Potential Association Between Bacterial Infections and Ischemic Stroke Based on Fifty Case-Control Studies: A Systematic Review and Meta-Analysis

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Keywords: Ischemic stroke, Chlamydia pneumonia, Helicobacter pylori, Mycoplasma pneumonia, Mycobacterium tuberculosis, Meta-analysis, Bacterial infection

DOI: https://doi.org/10.21203/rs.3.rs-44791/v1

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Abstract

**Background:** Stroke is considered as one of the most concerns in health services facilities worldwide, and occurs in two types, ischemic stroke and hemorrhagic stroke. However, almost the three quarters of stroke cases are ischemic stroke which occur in effect of several risk factors such as hypertension, obesity, atherosclerosis, diabetes mellitus, arteritis, and inflammatory response. In recent years, infectious diseases are considered as one of the most important risk factors of ischemic stroke. In this regard, some bacteria causing the chronic infections in particular *Chlamydia pneumonia*, *Helicobacter pylori*, *Mycoplasma pneumonia*, and *Mycobacterium tuberculosis* get more attended.

**Methods:** In the present meta-analysis, we studied 50 case-control studies and evaluated potential relevance of these infections with creation and development of ischemic stroke.

**Results:** We surveyed the information of 33,978 participants in several nested case-control studies and demonstrated that bacterial infections can increase the risk of ischemic stroke.

**Conclusions:** In this meta-analysis we demonstrated a meaningful relationship between infection by three bacteria *C. pneumoniae*, *H. pylori*, and *M. tuberculosis* with occurrence of ischemic stroke.

1. Background

Nowadays stroke is accounted as one of the most striking complications of cardiovascular disorders, and is classified into the two groups, ischemic stroke and hemorrhagic stroke. The frequency of ischemic stroke is more than the hemorrhagic stroke, so that about 71% of strokes are ischemic and others are hemorrhagic (1). In general, strokes (ischemic and hemorrhagic) are known as the second most common cause of death in the world, and have affected 13.7 million worldwide (2). This disease is turn to one of the global health concerns, so that is estimated that one out of four people would be experienced it during life (3). Several risk factors play a fundamental role in stroke occurrence which include obesity, hypertension, smoking, dyslipidemia, diabetes mellitus, alcohol consumption, atrial fibrillation, carotid stenosis, inflammation, and epigenetic events of host (4). Lately the role of inflammatory process in forming and promoting atherosclerotic plaques, carotid intima-media thickness (CIMT), arterial wall disruption, and vascular wall instability has been well documented (5). However, it is not well known the role of infectious agents as inflammatory response, but there are various documents regarding microorganisms such as *Cytomegalovirus* (CMV), *Hepatitis C virus* (HCV), Human immunodeficiency virus (HIV), *Herpes simplex virus type 1–2* (HSV 1–2), *Epstein Barr virus* (EBV), *Influenza virus*, periodontal microflora, *Helicobacter pylori*, *Chlamydia pneumoniae*, *Haemophilus influenza*, *Mycoplasma pneumoniae*, *Mycobacterium tuberculosis*, *Streptococcus pneumonia*, *Tannerella forsythia*, and their role in formation of atherosclerotic lesions, metabolism disorders, hypertension, and promotion of cardiovascular disease (CVD) indexes (6–11). It seems that human pathogenic bacteria can be assumed as risk factors in developing CVD through mechanisms such as toxins, enzymes, influence on host immune response during chronic infections, and infective endocarditis (3, 6). According to review of the literature, endocarditis and septicemia increase the risk of infection to stroke (12). Nevertheless, information is limit in this context. The present study was done for the purpose of plausible relationship between ischemic stroke and infection by *H. pylori*, *C. pneumoniae*, *M. pneumoniae*, and *M. tuberculosis*. Also, potential risk for affecting to stroke was estimated for each group of infective agents.

