

# The relation between *Helicobacter pylori* gastrointestinal tract infection and central serous chorioretinopathy among patients in Al-Diwaniya province

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## Abstract:

**PURPOSE:** Central serous chorioretinopathy (CSR) is a serous detachment of the central retina. This condition usually affects young males. Its pathogenesis is not fully understood. *Helicobacter pylori* is the most prevalent stomach and gastrointestinal tract (GIT) infection worldwide, and a possible correlation between these two conditions was examined in this study.

**METHODS:** Sixty-two patients with CSR (fifty-five males and seven females) were included in this study. All patients were examined by a senior ophthalmologist and fluorescein angiography was performed for each patient to confirm CSR, which has specific ophthalmic findings. It was found to be the first attack of CSR in 49 patients with the help of history and optical coherence tomography and an Amsler grid test, while in 13 patients it was shown to be recurrent disease. Diagnosis of *H. pylori* was done using the urea breath test at the GIT center in Diwaniya Teaching Hospital, Iraq. The control group contained 162 patients attending the GIT Department at Diwaniya Teaching Hospital with 79 patients with a positive *H. pylori* test and normal comprehensive eye examinations. Patients with any other ophthalmic diseases were excluded from the study.

**RESULTS:** The rate of infection was significantly higher in patients than in control group (47/75.8% vs. 79/48.8%;  $P < 0.001$ ). The odds ratio was 3.29 with 95% confidence interval of 1.71–6.36; therefore, patients with CSR are 3.29 times more susceptible to *H. pylori* infections than control subjects.

**CONCLUSION:** A statistically significant relationship between the presence of *H. pylori* infections with CSR development among young patients was shown. More multi-center studies are needed to confirm this relationship.

## Keywords:

Central serous chorioretinopathy, *Helicobacter pylori*, macula

## INTRODUCTION

*Helicobacter pylori*, previously known as *Campylobacter pylori*, is a Gram-negative, helical-shaped, microaerophilic bacteria that is considered the most prevalent infection of the stomach and upper gastrointestinal tract (GIT). This bacterium is usually associated with the development of gastric ulcers, gastritis, gastric tumors, and lymphoma.

*H. pylori* infections are usually associated with extra-gastric manifestations, such as

cerebrovascular and coronary artery diseases and neurodegenerative and autoimmune allergic disorders. Many pathogenic mechanisms have been hypothesized in the attempt to understand the occurrence of these manifestations, including what is called “molecular mimicry,” which is an induced low-grade inflammation that finally leads to occlusive lesions at the level of small arteries.<sup>[1]</sup>

Central serous chorioretinopathy (CSR) is an idiopathic disease that commonly affects young males 25–50-year-old who usually present with central vision clouding due to fluid accumulation under the retina at the macular region as a result

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of a leaky choriocapillaris at one or more sites beneath the hyperpermeable retinal pigment epithelium (RPE). This condition is rare in females. The male to female ratio was 3:1.<sup>[2]</sup>

Understanding of the pathogenesis of the disease is incomplete, and recent multimodal imaging studies have revealed some new information. It is well-known, however, that the source of subretinal fluid is from the choroid as demonstrated by dye leakage in fluorescein angiography due to simple breakdown at the level of blood retinal barrier.<sup>[3]</sup> A single-nucleotide polymorphism involving the complement factor H gene on chromosome 1 predisposes an individual to CSR, especially the chronic form.<sup>[2]</sup>

The usual presentation of a patient with CSR consists of cloudy central vision, referred to as central scotoma. Vision impairment can be detected by examining the patient with an ordinary Snellen chart, and a central scotoma can be detected using the Amsler grid test, which is a type of central microperimetry. Color vision is also affected, and it can be examined with the Ishihara test.<sup>[4]</sup> Ancillary tests are usually needed to confirm the diagnosis. Optical coherence tomography (OCT) is a good diagnostic tool, but the use of fluorescein angiography is more specific as it shows specific leakage patterns.<sup>[5]</sup> Fortunately, the disease has a limited and benign course with symptom resolution in most of the patients within a few weeks with good prognosis and favorable outcome. In a minority of patients, CSR has a chronic, progressive, and sometimes recurrent course with severe visual loss.<sup>[6]</sup>

Although the exact pathogenesis is not fully understood, emotional stress, especially in a male with type A personality, is considered the most common predisposing factor. Corticosteroids and psychosomatic drugs, organ transplant, pregnancy, and connective tissue diseases also play a role in the predisposition to this disease.<sup>[5]</sup>

It has been documented that a specific strain of *H. pylori* cytotoxin, called *Cag A* strain, which cross-reacts with specific antigens on the endothelial cells that cover the inner surface of the arteries. This reaction leads to vascular wall damage and inflammatory responses, which accelerate atherosclerosis in the early stages. This process does not happen not in all patients with infection and is probably associated only with specific strains of *H. pylori*. This process is considered the most important extragastric manifestation of *H. pylori* infection.<sup>[7]</sup> When this process happens at the level of choriocapillaris, it leads to focal leakage, which may explain the pathogenesis of CSR.

