Original Article

Microbial Biosystems 10(3) (2025) 2025.367747
10.21608/mb.2025.367747.1268

Contents lists available at Egyptian Knowledge Bank
Microbial Biosystems
Journal homepage: http://mb.journals.ekb.eg/

Relationship between *Chlamydia pneumonia* and multiple sclerosis in Iraqi patients

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ARTICLE INFO

Article history
Received 12 March 2025
Received revised 09 April 2025
Accepted 20 August 2025
Available online 01 September 2025

Corresponding Editors
Tofiq, S. H.
Hashem, S.

Keywords
IgM,
IgG,
IL-6,
IL-10,
multiple sclerosis.

ABSTRACT

The mandatory intracellular bacterial infection *Chlamydia pneumoniae* has been extensively researched as a potential contributor to the onset or exacerbation of certain disorders. This obligate intracellular pathogen is being studied as a potential mediator of chronic inflammatory illnesses due to its unique lifestyle and ability to proliferate within the host while evading immune identification. From October 2023 to February 2024, 90 blood samples were obtained from patients aged 15 to 75 years. The consulting medical staff of Dr. Saad Al-Witry Hospital for Neurosciences rendered diagnosis for these patients. Three categories were created from the patient's groups: In the first group, there were 14 patients with multiple sclerosis and *C. pneumonia*; in the second group, there were 46 patients with multiple sclerosis but no *C. pneumonia*; and in the third group, there were 30 people who are apparently healthy individuals. Using the Enzyme-Linked Immunosorbent Assay (ELISA) technique, the levels of interleukin-10 (IL-10), interleukin-6 (IL-6) and IgM and IgG antibodies against *C. pneumonia* were measured in each of the studied groups. When compared to the control group, the statistical analysis reveals a highly significant increase (P≤0.01) in anti- *C. pneumonia* IgM and anti- *C. pneumonia* IgG as well as interleukin-10 (IL-10) and interleukin-6 (IL-6) in the sera of MS patients with *C. pneumonia* comparing it to the control group, it also demonstrates a highly significant increase (P≤0.01) in MS diseases without *C. pneumonia* IgM, *C. pneumonia* IgG, IL-10, IL-6 respectively. In conclusion, *C. pneumonia* may play a role as trigger factor of neurological disease such as multiple sclerosis.

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Introduction

Myelin breakdown caused by the immune system is a chronic autoimmune illness of the central nervous system (CNS) that manifests as multiple sclerosis (MS) (Tafti *et al*. 2024). The clinical manifestations of multiple sclerosis are incredibly diverse and might involve problems in the motor and coordination systems as well as vision impairment (Klineova & Lublin 2018).

Typically, multiple sclerosis (MS) is characterized by dysfunction in multiple neurological axes, including numbness or paresthesia, motor weakness, dizziness, diplopia, sensory complaints, bladder and sexual dysfunction, ataxia, and vertigo (Soud & Al-Rubae'i 2022).

The etiology of this disease is known to include a number of elements, including genetics, environmental factors, and infectious agents (viruses and bacteria), even if the exact cause of the condition is still unknown (Eshaghi *et al.,* 2021). There is increasing evidence that this bacterium plays a role in chronic neurological illnesses, including Multiple Sclerosis (MS) (Cossu *et al.* 2018).

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Magnetic resonance imaging (MRI) reveals discrete regions of inflammation and demyelination in the white matter, which are the most typical lesions (Papiri et al., 2023). Following the acute period of inflammation, MS lesions may transition into a chronic state characterized by remyelination, inflammation resolution without repair, or a condition known as "smoldering," in which myelin degradation and inflammation coexist (Frischer *et al.,* 2009).

One of the potential causes of MS is bacteria, which are among the most prevalent infectious agents in human civilizations (Sospedra & Martin, 2005). More than viruses, bacteria have the ability to induce multiple sclerosis by molecular mimicry (Kurtzke & Hyllested, 1987).