2. Methods

2.1. Literature search strategy

The comprehensive systematic search up to May 2020 was used databases Scopus, PubMed, Cochrane Library, Embase, and Google scholar. For searching, we used keywords "*Helicobacter pylori*" AND "Ischemic Stroke" OR "*Chlamydia pneumoniae*" AND "Ischemic Stroke" OR "*Mycoplasma pneumoniae*" AND "Ischemic Stroke" OR "*Mycobacterium tuberculosis*" AND "Ischemic stroke" OR "Bacterial infection" AND "Ischemic stroke". Without limitation in date of publication, all published English article were retrieved. Searching strategy was done by two authors, separately; in disagreements, the third author judged and made decision.

2.2. Study selection criteria

In the present meta-analysis inclusion criteria were contained four items: 1) case-control studies on the role of bacterial infections in developing to ischemic stroke; 2) the only included studies on the role of infection by *H. pylori*, *C. pneumoniae*, *M. pneumoniae*, and *M. tuberculosis*; 3) accordance of methods based on standard protocols including ELISA and other immunoassays, conventional microbiology methods, PCR, blotting assay, and finally urease breath test; 4) clarity in the results of studies. In addition, the studies consist of case-report, letter to editor, review, congress abstract, non-English, prospective or cohort, and also other studies such post-stroke infections, repetitive results, and unclear studies, were considered as exclusion criteria. The flowchart of included studies is presented in Fig. 1.