In fact, the IgG response of the immune system of our body to specific pathogens can also be considered a risk factor for endothelial cell damage in cases of *H. pylori* infections.<sup>[8]</sup> Although the infection and its interactions cannot completely explain the angiopathy of CSR, which is most likely a multifactorial organ response,<sup>[9]</sup> all of these steps lead to focal occlusion of the choriocapillaris, which predisposes an individual to focal ischemia through the actions of endothelial

growth factors and lead to the formation of new vessels (angiogenesis), which are leaky and often lead to CSR.

Although this mechanism is not fully understood, most ophthalmologists believe that CSR is due to focal circulatory disturbances at the level of choroid, which finally leads to localized serous detachment of the macula through a small leak in the RPE.<sup>[10]</sup>

## METHODS

Sixty-two patients were enrolled in the study from January 2018 to December 2019. They were attending the Ophthalmology Department in Diwaniya Teaching Hospital complaining of symptoms of cloudy central vision. The mean age was  $36.68 \pm 8.82$  years. All 62 patients underwent a visual acuity examination. They were then examined by the senior ophthalmologist using a slit lamp. The fundus examination showed a detached sensory retina at the macular region. Ancillary tests for each patient included a color vision with Ishihara test, central vision micro-perimeter test, such as the Amsler test, and OCT, which is a highly sensitive imaging technique for examining the retina. OCT results were highly suggestive of a CSR diagnosis. The diagnosis was confirmed by fluorescein angiography showing the leaking at the RPE level.

All patients were sent to the GIT department in which a complete history and physical examination were done. All patients presented a negative history regarding previous GIT diseases. Their drug histories were also negative (all patients with systemic diseases or histories of drug abuse were excluded from the sample). The diagnosis of *H. pylori* was done using the urea breath test (C13 urea breath test), and patients were classified as *H. pylori* positive when the test was positive.

One-hundred and sixty-two patients (143 males and 19 females with a mean age of  $39.57 \pm 12.15$  years) who attended the GIT department and had negative histories except for a positive test for *H. pylori* underwent a complete eye examination. If their results showed no CSR or other pathology, they were added to the control group in the study.

## Ethical issues

Informed consent was taken from all patients, the study protocol was approved by the Ethical committee of Al-Qadisiyah university medical college.

## Statistical analysis

Statistical analysis was done using the SPSS statistical package for social sciences (IBM, Chicago, Illinois, USA, version 23) and Microsoft Office Excel 2010. Quantitative variables were expressed as mean, standard deviations, and ranges, whereas qualitative variables were expressed as numbers and percentages. An independent sample *t*-test was used to compare mean difference between two groups, while the Chi-squared test was used to study the association between categorical variables. The risk was estimated using an odds ratio and 95% confidence interval (CI) levels. The level of significance was considered at  $P \leq 0.05$ .

## RESULTS

The characteristics of patients and control subjects are shown in Table 1. There was no significant difference in mean age between study and control groups ( $36.68 \pm 8.82$  years and  $39.57 \pm 12.15$  years, respectively;  $P = 0.088$ ); in addition, there was no significant difference in frequency distribution of patients and controls according to gender ( $P = 0.093$ ). Most patients presented for the first time (79.0%) and a minority of them had recurrent attacks (21.0%). There was a comparable involvement of left and right eyes with 30 (48.4%) and 28 (45.2%), respectively; however, some patients had bilateral involvement (6.5%) as shown in Table 1.

The rate of positive *H. pylori* test in both groups is shown in Table 2. The rate of infection was significantly higher in the study group than in the control group (47/75.8% vs. 79/48.8%;  $P < 0.001$ ). The odds ratio was 3.29 with 95% CI of 1.71–6.36; therefore, patients with CSR are 3.29 times more susceptible to *H. pylori* infections than controls as shown in Table 2.

There was no significant association between frequency of attacks (first attack versus recurrent) and *H. pylori* infection ( $P = 0.324$ ), as shown in Table 3.

