Association Between *Chlamydia pneumoniae* and Migraine: A Study from a Tertiary Center in India

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Aims: To investi*gate t*he association between circulating *Chlamydia pneumoniae (C pneumoniae)* immunoglobulin G (IgG) antibody and migraine in Indian patients. **Methods:** A total of 300 migraine patients and 150 age-matched and sex-matched controls were recruited from the Department of Neurology at Yashoda Hospital in Hyderabad, India, during the study period between August 2011 and July 2013. All patients and controls were assessed for the presence of the *C pneumoniae* IgG antibody and also C-reactive protein (CRP) as well as for depression, which was assessed by the Hamilton Depression Rating Scale (HDRS). **Results:** Of the patients with migraine, 69% were female and the mean age ± standard deviation (SD) was 45.8 ± 4.8 years (range 18 to 62 years). The *C pneumoniae* IgG antibody was present in 151 of the patients (50.3%; $P < .0001$), CRP in 180 (60%; $P < .0001$), depression in 270 (90%; $P < .0001$), and history of sleep disturbances in 70 (23.3%; $P < .0001$); all measurements were significantly higher in migraine patients compared with controls. After adjustment for multiple logistic regression analyses, *C pneumoniae* IgG antibody positivity (odds ratio [OR] 2.6; 95% confidence interval [CI] = 1.3 to 3.7), CRP positivity (OR 6.2; 95% CI = 3.3 to 11.6), mild depression (OR 16.9; 95% CI = 6.5 to 39.4), and history of sleep disturbance (OR 2.1; 95% CI = 1.1 to 3.1) were independently associated with migraine. **Conclusion:** This study showed that the presence of *C pneumoniae* IgG antibody was independently associated with migraine in Indian patients. *J Oral Facial Pain Headache 2016;30:150–155. doi: 10.11607/ofph.1570*

Keywords: C pneumoniae *positive, C-reactive protein, history of sleep disturbance, Indian population, migraine*

Migraine is a chronic neurologic disorder characterized by throbbing headache associated with nausea, vomiting, and sensitivity to light, smell, and sound.[1] Migraine affects 12% to 15% of the world population[2] and is caused by a complex interaction of environmental, hormonal, dietary, genetic, and other factors.[3] Some studies have found that migraine can be precipitated by neurogenic mechanisms, hypoxia, and inflammatory markers, but its pathogenesis is still unclear.[4] Several studies have found an association between migraine and infection and inflammation,[5,6] and a recent study has suggested an association between migraine and *Chlamydia pneumoniae* (*C pneumoniae*).[6]

Infectious diseases are generally more common in India than in western countries. *C pneumoniae* is a gram-negative bacterium associated with chronic diseases.[7] The microorganism acts by multiple mechanisms and causes the type of chronic inflammation thought to be associated with migraine, especially in blood vessels. Additionally, C-reactive protein (CRP) is a marker of inflammation and has been found to be elevated in *C pneumoniae* infections.[8] Furthermore, there is evidence that chronic infections can cause depression.[9] The relationship between depression and migraine is synergistic and bidirectional.[10] There has not yet been any study assessing the association between the *C pneumoniae* immunoglobulin (IgG) antibody and risk of migraine in Indian patients. Therefore, the present study aimed to investigate the association between circulating *C pneumoniae* IgG antibody and migraine in Indian patients.

Materials and Methods

The study recruited 300 migraine patients who were either admitted as inpatients or evaluated at the outpatient clinic of the Department of Neurology at Yashoda Hospital in Hyderabad, India. Yashoda Hospital is a referral center for the states of Andhra Pradesh and Telangana. A total of 150 age-matched and sex-matched controls were selected from the same hospital. The study period was from August 2011 to July 2013. The study was approved by the Institutional Ethics committee, and informed consent was obtained from all cases and controls.

Selection of Cases

Patients suffering from migraine, as defined by the Headache Classification committee of the International Headache Society[1] and confirmed by one migraine specialist and two neurologists, were included.

Selection of Controls

Controls were defined as healthy subjects with no history of migraine in the subject or the subject's family. They were selected from the attendants of inpatients admitted in the hospital, volunteers, and the staff of the hospital. The cases were divided based on age into five strata (18 to 30, 31 to 40, 41 to 50, 51 to 60, and over 60 years), and gender-matched controls (case:control ratio = 2:1) were selected from each stratum.

Inclusion Criteria

All migraine patients had at least five migraine attacks per year in the last 2 years with a combination of symptoms fulfilling the clinical criteria of migraine (including unilateral throbbing headache, sensitivity to light and sound, nausea, and vomiting).

Exclusion Criteria

Cases and controls with a present or past history of cardiovascular or cerebrovascular disease, chest X-ray abnormalities, asthma, and other chronic diseases were excluded.

