ANALYSIS OF OPTIC NERVE HEAD PARAMETERS, RETINAL NERVE FIBER LAYERS AND MACULAR THICKNESS IN HELICOBACTER PYLORI INFECTION PATIENTS

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DISCLAIMER

I hereby certify that the work in this my own except for the quotations and summaries which have been duly acknowledged.

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TABLE OF CONTENTS **Page**

CHAPTER 3: MANUSCRIPT

CHAPTER 4: STUDY PROTOCOL

ABSTRAK (BAHASA MALAYSIA)

Latar Belakang

Helicobacter pylori (*H. pylori*) telah diketahui mempunyai manifestasi extragastric. Bahagian mata juga tidak terlepas daripada menunjukkan perkaitan diantara *H. pylori* dengan glaukoma sudut terbuka dan "*chorioretinopathy serous"*. Kedua-dua penyakit ini boleh menimbulkan ancaman besar kepada penglihatan dan boleh menyebabkan kebutaan jika tidak dikenalpasti awal. Tujuan kajian ini adalah untuk menilai parameter saraf optik utama (ONH), ketebalan lapisan serat saraf retina (RNFL) dan ketebalan makular pada pesakit yang menghidapi jangkitan *H. pylori* dan membandingkannya dengan subjek kawalan.

Kaedah:

Satu kajian rentas perbandingan rawak telah dijalankan di Unit Endoskopik Hospital Universiti Sains Malaysia dari Mac 2017 sehingga Jun 2018. Parameter – parameter ONH, RNFL dan ketebalan makular telah diambil menggunakan Pemeriksaan OCT SD-Cirrus. Analisis statistik dilakukan menggunakan Pakej Statistik untuk Sains Sosial, Versi 24.

Keputusan:

Seramai 80 pesakit direkrut ke dalam kajian ini. Empat puluh orang calon dengan jangkitan *H. pylori* dikelompokkan di bawah kelompok positif *H. pylori* manakala 40 orang dewasa yang sihat dikelompokkan di bawah subjek kawalan. Umur minima bagi pesakit positif *H. pylori* adalah 52.43 ±15.67 tahun. Ketebalan RNFL adalah tidak simetri di kumpulan *H. pylori* 81.73% ± 12.81 (p = 0.015). Tiada perbezaan ketara yang dilihat terhadap lain – lain parameter ONH dan RNFL. Terdapat juga peningkatan parameter ketebalan makular di

bahagian “inferior inner” , “nasal inner” dan “nasal outer” selepas faktor umur dan jantina diambil kira.

Kesimpulan:

Kajian ini menunjukan ketebalan RNFL di kumpulan *H. pylori* adalah tidak simetri dan ini boleh memberi petunjuk terhadap tanda awal kecederaan saraf optik utama. Terdapat juga kenaikan purata ketebalan makular di beberapa kawasan retina pada pesakit yang dijangkiti bakteria *H. pylori*.

Kata kunci:

Helicobacter pylori, ONH, RNFL, ketebalan Macular

ABSTRACT (ENGLISH)

Background

Helicobacter pylori (*H. pylori*) has been known to have extra-gastric manifestations. The eye was not spared as in recent years studies have shown the association of *H. pylori* with glaucoma and central serous chorioretinopathy (CSCR). Both diseases posed a significant threat to the vision and can lead to blindness if untreated. This study aimed to evaluate the optic nerve head (ONH) parameters, retinal nerve fibre layers (RNFL) and macular thickness in patients with *Helicobacter pylori* infection and comparing it with controls.

Methods:

A randomised comparative cross-sectional study was conducted at Endoscopic Unit. of Hospital Universiti Sains Malaysia from March 2017 to June 2018. The ONH parameters, RNFL and macular thickness was taken using SD-Cirrus OCT examinations. Statistical analysis was done using Statistical Package for the Social Science, Version 24.

Results:

A total of 80 patients were included in this study. Forty candidates with *H. pylori* infection were grouped under *H. pylori* positive group while another 40 healthy adults were grouped under controls. The mean age for *H. pylori* positive patients were 52.43 ± 15.67 years old. There were asymmetrical RNFL thickness in *H. pylori* group, 81.73% ± 12.81 (p = 0.015). No significant differences were observed on other ONH and RNFL parameters. Macula thickness parameters showed an increase in thickness at the *inferior* inner, nasal inner and nasal outer quadrant after controlling for age and gender.

Conclusion:

This study showed that there is asymmetrical RNFL thickness in *H. pylori* patients and may suggest the possibility of optic nerve damage. There was also an increase in several areas of retinal thickening in patients with *H. pylori* infection patients.

