

## Association between *Chlamydia pneumoniae* IgG antibodies and migraine

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**Abstract** In this study, there is a confirmed association between cerebral infarction with migraine and *Chlamydia pneumoniae* infection, but the association between *C. pneumoniae* IgG antibodies and migraine in the general population has not been investigated. *C. pneumoniae* IgG antibody levels were compared in 329 adult Chinese patients, who met the International Classification of Headache Disorders 2nd Edition (ICHD II) criteria for migraine, and in 329 healthy subjects. Factors such as gender, age, smoking, consumption of pickle, and body mass index were evaluated. One hundred and ninety-five (59.2%) migraine sufferers and 70 (21.27%) controls were *C. pneumoniae* IgG antibody-seropositive ( $P < 0.05$ ). Based on a multivariate stepwise logistic model, the odds' ratios for *C. pneumoniae* IgG antibody seropositivity, body mass index, smoking, and consumption of pickle were 3.397 ( $P = 0.000$ ), 0.858 ( $P = 0.014$ ), 1.692 ( $P = 0.012$ ), and 5.469 ( $P = 0.0000$ ), respectively. In conclusion, *C. pneumoniae* IgG antibodies may be a risk factor for migraine.

**Keywords** *Chlamydia pneumoniae* IgG antibody · Migraine · Immunoglobulin

### Introduction

Migraine is a common type of headache with specific characteristics, including unilaterality, throbbing pain, photophobia or phonophobia, and nausea or vomiting [1]. Several large-scale epidemiological studies have revealed that the prevalence of migraine ranges from 6 to 13% in the general population [2–6].

Migraine is a recurrent neurovascular headache, but its mechanism is still unclear; it may be influenced by genetic, endocrine, neurological or immune mechanisms, as well as by other relevant factors. Headaches, in particular migraine, are known to be independent risk factors for ischemic stroke [4–13]. The association between migraine and stroke is more prominent in young women, particularly, in those taking oral contraceptives [8–11]. However, in middle aged and elderly adults of either sex, the association is controversial. Several epidemiological studies have indicated that severe headache and migraine should be considered as risk factors for future stroke, prior to the age of 70 [5, 12].

*Chlamydia pneumoniae* is an important pathogen in infections of the respiratory tract [13] and numerous reports have recently suggested its association with atherosclerosis. Infection of the vascular wall with *C. pneumoniae* has been linked to ischemic heart disease [14–17] and stroke [18–24] in epidemiological studies as well as in pathological studies using immunocytochemistry, polymerase chain reaction (PCR), and electron microscopy. In Japan, Miyashita et al. [25] reported a significant elevation in *C. pneumoniae* antibody levels in a patient with acute myocardial infarction and Kawamoto et al. [26] showed a significant relation between atherosclerotic lesions and common carotid arteries. Kawashima and Kawada [22] demonstrated a significant elevation

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of *C. pneumoniae* antibody levels in a patient with acute ischemic stroke.

A correlation between cerebral infarction with migraine and *C. pneumoniae* infection has been confirmed, but a correlation between *C. pneumoniae* IgG antibody levels and migraine has not been investigated in the general population. We therefore investigated this relationship between *C. pneumoniae* IgG antibodies and migraine.

## Subjects and methods

Three hundred and twenty-nine Chinese patients attending our hospital out-patient department between September 2005 and December 2007 and who met the International Classification of Headache Disorders 2nd Edition (ICHD II) criteria for migraine were included in the study. There were 112 men and 217 women. Their ages ranged from 20 to 42 years (mean age  $29.2 \pm 8.2$  years). Twenty patients had cerebellar atrophy, 30 had migraine with aura, 19 experienced bilateral pain, and 25 patients had relevant family histories. Ninety-one patients smoked (>5 years, >15 packs/month), 253 patients ate pickle (>3 years, >30 g/day). The average body mass index was  $23.82 \pm 1.56$  kg/m<sup>2</sup>. The control group consisted of 329 healthy subjects, including 133 men and 196 women, aged between 20 and 44 years old (mean age  $31.2 \pm 9.2$  years). Of these, 96 smoked, 103 ate salted, preserved foods, and the average body mass index was  $23.81 \pm 1.91$  kg/m<sup>2</sup>. Individuals with recent histories of respiratory tract infections were excluded (Table 1).

### Specimen collection

All blood samples were taken and separated in the morning.

### Experimental methods

Infection was determined by measuring anti-*C. pneumoniae* IgG-specific antibody levels (Cp IgG index) using an

**Table 1** Demographic characteristics of migraine and control subjects

	Control (N = 329)	Migraine (N = 329)	P value
Gender, male, N	112	133	0.5
Age (years)	$29.2 \pm 8.2$	$31.2 \pm 9.2$	0.000
Smoking, N (over 5 years, above 15 packs/month)	91	96	0.98
Pickle, N (over 3 years, above 30 g/day)	253	103	0.000
Body mass index (kg/m <sup>2</sup> )	$23.82 \pm 1.56$	$23.81 \pm 1.91$	0.000

enzyme-linked immunosorbent assay method (“HITAZYME *C. pneumoniae*”, Hitachi Chemical Co. Ltd., Tokyo, Japan). Levels were measured in serum from fasting blood, which had been preserved at  $-70^{\circ}\text{C}$ . Levels below the 1.10 Cp IgG index were classified as seronegative and those above 1.10 as seropositive [27].