Risk Factor Assessment

Present and past medical histories of all cases and controls were taken by a migraine specialist and one neurologist in a face-to-face interview. A standardized technique was used for behavioral risk factors. Migraine duration was noted in the cases, and any history of sleep disturbance was noted in both the cases and controls. All cases and controls completed the Hamilton Depression Rating Scale (HDRS) for depression (24 items) and were scored as:

- 0 to 4: Normal or no depression
- 5 to 8: Mild depression
- 9 to 11: Moderate depression
- 12 to 15: Severe depression[11]

All women over 40 years of age with absence of menses for 3 months or more at the time of the examination and with previously normal menstruation were considered postmenopausal.[12] Smokers were defined as those reporting daily smoking. Ex-smokers and occasional smokers were classified as nonsmokers. Alcoholics were defined as those in whom alcohol consumption was > 50 g/day (equivalent to 500 mL [two drinks] of wine, 1,000 mL [three drinks] of beer, or > five drinks [units] of spirits). Body mass index (BMI) kg/m^2 values > 30 were considered to reflect obesity, and CRP levels above > 0.6 mg/dL were considered as positive.[7]

Estimation of C pneumoniae IgG antibody

Blood collection was carried out at the time of enrollment of cases and controls; a 5-mL blood sample was obtained in both cases and controls. The seropositivity of the *C pneumoniae*-specific IgG antibody was estimated by ELISA (enzyme-linked immunosorbent assay) using a kit (Euroimmun). Euroimmun recommends the titer of IgG in serum be ≥ 1.10 to be considered positive and ≤ 1.09 to be considered negative. The Euroimmun kit sensitivity is 97% and specificity is 95%.

Statistical Analyses

Statistical analyses were performed with SPSS 15.0 for Windows (statistical package for the Social Sciences, SPSS Inc). Mean ± standard deviation (SD) was estimated for all continuous variables (mean age and duration of migraine). Differences in the continuous variables were tested by Student *t* test while chi-square test evaluated the association in the proportions that included risk factors (postmenopausal status, alcoholism, smoking, BMI, mild to severe depression, CRP, history of sleep disturbances, and *C pneumoniae*). The odds ratio (OR) and 95% confidence interval (CI) were obtained for all risk factors, including *C pneumoniae*. Multiple logistic regression was performed before and after adjustment for potential confounders. All tests were two-tailed and a *P* value < .05 was considered statistically significant.

Results

In this case-control study, the presence of *C pneumoniae* IgG antibody was significantly higher in migraine patients (50.3%) than in control subjects (21.3%) (*P* < .0001). Similarly, in the migraine

Table 1 Baseline Characteristics of Migraine Patients and Controls

Parameters	Migraine patients (n = 300)	Controls (n = 150)	*P* value
Men, n (%)	93 (31%)	48 (32%)	.9
Women, n (5)	207 (69%)	102 (68%)	.9
Mean age (y)	45.1 ± 8.9	45.8 ± 12.5	.4
Postmenopausal, n (%)	60 (20%)	30 (20%)	.8
Age range (y)	18–62	18–62	
Smoking, n (%)	39 (13%)	12 (8%)	.4
Alcoholism, n (%)	52 (17.3%)	19 (12.6%)	.3
Obesity, n (%)	22 (7.3%)	6 (4%)	.2
Chlamydia pneumoniae IgG antibody positivity, n (%)	151 (50.3%)	32 (21.3%)	< .0001
CRP positivity, n (%)	180 (60%)	26 (17.3%)	< .0001
History of sleep disturbance, n (%)	70 (23.3%)	18 (6%)	< .0001
Normal or no depression, n (%)	30 (10%)	138 (96%)	< .0001
Mild depression, n (%)	232 (77.3%)	12 (4%)	< .0001
Moderate depression, n (%)	25 (8.3%)	0	< .0001
Severe depression, n (%)	13 (4.3%)	0	< .0001

Table 2 Comparison of Characteristics Between *Chlamydia pneumoniae* IgG–Positive and IgG–Negative Migraineurs

