

Prevalence of *Helicobacter pylori* Infection in Patients with Central Serous Chorioretinopathy: A Review

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ABSTRACT

Helicobacter pylori is a prevalent cause of gastrointestinal infections. Recently, several studies have shown a relationship between *H. pylori* infection and a variety of extradigestive manifestations. The aim of this study was to review the literature regarding the prevalence of this infection in cases of central serous chorioretinopathy (CSR). We reviewed the EMBASE, Cochrane Library, and Google Scholar search engines; hand-searched many journals; and searched the cited references in published articles for relevant studies. We assessed 81 studies for eligibility. Finally, nine articles that met the inclusion criteria were included. The relationship between *H. pylori* infection (as the etiologic factor) and chorioretinal involvement was assessed by the effect size with 95% confidence interval (CI). Both fixed- and random-effects models showed that the prevalence of *H. pylori* infection in patients with CSR was significantly higher than in the control group (2.5-fold and 2.7-fold higher, respectively; $P < 0.01$). The results were not significantly different between the two models. Treatment of *H. pylori* infection should be considered in patients with CSR. However, additional randomized controlled clinical trials are required to determine the possible role of *H. pylori* eradication in the prognosis and treatment of patients with CSR.

KEY WORDS

Prevalence; *Helicobacter pylori*; Central Serous Chorioretinopathy; Systematic Review; Gastrointestinal Infections

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INTRODUCTION

Helicobacter pylori is a helix-shaped, Gram-negative microphilic bacterium that inhabits various regions of the stomach and duodenum. It is one of the most common causes of gastric infections worldwide [1] and the etiological basis of many diseases such as gastritis, gastric

ulcer, gastric cancer, and lymphoma. Notably, *H. pylori* is suspected as a possible cause of early-onset focal obstructive arterial diseases [2]. In the past decade, several studies have investigated the possible relationship between *H. pylori* infection and various



other complications and manifestations, such as Raynaud's phenomenon, cardiovascular diseases, pulmonary diseases, urticaria, and rosacea [3, 4]. Recently, the relationship between *H. pylori* infection and eye diseases, including blepharitis, uveitis, dry eye syndrome, glaucoma, and central serous chorioretinopathy (CSR), has been a matter of interest [5]. However, it is unclear how *H. pylori* might affect the eye [5, 6]. CSR is an idiopathic condition that is characterized by the development of a well-circumscribed serous detachment of the neurosensory retina (neuroepithelium), resulting from altered barrier and deficient pumping function at the level of the retinal pigment epithelium (RPE) in the macular region [7]. Studies have estimated the annual incidence rate of CSR, which is 10/100,000 in men (six times more common than in women) [8]. Many individuals with CSR may be asymptomatic or may suffer from visual disturbances, such as a sudden-onset decrease of vision (blurred vision), color vision deficiency, micropsia, metamorphopsia, or central scotoma [8].

A decrease in visual acuity (VA) can be detected with a Snellen visual acuity chart; color vision changes can be measured via standard testing (for example, using pseudoisochromatic plates such as the Ishihara plate, or by panel tests, such as the Lanthony 15-Hue Desaturated Test); central scotoma may be identified on macular perimetry (microperimetry) or by using the Amsler grid test [9]. Retinal lesions can be observed on optical coherence tomography (OCT) images. Occasionally, angiographic studies (fluorescein angiography, indocyanine green angiography, or three-dimensional angiography) are required for further investigation [10]. Fortunately, CSR exhibits a benign natural course and symptoms improve over a period of 3–4 months [11]. Because of the spontaneous resolution of the neurosensory retinal detachment (RD), the prognosis of patients with CSR is often favorable; however, a small percentage of patients can progress to chronic or progressive disease with severe visual loss for more than 6 months; this is defined as diffuse decompensation of the RPE [11]. Men become more susceptible in the third to fifth decades of life, and are more likely to be affected if they exhibit a Type A personality. Other known predisposing factors include corticosteroid therapy or psychotropic medications, emotional strain, organ transplant, pregnancy, and connective tissue diseases, such as systemic lupus erythematosus [8].