### Statistical analysis

The results are shown as mean value  $\pm$  standard deviation. The results were analyzed statistically using SPSS 10.0J (Statistical Package for Social Science Inc., Chicago, IL, USA) and compared using  $\chi^2$  tests. A value of  $P < 0.05$  was considered significant. The relationships between the presence of migraine and a positive Cp IgG index, gender (female 0; male 1), age, body mass index (BMI: body weight/height<sup>2</sup>), smoking, and consumption of pickle were examined by multiple logistic regression analysis.

## Results

One hundred and ninety-five (59.2%) migraine patients and 70 (21.27%) controls were Cp IgG antibody-seropositive. Based on multivariate stepwise logistic regression analysis, the odds' ratios for *C. pneumoniae* IgG antibody positivity, body mass index, smoking, and consumption of pickle were 3.397 (95% CI: 2.395–4.817,  $P = 0.000$ ), 0.858 (95% CI: 0.760–0.969,  $P = 0.014$ ), 1.692 (95% CI: 1.124–2.547,  $P = 0.012$ ), and 5.469 (95% CI: 3.631–8.237,  $P = 0.0000$ ), respectively (Tables 2, 3).

## Discussions

Migraine is a debilitating recurrent primary headache disorder, but its pathogenesis is still unclear. Migraine headaches have a complex pathophysiology and both vascular and neural theories have been proposed. One hypothesis suggests that the process begins with a series of destabilizing events within the brain that trigger cortical spreading depression (CSD) [28]. CSD can cause both migraine aura and trigeminal activation, which, in turn,

**Table 2** *Chlamydia pneumoniae* IgG antibodies in patients and controls

Group	Seropositivity	Negative	Seropositivity rates (%)
Study group	195	134	59.2
Control group	70	259	21.27

Migraine group compared with control group:  $\chi^2 = 98.7205$ ,  $P < 0.005$

**Table 3** Relation between migraine and *C. pneumoniae* IgG antibodies as determined by multiple regression analysis logistic

Study factor	$\beta$	SE	Wald	<i>P</i>	OR	95% CI
Body mass index (kg/m <sup>2</sup> )	−0.153	0.062	6.097	0.014	0.858	0.760–0.969
Smoking, <i>N</i> (%) (>5 years, >15 packs/month)	0.526	0.209	6.344	0.012	1.692	1.124–2.547
Pickle (>3 years, >30 g/day)	1.699	0.209	66.128	0.000	5.469	3.631–8.237
<i>C. pneumoniae</i> IgG	1.223	0.178	47.066	0.000	3.397	2.395–4.817

For each additional unit of body weight index, the risk of an occurrence of migraine increases 0.166 times; risk for the smokers who are likely to suffer from migraine is 1.692 times that of non-smokers; the risk for the people who are fond of pickle is 5.469 times than that of the group who prefer for fresh vegetables; the risk of the Cp-positive persons is 3.397 times than that of the Cp-negative

promotes neuropeptide release and triggers peripheral and central mechanisms that promote headache and autonomic activation. Susceptibility to CSD and to migraine is, in part, genetically determined. The best evidence to date comes from certain subtypes of migraine with aura, in which, point mutations in genes controlling the translocation of calcium, sodium and potassium have been implicated. When the dura mater cranial vascular wall by stimulating the trigeminal nerve endings, vasoactive peptide substances such as substance P, calcitonin gene-related peptide, and neurokinin are released [29, 30], causing neurogenic inflammation. Even minor chemical or mechanical stimulation of the sensitized trigeminal nerve also causes excessive excitement. Injury receptors at trigeminal nerve endings can stimulate the trigeminal nerve, thereby causing headache, activating the autonomic nervous system, and giving rise to symptoms such as nausea and vomiting. Trigeminal nerve inflammation and allergic trigeminal nerve provide a theoretical basis for migraine [31, 32]. *C. pneumoniae* IgG antibody production following infection can lead to inflammation and sensitization of the trigeminal nerve, so leading to migraine attack.

The results of this study showed that 195 (59.2%) migraine patients and 70 (21.27%) controls were *C. pneumoniae* antibody-seropositive, while Nabipour et al. found a seropositivity rate of 37.7% in healthy humans. The discrepancy between these results could be related to differences in case selection, the number of cases, or to regional differences [33].

## Conclusion

The results of this study suggest that there is a correlation between *C. pneumoniae* IgG antibodies and migraine. It is possible that *C. pneumoniae* IgG antibodies may damage the brain vasculature, promote atherosclerosis and disrupt endothelial cell function, thereby stimulating vasospasm and damaging the blood–brain barrier. Changes in the environment can also stimulate a migraine attack due to the inflammation and sensitization of the trigeminal nerve caused directly by *C. pneumoniae* IgG antibodies.

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**Conflict of interest** None.

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