	Chlamydia pneumoniae IgG–positive (n = 151)	*Chlamydia pneumoniae* IgG–negative (n = 149)	*P* value
Men, n (%)	31 (20.5%)	62 (41.6%)	.001
Women, n (%)	120 (79.4%)	87 (58.3%)	.0001
Mean age (y)	45.4 ± 8.7	44.7 ± 9.0	.3
Age range (y)	18–58	18–62	
Smoking, n (%)	28 (18.5%)	11 (7.3%)	.006
Alcoholism, n (%)	23 (15.2%)	29 (19.4%)	.5
History of sleep disturbance, n (%)	33 (21.8%)	37 (24.8%)	.6
Postmenopausal women, n (%)	45 (37.5%)	15 (17.2 %)	< .0001
C-reactive protein positivity, n (%)	151 (100%)	29 (19.4%)	< .0001
Mean duration of migraine (y)	4.30 ± 1.7	2.7 ± 1.3	< .0001
Normal or no depression, n (%)	12 (7.9%)	18 (12%)	.3
Mild depression, n (%)	120 (79.4%)	112 (75.1%)	.4
Moderate depression, n (%)	13 (8.6%)	12 (8%)	.8
Severe depression, n (%)	7 (4.6%)	8 (5.3%)	.3
Obesity, n (%)	12 (7.9%)	10 (6.7%)	.8

patients, CRP positivity (60%), history of sleep disorders (23.3%), mild depression (77.3%), moderate depression (8.3%), and severe depression (4.3%) were significantly higher than in controls ($P < .0001$) (Table 1). Of these patients with migraine, 69% were female and the mean age ± SD was 45.8 ± 4.8 years (range 18 to 62 years).

In the *C pneumoniae* IgG antibody–positive migraineurs (n = 151), smoking (18.5%), CRP (100%), female gender (79.4%), postmenopausal status among women (37.5%), and mean duration of migraine (4.30 ± 1.7 years) were significantly higher than in the *C pneumoniae* IgG antibody–negative group. No significant associations were noted between the presence of *C pneumoniae* IgG antibody and depression, history of sleep disorders, and obesity (Table 2).

Multiple logistic regression analysis after adjustment revealed that *C pneumoniae* IgG antibody positivity (OR: 2.6; 95% CI = 1.3 to 3.7), CRP positivity (OR: 6.2; 95% CI = 3.3 to 11.6), mild depression (OR: 16.9; 95% CI = 6.5 to 39.4), and history of sleep disturbance (OR 2.1; 95% CI = 1.1 to 3.1) were independently associated with migraine (Table 3).

Discussion

In this study, the presence of *C pneumoniae* IgG antibody was significantly associated with migraine when compared with controls. This is consistent with a previous study reporting *C pneumoniae* IgG antibody positivity in 59.2% of the sample of migraine patients and 21.2% in the controls.[6] The present

Table 3 Univariate and Multivariate Analysis

Parameters	Before adjustment		After adjustment		
	Odds ratio	95% CI	Odds ratio	95% CI	*P* value
Alcoholism	0.7	0.4–1.3	0.5	0.3–1.1	.4
Smoking	0.9	0.5–1.6	0.8	0.5–1.5	.01
CRP positivity	7.1	4.4–12.8	6.2	3.3–11.6	< .0001
C pneumoniae IgG antibody positivity	4.5	3.3–6.8	2.6	1.3–3.7	< .0001
Mild depression	17.3	7.1–45.0	16.9	6.5–39.4	< .0001
History of sleep disturbance	2.4	1.3–4.5	2.1	1.1–3.1	< .0001

CI = confidence interval.

study also noted that *C pneumoniae* IgG antibody positivity was significantly associated with smoking, postmenopausal status in women, CRP positivity, and longer duration of migraine.

The underlying pathophysiology of migraine is considered to be caused by cortical-spreading depression, which stimulates inflammation in the trigeminal neurovascular system with the release of various neuropeptides such as substance P, calcitonin gene-related peptide, and neurokinin.[13] There is recent evidence of the role of activation of Toll-like receptors (TLRs) in migraine. Microbial and nonmicrobial ligands can induce inflammation via activation of brain endothelial cells through their action on TLRs, resulting in stimulation of nuclear factor kappa B (NF-κB) pathway and thereby increasing the production of inflammatory mediators.[14] TLR-4 stimulation is known to be induced by ischemia, and it has been shown to increase oxidative stress and may result in brain damage and inflammation.[15,16] There is also evidence that TLR-4 signaling occurs in response to diverse microbial molecules including bacterial lipopolysaccharides (LPS), respiratory syncytial virus fusion protein, and chlamydial heat-shock protein 60.[17] TLR-4 polymorphism influences the production of inflammatory cytokines, thereby varying host susceptibility to bacterial infection, which may be a risk factor in the production of migraine.[18] According to the theory of neurogenic inflammation, the ions and inflammatory agents that are released act on perivascular nerve fibers and alter their sensitivity to subsequent stimuli, leading to migraine headache.[19–21] Furthermore, the 896A/G-mutation of TLR-4, encoded within the fourth exon, affects its ligand-binding region and is associated with hyporesponsiveness to LPS in macrophages and epithelial cells.[22] Thus, TLR-4 may serve as a conduit in the infection-mediated activation of migraine. The present study has revealed that the *C pneumoniae* IgG antibody may be an independent risk factor for migraine in Indian patients, as previously suggested by Lu et al.[6]