The pathophysiology of CSR remains unknown, and no effective treatment is available. Recently, immune-dependent mechanisms have been proposed. A possible

immune mechanism is based on the molecular mimicry between *H. pylori*-expressed antigens and homologous host proteins (e.g., vascular endothelial proteins) [12]. Many other studies have investigated the causal relationship between *H. pylori* infection and CSR [2, 13–15]. In a prospective pilot study of 16 patients with CSR and diffuse retinal pigment epitheliopathy (DRE), the prevalence of *H. pylori* infection was significantly higher in patients with CSR than in the general population [2]. In another study, the prevalence was also significantly higher in patients with CSR than in a control population from the same country [16]. Subsequent investigations confirmed that *H. pylori* is an important etiologic factor in CSR [12–21]. Nevertheless, the prevalence of *H. pylori* infection in patients with CSR remains controversial, as some studies have reported that the prevalence of this infection is not higher in patients with CSR than in controls [22, 23]. The aim of this study was to systematically review the literature regarding the prevalence of *H. pylori* infection in CSR to more clearly describe the relationship between *H. pylori* infection and chorioretinal involvement in CSR. All retrospective studies that investigated *H. pylori* infection as an etiologic factor in CSR were analyzed.

MATERIALS AND METHODS

This review study was conducted in accordance with the guidelines for systematic reviews in health care [24]. An extensive article search was conducted using the MEDLINE, EMBASE, and Cochrane Library databases, with a search period through March 2016 and no language restriction. Retrospective observational studies regarding the prevalence of *H. pylori* infection in patients with CSR were screened using a search strategy that was based on the following Medical Subject Heading (MeSH) terms:

"(((central serous Chorioretinopath*) OR (Chorioretinopath* AND central serous) OR (serous Chorioretinopath* AND central) OR (central serous Retinopath*) OR (Retinopath* AND central serous) OR (serous Retinopath* AND central) OR cscr OR CSR OR CSC)) AND (((campylobacter pylori) OR (rdxa protein AND h. pylori) OR (LPS AND h. pylori) OR (helicobacter pylori lipopolysaccharide) OR (antibacterial cecropin-like h. pylori peptide hp (2-20)) OR (vacuolating cytotoxin AND h. pylori) OR (hvlr protein AND helicobacter pylori) OR (vacuolating toxin AND helicobacter pylori) OR (helicobacter pylori vacuolating toxin) OR (hydrogenase nickel incorporation protein hypa AND h pylori) OR (hypa protein AND helicobacter pylori) OR (outer membrane protein homb AND h pylori) OR (tumor necrosis factor-alpha-inducing protein AND helicobacter pylori) OR (hp0596 protein AND h pylori) OR (tnf-alpha-inducing



protein AND helicobacter pylori) OR (clone p32 protein AND h pylori) OR (asd enzyme AND h pylori) OR (ylxh protein AND h pylori))”.

The search strategy for the MEDLINE, EMBASE, and Cochrane Library databases was similar to that utilized for the PubMed database. In the next step, we performed a comprehensive literature search using the Google Scholar search engine (scholar.google.com). Additionally, a manual search was conducted in the following journals: *American Journal of Ophthalmology* (www.ajo.com), *Retina Journal* (www.journals.lww.com/retinajournal), *British Journal of Ophthalmology* (bjo.bmj.com), and *European Journal of Ophthalmology* (www.eur-j-ophthalmol.com).

Finally, the cited references in the retrieved studies were manually reviewed for additional relevant results. After the structured search, we assessed 81 studies for eligibility, and their full-text versions were retrieved. All

papers were reviewed by three independent investigators to avoid potential bias or errors. Essential data extracted by researchers, and literature with an agreement rate above 80%, were included. Discrepancies were resolved by discussion or referral to a fourth investigator if necessary (Fig 1).

Of the included studies, two did not have a control group and two did not provide sufficient data for analysis. Therefore, the data of five studies were ultimately entered into Comprehensive Meta-Analysis (CMA.2) software for analysis. To assess the overall effect size, we used both fixed- and random-effects models (Fig 2). According to these models, the prevalence of *H. pylori* infection was 2.5-fold and 2.7-fold higher, respectively, in patients with CSR than in the control group (fixed-effects model: OR = 2.52, 95% CI 1.64–3.89; random-effects model: OR = 2.77, 95% CI 1.53–5.02) (Fig 2).

