56±9.80, and 80 people in the control group with a mean age of 51.80±12.96 (Table-1). The present findings showed a significant difference between age and treatment groups (p=0.049), such that the age of the case group was higher than the control group. Still, there was no significant difference between the average BMI and gender in the treatment groups (p=0.104).

Table 1. Mean and standard deviation of age and BMI

	groups	numbers	mean	SD	Sig
BMI	Case	82	26.26	2.70	0.104
	Control	80	23.23	2.46	
Age	Case	82	71.56	9.80	0.049
	Control	80	51.80	12.96	

The prevalence of IgG (p=0.349) and IgM (p-value=0.745) had no significant difference with treatment groups and gender. Still, positive IgA was significantly more in the case group than in the control group (p-value=0.001), and there was a significant difference between IgA and male (p=0.001) and female patients (p=0.018).

The prevalence of DM (Diabetes mellitus), HLP(Hyperlipidemia), and HTN was significantly more in the case group than in the control group (p=0.001) and had a significant difference in both genders, but smoking between treatment groups and also with gender had not a significant difference (p=0.211)(Table-2).

Discussion

The present survey findings showed that positive IgA was significantly higher in the case group than in the control group. It was also found that HTN, HLP, DM, and age risk factors were significantly higher in the case group than in the control group. Meanwhile, there was no significant difference in the serum levels of IgG, IgM, smoking, and gender in the studied groups.

Several studies have found an association between chlamydia pneumonia infection and stroke that infection with Chlamydia pneumonia increases the risk of brain disease, but others have not (11-12). The difference in these results may be due to the different sample sizes in other studies, the difference in the age of the participants in the current study, or the various detection methods for chlamydia pneumonia infection. In another study, chlamydia pneumonia infection was determined by CP-DNA PCR, whereas we checked

antibodies by ELISA (14); it is important to note that by measuring IgG or only one antibody, there can be no difference between recent infection and past infection, whereas PCR and IgM are more reliable tests that have higher sensitivity and specificity (15-16).

According to the studies that accompanied our study, it can be said that increased IgA antibodies are a sign of acute recurrent infections and, in these patients, create conditions for an acute

Table 2. The Demographic Characteristics of Ischemic Stroke Patients and Control Subjects

		Case group	control	p-value
Gender/Male		40(57.1%)	30(42.9%)	0.157
Gender/female		42(45.7%)	50(54.3%)	0.157
BMI(kg/m2)	0.5<BMI<18	0	1(100%)	**0.001**
	18.5<BMI<24.99	32(23.7%)	63(66.3%)	
	BMI>25	50(75.8%)	16(24.2%)	
DM*		48(76.2%)	15(23.8%)	**0.001**
Smoking use		25(59.5%)	17(40.5%)	0.211
HLP**		29(85.3%)	5(14.7%)	**0.001**
HTN***		54(76.1%)	17(23.9%)	**0.001**
CP-IgM****		0	1(100%)	0.745
CP-IgG		8(38.1%)	13(61.9%)	0.349
CP-IgA		16(84.2%)	3(15.8%)	**0.001**

DM, Diabetes mellitus ; HLP, Hyperlipidemia; HTN, Hypertension; CP, Citrullinated Peptides; IGM, ImmunoglobulinM

ischemic event in association with other risk factors for atherosclerosis, while Chlamydia pneumoniae IgG antibody is considered a "chronic" infection marker, it can remain in the circulation for 3-5 years after infection (17).

According to our results, there is no significant association between Chlamydia pneumoniae infection with IgM and IgG antibodies, while according to another retrospective study, patients with other atherosclerotic disorders (acute coronary syndrome) had significantly higher serum levels of anti-chlamydia IgM and not IgG or IgA than patients with ischemic heart disease or the control group (18), while in our study, anti-chlamydia IgA titers were significantly higher, which indicates acute chlamydia pneumonia infection with immune reactions that contribute to the pathophysiology of acute ischemic attack.

Evidence has shown that inflammatory immune reactions are effective in the pathogenesis of cerebral ischemia. It has been reported that Neopterin, which is known as a sensitive marker for diseases associated with increased activity of the cellular immune system, is increased in patients with systemic inflammatory strokes at the time of ischemic stroke (19).