The etiology of MS has been examined in several investigations in relation to *Acinetobacter*, *Helicobacter pylori*, *Spirochetes*, *Campylobacter*, *Mycobacteria*, and *Chlamydia pneumonia* (Hughes *et al.,*2001; Grab *et al.,*2005; Gavalas *et al.,*2015; Cossu *et al.,*2018; Landry *et al.,*2023).

Gram negative, obligatory intracellular, non-motile bacteria called *C. pneumoniae* is the source of acute respiratory illnesses like pneumonia Honeybourne (Cook & Honeybourne, 1994). In addition to epithelial cells, macrophages and monocytes have been shown to be infected by *Chlamydia*. Additionally, blood artery smooth muscle cells and endothelium are infected by *C. pneumoniae*. All chlamydial illnesses appear to have immune-mediated tissue damage (Grayston, 1992).

Numerous researches have examined the connection between *C. pneumoniae* infection and multiple sclerosis. The aim of present study was to evaluate the role of *C. pneumoniae* as trigger for multiple sclerosis (MS).

Materials and Methods

Sampling

In this study, ninety Iraqi patients, ranging in age from 15 to 72 were involved. The patient groups were divided into two groups: the first group was carried patient who had MS with *C. pneumonia* and the second group MS without *C. pneumonia*. They were hospitalized to the neurological disease department of the two Imams Kazemin Hospitals, as well as the Dr. Saad Al Watri for Neurological Sciences at Medical City Hospital. Between October 2023 and March 2024. Additionally, third group involved thirty healthy people who were included in the study as a control group (this group represented healthy people who do not show symptoms of the disease), and their average age ranged from 15 to 75 years.

Blood collection

Five milliliters of blood were collected using a sterile syringe, and then transported into a vacuum gel plain tube, and left several minutes for clots at room temperature in order to separation the serum. After that, the tubes were centrifuged for five minutes at a speed of 3000 rpm. Before being kept at (-20 C) for immunological testing, each sample was labeled with the name, date, and number to next step.

Immunological antibodies detection

The level of interleukin 10 (IL-10), interleukin (IL-6), antibodies of *C. pneumonia* IgM and IgG were reportedly estimated for each of studied patient groups and control group by using the Enzyme Linked Immunosorbent Assay (ELISA) technique in accordance with the kit's protocol.

Statistical analysis

To determine the impact of the patient and control groups on the study parameters, the Statistical Analysis System (SAS, 2018) program was utilized. We employed both the T-test and the Least Significant Difference (LSD) test to compare means that were significant. Additionally, the Chi-square test was utilized to compare the percentages (0.05 and 0.01 likelihood) significantly. The study's estimate of the correlation coefficient between the variables.

Results

The distribution of study groups by sex is displayed in Table (1). The statistical analysis reveals there were non-significant difference ($P \geq 0.05$) between female and male in group of MS with C. *pneumonia* and in control group while there was highly significant difference ($P \leq 0.01$) between female and male in MS without *C. pneumonia.*

Table (2) shows the percentage and distribution of sample study of studied group according to group age. The results showed the most influenced group was age group (40-50 yr.). There were highly significant differences ($P \leq 0.01$) in age group (<40 yr.) and (40-50 yr.) while there was no significant difference in (>50 yr.) of all studied groups. The level of IgM and IgG antibodies against *C. pneumoniae* in the all studied groups were shown in Table 3 was appeared the IgG Ab level for the MS with *C. pneumoniae* infection group was demonstrated a highly significant difference (0.483±0.062 IU/ml) when compared to the control group (0.184±0.003 IU/ml), also, compared to the MS without *C. pneumoniae* infection group (0.193±0.003 IU/ml). The level of IgM Ab in MS with *C. pneumoniae* infection group was highly significantly different ($P \leq 0.01$) compared to control group (0.219±0.008 IU/ml) and MS without *C. pneumoniae*