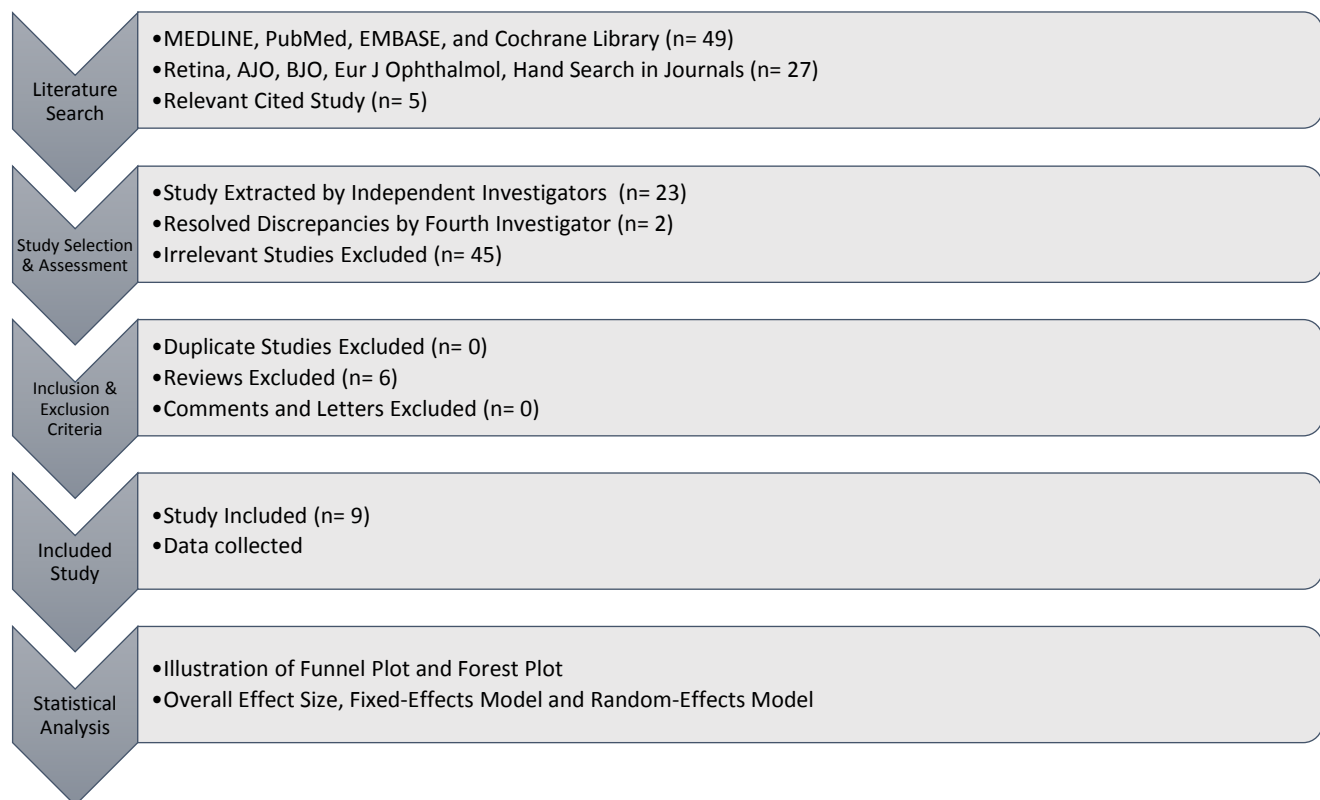


Figure 1. This figure shows the methodology of the study, in a stepwise fashion.

In this study, the final agreement rate among the reviewers was 90%. The following information was obtained from all studies and entered in an extraction table: the first author’s surname, the publication year, the city and country, the number of subjects, and the odds ratio (OR) with P-value (for studies that contained a

control group). Data were analyzed by CMA.2 software. The relationship between *H. pylori* infection (as an etiologic factor) and chorioretinal involvement was assessed by the effect size with 95% confidence interval (CI). To estimate the overall effect size, we used fixed- and random-effects models. In addition, by utilization of



a funnel plot, these two models were evaluated to identify any potential publication bias.

RESULTS

Of the 81 studies assessed for eligibility, a total of nine retrospective studies met the criteria for entry and were included in the analysis. The studies examining the prevalence of *H. pylori* infection in CSR included a total of 309 patients with CSR and 295 cases in control groups, or

in a historical control population (as in two studies). The extracted data are listed in Table 1.

The prevalence of *H. pylori* infection was significantly greater in patients with CSR than in the control group ($P < 0.01$) and there was no difference between the two models (Table 2).

Furthermore, funnel plot analysis revealed that there was no publication bias (Fig 3).