In the present study, CRP positivity was significantly associated with migraine patients (a prevalence of 60%) when compared with controls, which is consistent with an earlier report.[23] A study by Welch et al noted a CRP prevalence of 43% in migraine patients,[24] and in a study by Salehi et al, the mean CRP was noted to be 16.40 mg/dL in migraine patients and 9.76 mg/dL in controls.[25]

The mechanisms involved in migraine and their connection to high CRP levels are not fully understood, and which triggers the other is still debatable. CRP is an acute inflammatory marker and possibly signifies the presence of increased inflammatory agents in the blood. As mentioned above, the ready availability of these markers may lower the threshold for attacks of migraine. On the other hand, high levels of CRP may be induced by various mechanisms such as leukocyte activation, oxidative stress, and inflammatory cytokines produced during and between migraine attacks.[26]

The present study showed that CRP is an independent predictor of migraine. Similar findings have been noted by others.[27–29] However, no association between CRP and migraine has also been reported.[30]

The present study also showed that CRP positivity was significantly higher in *C pneumoniae* IgG antibody–positive migraineurs than in *C pneumoniae* IgG antibody–negative migraineurs. This reemphasizes the point that *C pneumoniae* infection can induce a state of chronic inflammation.

In the present study, *C pneumoniae* IgG antibody positivity was significantly higher in women suffering from migraine compared with men suffering from migraine and this was more so in postmenopausal women. A recent study has noted that the *C pneumoniae* IgG antibody was positive in 60% of postmenopausal women.[31] This suggests a possible role of the declining effect of estrogen and progesterone and their interaction in increasing the predisposition to *C pneumoniae* infection. Aging also is associated with an increased prevalence of *C pneumoniae* positivity and may be a confounding factor.[32]

In the present study, mild depression was found in 77.3% and moderate to severe depression in 12.6% of the patients with migraine, consistent with

an earlier study.[33] Siniatchkin et al showed that stress and anxiety were the most frequent triggers of headache[34] and Tan et al found anxiety in 15.7% of migraineurs.[35] The association between migraine and depression is complex and has been shown in some studies to be bidirectional. The exact mechanisms are not known, but it has been postulated that migraine pain can cause a state of anxiety and may predispose the migraineur to depression; although, on the other hand, migraine and pain may be the somatic manifestation of depression. A heightened association has been reported between migraine with aura (as well as migraine associated with focal neurologic deficits) and depression, implying a common factor underlying both disorders.[36] Furthermore, depression is known to be associated with elevated CRP, and a psychoneuroimmune link has been postulated as a possible mechanism in chronic diseases such as cardiovascular and cerebrovascular disorders.[37] Thus, depression may contribute to migraine via activation of inflammatory markers such as CRP.

The present study revealed that mild depression was independently associated with migraine. A recent study has noted that infections are associated with depression,[9] but the present study found no significant association between depression and *C pneumoniae* IgG antibody positivity. A previous study also found no significant association between *C pneumoniae* and depression.[38]

It has been shown that sleep influences headache and some headaches occur exclusively in relation to sleep cycles.[39–41] Migraine attacks usually occur early in the morning around 4 am, which suggests a relationship to circadian rhythm or sleep.[39] Sleep deprivation or changes in sleep patterns such as shift work and jet lag may trigger migraine. Sleep can alleviate the symptoms of migraine, but headache can impair sleep.[40] In the present study, a history of sleep disturbance was significantly higher in migraine patients compared with controls. A previous study reported sleep disorders in 72.9% of migraineurs.[42] A multifaceted interplay of neurotransmitters such as serotonin and norepinephrine may underlie both sleep abnormalities and migraine.[41] The present study established a history of sleep disturbance to be independently associated with migraine. However, the lack of a difference in the prevalence of sleep disturbance in migraine patients with and without *C pneumoniae* IgG positivity suggests no association with infection.

The present study showed that *C pneumoniae* IgG antibody positivity was significantly more common in migraineurs who were smokers. Other studies have also suggested that smokers are more likely to show *C pneumoniae* positivity.[43] Smokers have a reduced immunity, and *C pneumoniae* infection may be aggravated by smoking-induced chronic inflammation.[44] Atherosclerosis induced by smoking may also be linked to its increased association with *C pneumoniae* infection.[45]

Although a recent Chinese study showed the prevalence of migraine to be higher in obese individuals,[46] the present study did not find a significant association between obesity and migraine. The present study also found no significant association between obesity and *C pneumoniae* IgG antibody.

Conclusions

The present study has revealed that the *C pneumoniae* IgG antibody may be a risk factor for migraine in Indian patients. To the authors' knowledge, this is the first study of its kind from the Indian subcontinent.

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