infection group (0.194±0.019 IU/ml). The level of IL-10 in each of the study groups was displayed in Table 4. The levels of IL-10 in MS groups infected with C. pneumonia (361.98 ±23.76 Pg/ml) were significantly higher (P≤0.01) compared to healthy control group (101.20 ±2.62 Pg/ml) and the level of IL-10 in MS without C. pneumonia infection groups (284.17 ±13.07 Pg/ml) were highly significant (P≤0.01) compared to healthy control group (101.20 ±2.62 Pg/ml). While the level of IL-6 in different groups of the study was showed highly significant difference (P≤0.01) in MS with *C. pneumonia* infection groups (55.92±2.99 Pg/ml) as compared with healthy control (29.90±1.62 Pg/ml) and there was highly significant difference (P≤0.01) in the level of IL-6 in MS without *C. pneumonia* infection groups (51.74±2.14 Pg/ml) as compared with healthy control (29.90±1.62 Pg/ml)

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Table 1 Distribution of sample study according to gender in difference groups

Factor		Control (No= 30)	MS with *C. pneumonia* (No= 14)	MS without *C. pneumonia* (No= 47)	P-value
Sex: No (%)	Male	13 (43.33%)	5 (35.71%)	11 (23.40%)	0.0261 *
	Female	17 (56.67%)	9 (64.29.19%)	36 (76.60%)	0.0001 **
	P-value	0.287 NS	0.255 NS	0.0001 **	---

* (P≤0.05) , ** (P≤0.01) , NS: Non-Significant.

Table 2 Distribution of sample study according to age groups in difference groups

Factor		Control (No= 30)	MS with *C. pneumonia* (No= 14)	MS without *C. pneumonia* (No= 47)	P-value
Age: No (%)	<40 yr.	19(63.33%)	4(28.57%)	21 (44.68%)	0.0001 **
	40-50 yr.	4 (13.33%)	5(35.71%)	22 (46.81%)	0.0001 **
	>50 yr.	7 (23.33%)	5(35.71%)	4 (8.51%)	0.684 NS
	P-value	0.0085 **	0.902 NS	0.0001 **	---
Mean ± SE of Age (year)		37.80 ±3.08	44.92 ±3.49	39.21 ±1.29	0.0767 NS

** (P≤0.01), NS: Non-Significant.

Table 3 Mean level of anti- *C. pneumoniae* Ab IgG and IgM among studied group

Group	Mean ± SE Conc.IgG CH (IU/ml)	Conc.IgM CH (IU/ml)
Control	0.184 ±0.003 a	0.219 ±0.008 a
MS with *C. pneumoniae*	0.483 ±0.062 b	0.336 ±0.073 b
MS without *C. pneumoniae*	0.193 ±0.003 c	0.194 ±0.019 c
LSD	0.053 **	0.084 **
P-value	0.0001	0.0086

Means having with the different letters in same column differed significantly, ** (P≤0.01).

Table 4 Mean level of IL-10 and IL-6 (pg/ml) among studied groups

Group	Mean ± SE	
	IL-10 (pg/ml)	IL-6 (pg/ml)
Control	101.20 ±2.62 c	29.38 ±1.21 b
MS with *C. pneumonia*	361.98 ±23.76 a	55.41 ±3.15 a
MS without *C. pneumonia*	284.17 ±13.07 b	52.53 ±2.09 a
LSD	42.454 **	6.870 **
P-value	0.0001	0.0001

Means having with the different letters in same column differed significantly, ** (P≤0.01).

Discussion

According to an Iraqi study carried out in 2016, the incidence rate of female to male was 35/25, their Mean±SD

(9.48±5.78 and 7.51±4.83) (Khaliel & Abbas, 2016). Another study agrees with the current result, which demonstrated that Anti-*C. pneumoniae* was discovered to be substantially greater in MS patients than in the control group (Kazemi et al., 2020).