## DISCUSSION

Many studies show the probable correlation between *H. pylori* infections and the development of CSR.<sup>[9,11,12]</sup> These studies described an increase in the incidence of *H. pylori* infections in those with CSR versus the control subjects. CSR is a serous detachment of the retina at the macula. Although the exact pathogenesis is not fully understood, it has been shown to be

associated with some toxins and drugs use, such as tobacco, steroid therapy, sympathomimetic and some psychiatric drugs, Sildenafil citrate, pregnancy, high blood pressure, and some vascular collagen diseases, such as systemic lupus erythematosus.<sup>[13,14]</sup> To date, no specific treatment for this disease exists.<sup>[3]</sup>

In our study, the incidence of *H. pylori* infection was higher in the study group than in the control group (47/75.8% vs. 79/48.8%;  $P < 0.001$ ). The odds ratio was 3.29 with a 95% CI of 1.71–6.36, a result that agrees with most of the previous studies.<sup>[9,11,12]</sup> The incidence of CSR is more common in young male 25–55 years. The mean age in our study was  $36.68 \pm 8.82$  years, a value that corresponds to previous studies. The reason why it is more common in this age group is not clear, but a possible relationship with the hypothesis that CSR is a micro-occlusive disorder associated with the early development of atherosclerosis might be applicable.<sup>[7]</sup>

One study reveals the role played by *H. pylori* in the pathogenesis of CSR and suggests a positive impact of the eradication program of *H. pylori* on the resolution of CSR and improvement in visual outcomes. These actions provide a base for future case–control studies to establish a solid base for CSR treatment strategies.<sup>[15]</sup>

Another theory correlating the CSR pathogenesis involves the heat shock protein (HSP), which is a specific type of protein secreted by specific microorganisms, including *H. pylori*. Secretion of HSP leads to immune reactions since HSP antibodies cross-react with host proteins on endothelial cell walls thus elucidating an inflammatory reaction. This mechanism has been thoroughly studied in coronary artery diseases.<sup>[16]</sup>

Several studies show a relationship between *H. pylori* infections and interactions with plasma and other blood cells. Among the recent studies, it was shown that *H. pylori* infections cause an increase in fibrinogen and plasma lipid levels as a response to low-grade inflammation. This response leads to up-regulation of adhesive molecules on the vascular endothelial cells, which elicit inflammatory reactions, lead to occlusion and ischemic changes, and development of CSR.<sup>[17]</sup>

In spite of these theories, further multi-centers case–control studies are needed to verify the role of *H. pylori* infections in CSR development and the role of an *H. pylori* eradication program on symptom resolution and final visual outcomes. Such a program might lead to the novel discovery of a vaccine to prevent such infections and its associated complications.

**Table 1: Characteristics of patients and controls**

Characteristic	Study group (n=62)	Control group (n=162)	P
Age (years)			
Mean±SD	36.68±8.82	39.57±12.15	0.088 <sup>†</sup> (NS)
Range	21-56	21-70	
Gender, n (%)			
Male	55 (88.7)	128 (79.0)	0.093 <sup>‡</sup> (NS)
Female	7 (11.3)	34 (21.0)	
Attack, n (%)			
First time	49 (79.0)		
Recurrent	13 (21.0)		
Involved eye, n (%)			
Left	30 (48.4)		
Right	28 (45.2)		
Bilateral	4 (6.5)		

<sup>†</sup>Independent samples test, <sup>‡</sup>Chi-square test. NS at  $P > 0.05$ . n=Number of cases; SD=Standard deviation; NS=Not significance

**Table 2: Rate of positive *Helicobacter pylori* serology in patients and control group**

<i>H. pylori</i>	Study group (n=62), n (%)	Control group (n=162), n (%)	P	OR	95% CI
Negative	15 (24.2)	83 (51.2)	<0.001 <sup>‡</sup> (HS)	3.29	1.71-6.36
Positive	47 (75.8)	79 (48.8)			

<sup>‡</sup>Chi-square test. HS at  $P \leq 0.01$ . HS=Highly significant; n=Number of cases; OR=Odds ratio; CI=Confidence interval

**Table 3: Association between frequency of attacks (first attack versus recurrent) and *helicobacter pylori* infection**

<i>Helicobacter pylori</i>	First attack (n=49), n (%)	Recurrent (n=13), n (%)	P
Positive	39 (79.6)	8 (61.5)	0.324
Negative	10 (20.4)	5 (38.5)	Y (NS)

NS at  $P>0.05$ . Y= Yates correction for continuity; n=Number of cases; NS=Not significance

## CONCLUSION

Our study shows an increase in the prevalence of *H. pylori* infections among patients with CSR versus the ordinary population. This finding might support a possible correlation between both factors and establish a base for future studies.

## Compliance with ethical standards

The study is self-funded, all authors declare no conflict of interest, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards and its approved by the Local Ethical Committee at Al-Qadisiyah University College of Medicine, Informed consent was obtained from all individual participants included in the study.

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## Conflicts of interest

There are no conflicts of interest.

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