Table 1. Extracted Data from All Included Studies

Authors	Year	City, country	Prevalence of <i>H. pylori</i> infection in patients with CSR	Prevalence of <i>H. pylori</i> infection in the control group	Odds ratio (P-value)
Roshani et al. [21]	2014	Tehran, Iran	30/35 (85.7%)	76/138 (55.1%)	4.895 (0.001)
Warrow et al. [23]	2012	New York, USA	3/18 (16.7%)	----	----
Misiuk-Hojlo et al. [13]	2009	Wroclaw, Poland	37/55 (67.0%)	26/55 (47.0%)	2.29 (<0.05)
Kmera-Muszynska et al. [18]	2008	Warszawie, Poland	11/14 (78.5%)	----	----
Fegghi et al. [22]	2008	Ahvaz, Iran	37/54 (68.5%)	38/59 (65.0%)	1.20 (0.64)
Asensio-Sanchez et al. [14]	2008	Valladolid, Spain	11/16 (68.75%)	6/20 (30.0%)	5.13 (<0.05)
Cotticelli et al. [15]	2006	Napoli, Italy	18/23 (78.2%)	10/23 (43.5%)	4.6 (<0.03)
Ahnou-Zabsonre et al. [16]	2004	Côte d'Ivoire, France	31/78 (39.7%)	Overall population of 58,419,710 inhabitants of France in 1999 (25.4%)	----
Mauget-Faysse et al. [2]	2002	Lyon, France	9/16 (56.3%)	Historical control population (27.5%)	----

H. pylori, *Helicobacter pylori*; CSR, central serous chorioretinopathy

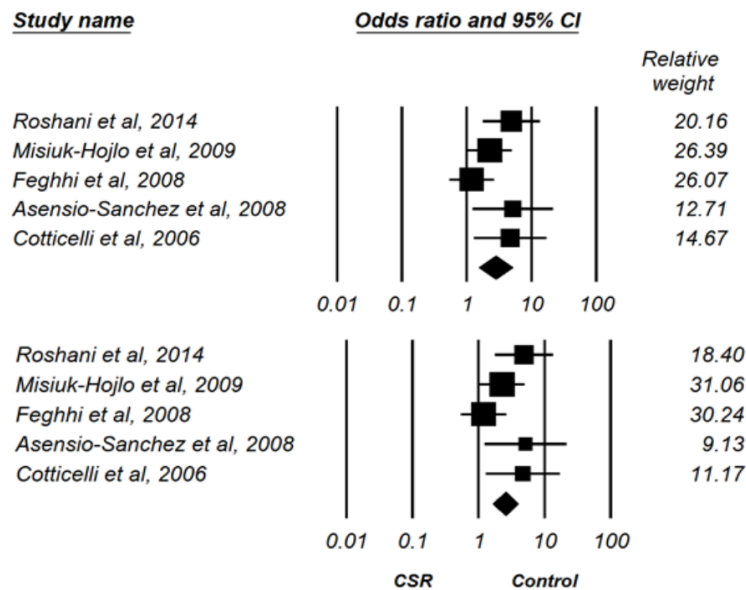
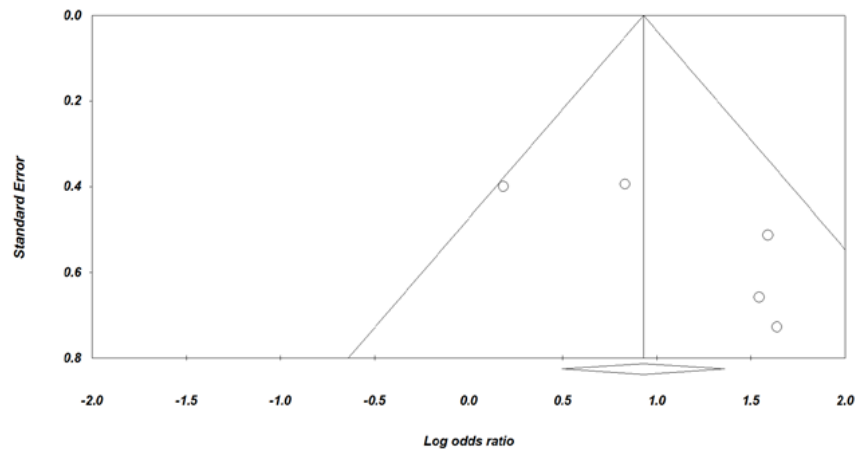


Figure 2. Prevalence of *Helicobacter Pylori* Infection in Central Serous Chorioretinopathy (CSR) Group versus Control Group based on Random-Effects Model (up) and Fixed-Effects Model (down).