In Iran, a study done in 2011 demonstrated that MS disease is an autoimmune disease which is more common in women than men, at a ratio of 3.5:1 (Aghaei et al., 2011). Also, other research was consonant with the current result: the average patient's age was 37.7 and the relation between genders was 3.13F:1M (Moreira et al., 2000).

A study reported by Habbestad et al. (2024) found a considerable increase in the age at which MS onset occurred. The primary cause of this was the rise in the number of MS patients, mostly women, who got the disease after the ages of 40 to 45. This bimodal distribution (a bimodal distribution is when there are two very common data values found in a graph such as a dot graph or bar graph) may represent distinct MS susceptibility phases or variations in risk factor exposure over the course of the observation period. According to a recent Italian study, the age at onset increased over time, the duration between onset and diagnosis was shorter, and the ratio of females to males was higher in older age groups (Prosperini et al., 2022).

On the other hand, a study by Małecka et al. (2021) was in disagreement with the current study. They evaluated the clinical, biochemical, and demographic features of MS patients according to the age at which the disease was discovered. The research concluded that MS, the most prevalent of the acquired demyelinating illnesses, is regarded as the most typical and distinctive. Although beginning at younger or older ages is not uncommon, the majority of symptomatic onset occurs in the age range of 20 to 40.

As a result of its ability to cause a persistent infection in the brain, *C. pneumoniae* has been linked to a number of chronic inflammatory disorders, including Alzheimer's and multiple sclerosis (MS) (Kern et al., 2009). The relationship between MS and *C. pneumoniae* was thoroughly studied, yielding conflicting findings that are still up for discussion. Subgroups of MS patients had higher intrathecal *C. pneumoniae* antibodies in their CSF than did healthy controls (Fainardi et al., 2008; Ivanova et al., 2015); however, these antibodies were also found in other inflammatory neurological conditions, such as NMOSDs (Yoshimura et al., 2013), a different type of inflammatory disease of the CNS that shares characteristics with MS. These findings were based on molecular and seroprevalence studies.

The current study's findings concur with those of many researchers. Munger showed that a correlation exists between the risk of multiple sclerosis and serum titers of anti-*C. pneumoniae* IgG antibodies. In comparison to relapsing-remitting MS, this connection was stronger for progressive MS. Whether *C. pneumoniae* infection or reactivation predates MS and affects its start or course is still unknown (Munger et al., 2003).

The majority of *C. pneumoniae* exposure happens during childhood, and it increases with age and frequently leads to several infections over the course of a lifetime. IgG antibodies specific to *C. pneumoniae* are present in most adult populations, suggesting prior exposure. IgG antibody titres increase and thereafter decline gradually following an acute infection with *C. pneumoniae*. IgG antibodies have a half-life of 23–28 days (Atikcan et al., 2021).

Another study done by Arjmandi (2023) confirmed the strong positive correlation between MS and *C. pneumoniae* infection. The determination of acute or chronic infection is based on the kinetics of immunoglobulin IgM, IgG, and IgA secretion. IgM levels do not increase after a repeat infection, peak 2–4 weeks after the original infection and become undetectable 2–4 months later. On the other hand, IgG normally peaks 7–8 weeks after the first infection and is quickly induced after successive infections (1–2 weeks). Since IgG has a half-life of weeks to months and may therefore be present for some time after acute infection, chronic infection is somewhat more difficult to diagnose and necessitates the detection of persistent IgG levels (Dowell et al., 2001).

Aghaei (2011), on the other hand, discovered that in Iranian MS patients there was no correlation between MS and *C. pneumoniae*, due to differences in sample size or the stage of disease that the patients were suffering from.