2.3. Quality assessment and data collection

The quality assessment of included studies was evaluated by The Newcastle-Ottawa Scale (NOS). Required information include first author, publication year, location of each studies, type of infection agents, diagnostic methods for infection, age, gender, case group, control group, and number of infected cases in both case and control groups (Table 1).
| First Author | Year | Area   | Age (year) | Gender (F/M) | Case group (n) | Control group (n) | Microorganism type | Number of bacterial infections (n) | Method |
|--------------|------|--------|------------|--------------|----------------|-------------------|-------------------|----------------------------------|--------|
| Masoud       | 2005 | Iran   | 64.3       | 61.7         | 43/48          | 40/40             | H. pylori         | 59/36                            | ELISA  |
| Srivistava   | 2014 | India  | 43.6       | 43.2         | NA             | NA                | C. pneumoniae     | 42/26                            | ELISA  |
| Muller       | 2003 | Denmark| 69.0       | 45.0         | 84/109         | 125/243           | C. pneumoniae     | 20/29                            | PCR    |
| Jozwik       | 2007 | Poland | 44.0       | 40.0         | 40/54          | 44/59             | C. pneumoniae     | 63/15                            | ELISA  |
| Kongoji      | 2005 | Japan  | 63.5       | 62.7         | 7/6            | 2/5               | C. pneumoniae     | 5/0                              | PCR    |
| Kawamoto     | 2003 | Japan  | 75.0       | 74.0         | 17/23          | 48/37             | C. pneumoniae     | 29/52                            | ELISA  |
| Gabrielli    | 2003 | Italy  | 68.0       | 66.0         | 56/49          | 66/64             | H. pylori         | 75/81                            | ELISA  |
| Sagar        | 2016 | India  | 47.8       | 46.6         | 14/25          | 8/22              | H. pylori         | 26/12                            | ELISA  |
| Majka        | 2002 | Germany| NA         | NA           | NA             | NA                | H. pylori         | 69/54                            | ELISA  |
| Mrden        | 2017 | Croatia| 72.8       | 72.8         | 34/32          | 34/32             | H. pylori         | 21/32                            | ELISA  |
| Ashtari      | 2008 | Iran   | 65.4       | 60.2         | 43/38          | 24/19             | H. pylori         | 57/29                            | ELISA  |
| Lin          | 2008 | Taiwan | 64.2       | 63.2         | 202/248        | 198/252           | C. pneumoniae     | 334/257                          | ELISA  |
| Ponzetto     | 2002 | Italy  | 56.7       | 57.4         | 22/58          | 88/232            | H. pylori         | 64/190                           | UBT    |
| Bandaru      | 2008 | India  | 47.8       | 47.8         | 149/51         | 149/51            | C. pneumoniae     | 72/35                            | ELISA  |
| Mousavi      | 2011 | Iran   | 65.6       | 62.9         | 46/50          | 36/57             | H. pylori         | 44/39                            | ELISA  |
| Hassanein    | 2014 | Egypt  | 53.0       | 52.6         | 35/55          | 25/35             | H. pylori         | 70/32                            | ELISA  |
| Rasura       | 2013 | Italy  | NA         | NA           | NA             | NA                | C. pneumoniae     | 26/8                             | ELISA  |
| Eini         | 2014 | Iran   | 68.9       | 66.9         | 60/81          | 60/81             | C. pneumoniae     | 111/74                           | ELISA  |
| Cook         | 2016 | UK     | 67.9       | 56.5         | 73/103         | 674/844           | C. pneumoniae     | 81/280                           | MIF    |
| Bastiani     | 2008 | Italy  | 76.6       | 76.5         | 51/55          | 51/55             | H. pylori         | 67/57                            | UBT    |
| Elkord       | 2000 | USA    | 68.5       | 68.5         | 47/42          | 47/42             | C. pneumoniae     | 72/74                            | ELISA  |
| Elkord       | 2006 | USA    | 72.3       | 72.3         | 125/121        | 219/38            | C. pneumoniae     | 156/257                          | ELISA  |
| Ebrahimi-Rad | 2014 | Iran   | NA         | NA           | NA             | 27/25             | C. pneumoniae     | 20/13                            | ELISA  |
| Hasani       | 2011 | Iraq   | 58.02      | 56.1         | 18/32          | 18/22             | C. pneumoniae     | 36/21                            | ELISA  |
| Wincup       | 1996 | UK     | 54.0       | 53.5         | NA             | NA                | H. pylori         | 93/78                            | ELISA  |
| Park         | 2006 | Korea  | 66.7       | 66.8         | 62/63          | 62/63             | H. pylori         | 100/75                           | ELISA  |
| Heuschmann   | 2016 | Germany| 74.6       | 74.6         | 77/68          | 138/122           | H. pylori         | 67/117                           | ELISA  |
| Salmasi      | 2017 | Iran   | 66.7       | 65.9         | 38/32          | 39/31             | H. pylori         | 61/51                            | ELISA  |
| Madre        | 2002 | Spain  | 70.0       | 70.0         | 46/45          | 53/59             | C. pneumoniae     | 40/34                            | IFI    |
| Kęsinska     | 2011 | Latvia | 65.8       | 64.3         | 41/61          | 22/26             | C. pneumoniae     | 64/17                            | ELISA  |
| Moayyedi     | 2003 | UK     | 70.5       | 70.2         | 228/239        | 227/161           | H. pylori         | 274/206                          | ELISA  |
| Ngeh         | 2003 | UK     | NA         | NA           | 59/41          | 60/27             | C. pneumoniae     | 71/57                            | ELISA  |
| Roham        | 2016 | Iran   | 69.1       | 67.2         | 61/36          | 51/46             | M. pneumoniae     | 4/0                              | ELISA  |
| Ngeh         | 2004 | UK     | 80.0       | 80.0         | 59/41          | 57/25             | M. pneumoniae     | 95/82                            | ELISA  |
| Njamnshi     | 2006 | Cameroon| NA         | NA           | 64/0           | 64/0              | C. pneumoniae     | 41/35                            | ELISA  |
| Rai          | 2011 | India  | 53.6       | 38.6         | 16/35          | 14/34             | C. pneumoniae     | 32/38                            | ELISA  |
| Pietroisti   | 2002 | Italy  | 63.2       | 63.9         | 11/50          | 89/62             | H. pylori         | 43/106                           | PCR    |
| Wu           | 2014 | Taiwan | 53.0       | 53.2         | 1922/3882      | 1925/3879         | M. tuberculosis   | 176/207                          | Culture |
2.4. Quantitative synthesis

Analyzing of data was done by use of Comprehensive Meta-Analysis (CMA) software version 2.2 (Biostat, Englewood, NJ). For this purpose, first the frequency of either bacterial infection including H. pylori, C. pneumoniae, M. pneumoniae, and M. tuberculosis for both case and control groups was measured and reported according event rate (%). Next, potential role of bacterial infection in forming and developing to ischemic stroke was calculated using Odds ratio (OR) with 95% Confidence intervals (CIs). Moreover, by Cochran’s Q and $I^2$ statistic parameters, we analyzed heterogeneity of included studies. Based on our default, the cases with Cochrane $Q$ statistic p < 0.1 and $I^2$ > 25% were considered as high heterogeneity cases. According to the Dersimonian and Laird method, the random effect model and the fixed effect model were applied in high heterogeneity and low heterogeneity cases respectively. Finally, Egger's regression was used for estimating asymmetry of funnel plot and also publication bias.