Given that IgA is an antibody that plays a role in mucosal immunity, Chlamydia pneumonia plays a vital role in increased systemic inflammation and vascular damage by the immune system, changing lipid metabolism, and inducing the production of cytokines and lipoproteins. Therefore, the IgA

antibody of Chlamydia pneumonia is linked with inflammatory biomarkers, and Chlamydia pneumonia can produce a large amount of HSP 60 in chronic and persistent infections, leading to close coordination between the acute phase antibody with the incidence of strokes (20).

Another study showing the association of Chlamydia with raised CRP in stroke patients lends more credence to the hypothesis that acute or chronic Chlamydia pneumoniae infection may be associated with atherosclerosis through inflammatory mechanisms (21). Nabipour et al., who studied the relationship between metabolic syndrome and infections, concluded that chronic inflammation and increased CRP levels are common pathways in metabolic syndrome and infectious agents to advance the atherosclerotic process. HSV-1, CMV, Helicobacter pylori, and Chlamydia pneumonia induce the production of pro-inflammatory cytokines, such as TNF-alpha and IL-6, leading to subclinical chronic inflammation, insulin resistance, and metabolic syndrome (22).

Previous studies reported that C.pneumoniae seropositivity is most prevalent in strokes caused by large artery atherosclerosis but less prevalent in strokes caused by small-vessel occlusions(23). According to two metanalyses, IgG and IgA positivity confirms the role of C pneumonia in the development of atherosclerosis. Still, our study found no significant relationship between CVA and IgG and IgM. It could be due to the limitations of our study (24-25).

Similar to the present study and previous studies(26-27), a case-control study by Srivastava et al. (28) showed that acute infection with Chlamydia pneumoniae (IgA antibody) is associated with acute ischemic stroke in young patients under 45 years of age, in our study the average age of the subjects was The case group was 61 years old.

In other studies, the relationship between Chlamydia pneumoniae and atherosclerosis was investigated; they found that 42% of men under 50 years of age and 45% of men over 50 years of age with persistently high IgG and IgA antibodies indicating chronic C. pneumoniae infection and were overweight (bmi>28) were consistent with the study that 50 people in the BMI case group had a BMI higher than 25. (29). In another study confirming this finding, the relationship between c. pneumonia and BMI has been discussed, which considers the hypotheses for this relationship as probable, that these findings may not have a causal relationship. Still, the production of hyperinsulinemia and an increase in body mass index and male gender may be Causally associated with infection with C pneumonia. High BMI is most commonly associated with infection, which can be caused by immunodeficiency and low socioeconomic status in individuals with high BMI (30).

Our findings support the theory that inflammation and secondary immune response to acute infection with Chlamydia pneumonia may be the triggering factor in acute stroke manifestation in some stroke patients.

Conclusion

Chlamydia IgA antibody can be a helpful marker to predict prognosis and monitor new treatments in ischemic stroke. Antibiotic treatment as an effective measure in the prevention of Stroke is considered in high-risk people and significantly helps to reduce mortality and complications from a stroke.

Limitation

Our study did not perform phenotypic classification of strokes, so we could not compare these types with Chlamydia pneumonia titers. Different types of clinical and neurological markers can be used to predict stroke severity. The role of inflammatory mediators may have added value to predicting stroke severity indices.

On the other hand, in the present study, stroke severity was not measured based on the NIHSS(National Institutes of Health Stroke Scale). The diagnosis of stroke was based on clinical findings, and the control group probably had subclinical levels of vascular occlusion, and another limitation of our study includes not adjusting the final results for BMI, DM, HLP, and HTN basis. Conflict of Interest:

Acknowledgment

Declaration

The authors declare that they have no conflict of interest

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Ethical approval

Ethical considerations in this study included obtaining permission from the Ethics Committee of the Kashan University of medical science (IR.KAUMS.REC.1395.39) and obtaining written consent to participate in the survey from the participants.

Patient consent

Patients were introduced to the importance of the study and were willing to participate after being informed of its importance. Since all patients had health insurance, the laboratory tests in the hospital were free, and their files remained confidential.

Authors contribution

SAM, SAAA, EK, and MH contributed substantially to the idea, and ZH MH and SAAA analyzed and interpreted the data. JA, SAAA, SAM, and MH approved the draft of the work and critical revision. SAAA's revised article and final version for publication.

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