Interleukins and antibodies have garnered significant interest from immunologists and medical researchers over their potential role in various illnesses (Al-Jumaily et al., 2023; Mohammed et al., 2024). The results of the current study agree with research done by Kallaur et al., who demonstrated that the level of IL-10 was higher in patients suffering from MS disease. Patients in this study had greater IL-10 levels than controls, although this difference did not seem significant (P=0.1901) (Kallaur et al., 2013). This result occurred because IL-10 production has been linked to varying degrees of MS severity, according to several studies (Luomala et al., 2003). Another study in Iran showed a substantial reduction in MS patients' levels of TGF-β, IL-23, and IL-10 (Shaygannejad et al., 2014).

MS and other autoimmune illnesses are caused by the decrease of Treg cell activity, which is responsible for producing TGF-β and IL-10, the primary anti-inflammatory cytokines (Ruiz et al., 2005; Miyara et al., 2007; Stritesky et al., 2008; Wiesemann et al., 2008; Mirandola et al., 2009; Axtell et al., 2010). These findings are consistent with earlier data, indicating a decline in TGF-β and IL-10 cytokine concentrations in MS patients

(Shaygannejad et al., 2014). IL-10 exhibits diverse effects on molecules essential to the immune response, potentially providing an opening for intracellular pathogens to evade immune system defenses. These effects may include suppressing the Th1 response, diminishing the antibacterial activity of immune cells, or decreasing the elimination of intracellular microbes. The production of IL-10 triggered by *C. pneumoniae* may facilitate bacterial evasion of the immune system and lead to cellular proliferation (Xiang et al., 2021).

A study in 2003 by Petereit et al. suggested that cytokines such as IL-10 may influence both the severity of the disease and its pathological process in multiple sclerosis. The intricate management of the cytokine network refutes the notion that multiple sclerosis is a cytokine abundance or deficiency condition. Human brain neurons and glial cells have been shown to contain IL-10 and IL-10 receptors (Vitkovic et al., 2001; Strle et al., 2001; Molina-Holgado et al., 2001; Hulshof et al., 2002). A potential mechanism by which IL-10 produces its advantageous effects is a down-regulation of proinflammatory cytokines, whether derived from brain or peripheral blood, resulting in a decrease in cytokine-mediated cytotoxicity in CNS cells, as has previously been shown in oligodendrocyte cultures.

The aforementioned finding adds to the data that MS patients had significantly higher average blood concentrations of IL-6 (23.8±2.1 vs. 15.6±2.7 pg/mL, P=0.043) than did healthy controls (Eslami et al., 2003). The outcomes are in line with previous studies that found no significant difference (P=0.09) between MS and healthy subjects, but the mean serum level of IL-6 in the neuromyelitis optic (NMO) group was significantly lower than that of MS and healthy subjects (P=0.02 for NMO and MS, P=0.001 for NMO and healthy subjects) (Ashtari et al., 2019). One of the proinflammatory cytokines released in response to injury, including infections, trauma, and cardiovascular causes, is IL-6, which is secreted by phagocytes, T- and B-lymphocytes, endothelial cells, and fibroblasts (Vlachogiannis et al., 2019; Grebenciucova et al., 2023). The synthesis of various chemicals and the secondary physiology of neurons may be impaired by a persistent increase in this cytokine. Increases in it have been linked to a number of illnesses, including infectious and autoimmune diseases (Prasad et al., 2014).

Conclusion

The findings of this study indicate that there may be a meaningful relationship between *Chlamydia pneumoniae* infection and multiple sclerosis. While the evidence supports a possible link, further investigation is needed to clarify the exact nature of this association.

Recommendation

Future studies should build on these results by applying genetic methods to provide stronger confirmation and deeper insight into how *C. pneumoniae* infection might influence the development or progression of multiple sclerosis.

Declaration of interests

In this article, all authors declare that they have no known financial interests, competing interests, or personal relationships that could have influenced the research work described.

Declaration of ethics

Every participant agreed to give blood samples to the researchers. Per the Declaration of Helsinki, each subject gave their informed approval. The present work was approved by the Ethics Committee of the Baghdad health department, Iraq; the reference number was 485/11-8-2024.

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