3. Results

3.1. Characterization of included studies

Regarding primary searching, 238 documents of 1996–2017 was identified and finally in accordance with inclusion criteria 50 studies were selected. Of these studies, 28, 18, 2, and 2 studies were related to C. pneumoniae, H. pylori, M. pneumoniae, and M. tuberculosis respectively. In addition, the diagnostic methods included ELISA, PCR, UBT, MIF, IFI, and conventional microbiology. In the present study the information of 33,978 individuals including 13,652 patients (case) and 20,326 healthy (control) was investigated. Average of age in case and control groups was 61.7 and 59.8 respectively. The frequency of men in both case and control groups was measured 62.6% and 56.1% respectively. According to statistical analysis, the bacterial infection in both case (ischemic stroke) and control groups was 38% (37–39 with 95% CIs) and 26% (25–27 with 95% CIs) respectively. We also found a meaningful relationship between bacterial infections and progression into the ischemic stroke (OR: 1.704; 1.57–1.84 with 95% CIs; p-value = 0.001; $I^2$ = 78.55; Q-value: 219.11; df = 47; Egger’s intercept = 1.23).

3.2. The possible association between C. pneumonia infection and ischemic stroke

We found twenty articles which were about the role of infection by C. pneumonia in progression to stroke. The rate of infection was estimated in both stroke and healthy groups 57% (54–59 with 95% CIs) and 36% (34–37 with 95% CIs) respectively. A significant relevance was observed between infection by C. pneumonia and stroke (OR: 2.14; 1.91–2.38 with 95% CIs; p-value = 0.001; $I^2$ = 71; Q-value = 93.29; df = 27; Egger’s intercept = 0.06).

3.3. The possible association between H. pylori infection and ischemic stroke

Of total of fifty case-control articles which was been included to this meta-analysis, eighteen articles were about the relevance of infection by H. pylori and stroke. The infection rate in both patient and healthy groups was 63% (60–65 with 95% CIs) and 55% (52–57 with 95% CIs) respectively. In accordance with statistical results, it seems that there is a meaningful relationship between infection by H. pylori and ischemic stroke (OR: 1.64; 1.44–1.87 with 95% CIs; p value = 0.001; $I^2$ = 72.88; Q-value = 59; df = 16; Egger’s intercept = 1.87).

3.4. The possible association between M. pneumonia infection and ischemic stroke
In relating of plausible role of infection by *M. pneumonia* and occurrence of ischemic stroke we found only two eligible studies. The incidence rate of infection in both case and control groups was 55% (39–70 with 95% CIs) and 47% (11–86 with 95% CIs) respectively. We did not find any significant relationship between *M. pneumonia* infection with ischemic stroke (OR: 0.97; 0.12–7.69 with 95% CIs; p-value = 0.98; 12 = 77.94; Q-value = 4.53; df = 1).

### 3.5. The possible association between *M. tuberculosis* infection and ischemic stroke

Finally, for evaluating the relevance between infection by *M. tuberculosis* and stroke we used two studies. Based on statistical analysis, the rate of infection by *M. tuberculosis* in both ischemic and age-gender matched healthy groups was 4% (3.6–4.5 with 95% CIs) and 3% (3.3-4 with 95% CIs) respectively. However, we observed a significant relationship between infection by *M. tuberculosis* and development into the ischemic stroke (OR: 1.15; 0.99–1.34 with 95% CIs; p-value = 0.05; 12 = 94.73; Q-value = 18.98; df = 1). Generally in the present study we appraised the potential role of bacterial infections by *C. pneumoniae, H. pylori, M. pneumoniae, M. tuberculosis*, and progression to ischemic stroke. In this meta-analysis we demonstrated a meaningful relationship between infection by three bacteria *C. pneumoniae, H. pylori, and M. tuberculosis* with occurrence of ischemic stroke. Nevertheless, the high heterogeneity and low validity of studies affected on our results. In addition, due to the limitation of results we could not evaluate the role of underlying factors such as age and gender.