**Table 2.** The Results of Systematic Review and Meta-analysis

Model	Number of Studies	Point estimate	Lower limit	Upper limit	P-value
Fixed	5	2.528	1.643	3.890	< 0.001
Random	5	2.778	1.535	5.027	0.001

**Figure 3.** Funnel Plot of Standard Error against Log Odds Ratio.

DISCUSSION

This review of the literature was conducted to elucidate the relationship between *H. pylori* infection and CSR. Data from 302 patients with CSR were included in this study. A total of nine papers were selected to study the possible relationship between *H. pylori* infection and CSR, and five papers were included in the final analysis. The results of fixed- and random-effects models showed that the prevalence of *H. pylori* infection in patients with CSR is 2.5 and 2.7 times higher, respectively, compared with the control group. Similarly, in a prospective pilot study of 16 patients with CSR and DRE, the prevalence of *H. pylori* infection was significantly higher in patients with CSR than in the general population [2]. In another study, the prevalence was also significantly higher in patients with CSR than in a control population from the same country [16]. These results have been confirmed by many other studies [2, 13-16, 18, 22]. For example, in a prospective study involving 35 CSR cases and 135 controls, Roshani et al. (2014) demonstrated that the prevalence of *H. pylori* infection was significantly higher in patients with CSR than in controls. They reported that the symptoms of patients with CSR improved after successful *H. pylori* eradication using standard therapy, and suggested additional randomized controlled clinical trials were needed to confirm the usefulness of *H. pylori*

eradication as a therapeutic option for patients with CSR who exhibit an *H. pylori* infection [21].

In contrast, a prospective study by Warrow et al. (2012) reported a much lower prevalence of *H. pylori* infection in patients with CSR, compared with previous, predominantly retrospective studies (prevalence range: 44%–78%). This disparity may have arisen because *H. pylori* testing in the study by Warrow et al. was performed during periods of CSR quiescence in four of the negative subjects [23]. Ahnoux-Zabsonre et al. (2004) reported that recurrent CSR was always associated with the presence of *H. pylori* infection, whereas improvement in both symptoms (blurred vision and decreased visual acuity) and signs (fundoscopic findings) was associated with successful *H. pylori* eradication [16]. In a study by Mauget-Faysse et al. (2002), 16 patients with long-lasting CSR (> 6 months) or DRE were tested for gastric *H. pylori* infection. The authors reported that 56.3% of patients were positive for *H. pylori*, which was significantly higher than the rate of the historical control population (27.5%) [2]. The same study also reported that the prevalence of *H. pylori* infection was significantly higher in patients with CSR and DRE (39.7%), compared with the general French population (25.4%) [16]. The authors indicated that these results could provide a basis



for further studies regarding the etiopathogenesis of chronic CSR or DRE, which could provide evidence to support effective therapy, i.e., *H. pylori* eradication [2]. Kmera-Muszinska et al. (2008) suggested a role for *H. pylori* infection in the etiopathogenesis of CSR, based on a survey of 14 patients with histopathologically confirmed *H. pylori* infection [18]. The association between *H. pylori* infection and atherosclerosis has been documented in previous studies of *cagA*-positive strains [25]. This study provided new clues regarding the pathophysiology of CSR and its relationship with *H. pylori* infection. It has been suggested that antibodies against the CagA antigen may cross-react with vascular endothelial antigens, thus promoting vascular wall damage and atherosclerosis development [25, 26]. Endothelial cell dysfunction via the proposed mechanism could explain the pathophysiology of CSR in *H. pylori*-infected patients. However, further studies are needed to investigate this and other possible autoimmune mechanisms. One of the limitations of this study was the small number of included papers and the lack of a control group in two of these papers. In conclusion, this review

confirmed that the prevalence of *H. pylori* infection is significantly higher in patients with CSR. Treatment of *H. pylori* infection should be considered in patients with CSR. However, this recommendation merits further investigation. Additional clinical trials are required to clearly discern the role of *H. pylori* eradication in the prognosis and treatment of patients with CSR. If this relationship is confirmed, a new therapeutic protocol for CSR could be introduced in the future.

DISCLOSURE

This study was approved by the review board ethics committee of the training hospital and Tabriz University of Medical Sciences, Tabriz, Iran. No funding or sponsorship was received for this study. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

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