### 4. Discussion

It is clear that the stroke is one of the most highlight cardiovascular disorders, and traditional risk factors including hypertension, diabetes mellitus, smoking, hyperlipidemia, atrial fibrillation, atherosclerosis, age, male sex, and positive family history can increase the risk of it (13). Predisposing risk factors for emerging and developing of stroke are different regarding differences in individuals, so that increase of stroke in the youth and its trend to autumn and winter shows some interfering modifiable risk factors that are not well known (14). In recent decades understanding of the role of acute and chronic infections in the occurrence of stroke is interested, so that various nested case-control studies have been conducted in this regard. Obviously infection can be lead to inflammation, which in turn triggers some complications such as formation of fatty plaques in the vessel wall, atherogenic reactions, and alteration in host metabolism (15). These changes are as underlying factors for affecting on CVDs especially ischemic stroke (Fig. 2). Of all, the infections caused by pathogens such as *C. pneumoniae, H. pylori, M. pneumoniae*, HIV, HSV 1–2, and CMV are more considerable, so that these infectious microorganisms have been frequently isolated from atherosclerosis plaque (16). On the other hand, induction of CIMT and high portion of seropositive population affected by CVD confirm this phenomenon (17). Nowadays there are several documents about the role of bacterial infections in increasing of stroke; for example, infective endocarditis causes to create emboli and arteritis. Moreover, bacterial meningitis and chronic brucellosis can be caused vasculitis and thrombosis in brain arteries, and likewise, rickettsial infections lead to damage of small vascular endothelial cells and the onset of ischemic stroke (14). In recent study the impressive role of bacterial infections in increasing of ischemic stroke was demonstrated, and using statistical analysis of fifty case-control studies we showed that there is a significant relationship between bacterial infection and ischemic stroke cases (OR: 1.7; CI: 1.5–1.8). *C. pneumoniae* is a gram negative and obligate intracellular bacterium that was first introduced in 1980s. More than half of population is infected by this bacterium worldwide, and serological investigations has confirmed this fact (18, 19). In many studies researchers has isolated *C. pneumoniae* from carotid plaques, atherosclerotic plaques, and circulating leukocytes (15). Sander et al. (2004) showed that eradication of *C. pneumoniae* infection can be lead to stop CIMT (20). The clinical trial studies also have shown that the treatment of this infection can be caused reduction of vascular lesions in patients (21). In our study the rate of infection by *C. pneumoniae* in both case and control groups was evaluated 57% and 36% respectively. Also, we showed that there is a meaningful relationship between infection by this bacterium and emergence of ischemic stroke (OR: 2.14; CI: 1.9–2.3). *H. pylori* is a spiral, gram negative, and microaerophilic bacterium which is colonized in human gastric sub-mucosa about half of the world’s population (22). The rate of infection by this bacterium in developing countries is more than developed countries, so that in some regions of Africa infection by this pathogen reaches about 100% (23, 24). The bacterium is accounted as etiologic agent in disorders such chronic gastritis, peptic ulcer, as well as gastric cancer. However, *H. pylori*-related extra-gastrointestinal diseases have attracted a lot of attention, in which the relevance of *H. pylori* infection and CVD is well-known (25, 26). In addition to the several evidence regarding with isolation of *H. pylori* from atherosclerotic plaques, there are various documents about the effect of infection by this bacterium on some complications including insulin resistance, dyslipidemia, hypertension, and alteration in metabolism which describe the potential role of infection with this bacterium in increasing of ischemic stroke (27, 28). Based on our statistical analysis, the infection by this pathogen in both groups of ischemic stroke patients and age-gender matched healthy individuals was estimated 63% and 55% respectively. We observed a significant relationship between infection by this bacterium and development of ischemic stroke (OR: 1.6; CI: 1.4–1.8). *M. pneumoniae* is one of the respiratory pathogens that in spite of poor understanding about its pathogenicity, many of people have anti-*M. pneumoniae* antibodies (IgG and IgM). In recent several studies have noted to its role in extra-pulmonary manifestations such musculoskeletal, gastrointestinal, dermatologic, hematologic, neurological involvements, and cardiovascular complications (27, 29). According to review of the literature, near the 0.1% of infected to *M. pneumoniae* will get neurological disability during their lives (30). The vasculopathies lesions caused as a result of this bacterial infection are indicating the role of *M. pneumoniae* in increasing the ischemic stroke (14, 31). Two studies in this meta-analysis were related to the role of *M. pneumoniae* in susceptibility to ischemic stroke; infection by this bacterium in both groups of case and control was 55% and 47% respectively. Also, based on statistical analysis we observed no significant relationship between infection by *M. pneumoniae* and ischemic stroke (OR: 0.97; CI: 0.12–7.6). However, the low sample number could effect on outcomes, since only two studies allocated to this bacterium. In addition, high heterogeneity causes instability of results and we need furthermore studies in this regard. *M. tuberculosis* is one of the threatening pathogens of human life. Although this bacterium usually is known with the term “pulmonary tuberculosis”, but it is a facultative intracellular pathogen which also has extra-pulmonary manifestations (32). In recent years the role of bacterium in promoting of neurological manifestation has been evaluated, so that in result of arterial invasion, malignant vasculitis can be occurred during the tubercular meningitis (14).

### 5. Conclusion

In the present study the information of two nested case-control studies about the role of *M. tuberculosis* in ischemic stroke was appraised. The rate of infection by this pathogen in both groups of case and control was 4% and 3% respectively; we found a significant relevance between mycobacterial infection
and ischemic stroke (OR: 1.1; CI: 0.99–1.34). In this study we assessed the relationship between bacterial infections and development of ischemic stroke. Nevertheless, due to limitation of in results we could not evaluate the role existing factors such age and sex in our research. Overall, for understanding the role of bacterial infections in ischemic stroke, it is better to do more studies about the association between bacterial infections and traditional ischemic stroke risk factors, carotid intima-media thickness, atherosclerosis, and cardiovascular risk factor such as LDL and HDL. Another limitation of our studies were including low sample number, excessive heterogeneity, potential publication bias, and low sturdy number in particular *M. pneumonia* and *M. tuberculosis*. We recommend further studies with more sample volume for determining the bacterial infection and their determinative role in ischemic stroke.

6. Abbreviations

Carotid intima-media thickness  
CIMT  
Cardiovascular disease  
CVD  
Cytomegalovirus  
CMV  
Hepatitis C virus  
HCV  
Human immunodeficiency virus  
HIV  
Herpes simplex virus type 1–2  
HSV 1–2  
Epstein Barr virus  
EBV

7. Declarations  
- Ethics approval and consent to participate  
Not applicable (this paper was provided based on researching in global databases)

- Consent to publish  
All authors have informed consent about the content of this paper.

- Availability of data and materials  
All data will be available for anyone who requests those.

- Competing interests  
There is no any conflict of interest among the all authors.

- Funding  
We have not received any funding for this research.

- Authors’ Contributions  
1. MK was a major contributor in writing the manuscript  
2. MK was research director and translated this manuscript to English

All authors read and approved the final manuscript

- Acknowledgements  
We appreciate from both Mashhad University of Medical Sciences and Jiroft University of Medical Sciences.

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Figure 1

The flowchart of included studies.
Cardiovascular disorders caused by infection. Bacterial infections cause some cardiovascular disorders including parent atherosclerosis plaques, Carotid artery atherosclerosis, and Aortic arch atheroma. This figure was taken from the website https://smart.servier.com/image-set-download/.

Supplementary Files

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- PRISMAchecklist.doc