Keywords:

Helicobacter pylori, ONH, RNFL, Macular thickness.

CHAPTER 1

BACKGROUND

1.1 Helicobacter Pylori

Helicobacter pylori (H. pylori) is a gram-negative, spiral-shaped bacterium which is most commonly found in gastric mucosa. Eventhough Bottcher had first discovered an unknown bacterium that caused gastric ulcer in 1875, it was Warren and Marshal that had first cultured this bacterium and described it as a Campylobacter like bacterium (Bottcher, 1874; Warren and Marshall, 1983). This finding had led Warren and Marshal to receive a Nobel Prize in Medicine in 2005 for the discovery of *H. pylori* infection and its role in gastritis and peptic ulcer diseases. Further studies by Nomura et al. have found an association between gastric cancer and *H. pylori* infection (Nomura et al., 1991). Since then, the study of *H. pylori* has been enormous which subsequently leads to the discovery of multiple strains and virulence factors which spreads extensively across the world.

1.1.1 Virulence Factors

The pathogenicity of *H. pylori* was not contributed by only a single virulence factor but occurred in multifactorial. The effect of vacuolisation, carcinogenicity, formation of reactive oxygen species (ROS) and the ability to induce cell death by apoptosis, were the complications of *H. pylori* infection (Izzotti et al., 2009; Testerman and Morris, 2014).

1.1.1.1 Cytotoxin Associated Gene A

The most important virulence factor is cytotoxin associated gene A (CagA) which is responsible for the cell carcinogenesis and also formation of hydrogen peroxide (Butcher et al., 2017). *H. pylori* bacterium will directly inject CagA protein into the host cell cytoplasm and this will affect the host cell physiology as well as changing the cytoskeleton structure of the gastric epithelium (Higashi et al., 2002; Kao et al., 2016). These changes

can induce the release of tumor necrosis α (TNF-α) and interleukin 8 (IL-8), which are the inflammatory mediators, and promoting the migration of polymorphonuclear cell (PMN). Subsequently, PMN will release hydrogen peroxide (a component of ROS) to kill the bacterium (El Miedany et al., 2005). However due to the location of the bacterium itself which is located within the lumen of the gastric mucosa, elimination of *H. pylori* is difficult, and this will lead to chronic inflammation and prolonged infection (Butcher et al., 2017).

1.1.1.2 Vacuolating Toxin A

Vacuolating toxin A (VacA) is responsible for inducing cell death by apoptosis. VacA has the ability to produce vacuoles within the host cells and disrupt the membrane cell wall. VacA is also capable of inserting itself through mitochondria membranes and inducing mitochondrial dysfunction which resulting in cell death (Testerman and Morris, 2014).

1.2 Epidemiology of Helicobacter Pylori Infection

Epidemiologically, the prevalence of *H. pylori* infection varies among different populations worldwide with the highest observed incidence observed in Central/South America and Asia. It is also believed that that the prevalence of *H. pylori* infection among Asian population is often higher than 50% with the elderly and low socio-economic population was the most affected group (Eusebi et al., 2014).

Malaysian population, however, have different prevalence rate among its various multiracial communities. It is found that Chinese and Indian population have a higher percentage of *H. pylori* infection if compared to Malay ethnic group (Sasidharan et al.,

2011). Another interesting study that was done in northern peninsular of Malaysia among blood donors indicates that the prevalence of *H. pylori* is very low among Malay ethnic group which is around 4.2% (Uyub et al., 1994). It is believed that the different cultural background contributed to the difference in prevalence rate among ethnicity in Malaysia, environmental factors as well as dietary factors (Lee et al., 2012).

1.3 Extragastric Manifestation of Helicobacter Pylori Infection

The two main diseases in which *H. pylori* is commonly associated with are gastritis and peptic ulcer disease. In recent year, studies have shown that *H. pylori* also have multiple extragastric manifestations which have been described in various sites of *H. pylori* infection in human (Testerman and Morris, 2014).

Within the gastrointestinal tract, amongst the sites that were found to harbour *H. pylori* infection other than the stomach were the liver, gallbladder and the colon. *H. pylori* was seen to induce carcinogenesis in liver and colon which evidenced by the findings of *H. pylori* through histology and culture in hepatocellular cancer and colorectal adenocarcinoma (Hong et al., 2012; Tian et al., 2008). Within the gallbladder, in chronic cholelythiasis patients, *H. pylori* was also found to induce adenomyomatosis and metaplasia of the gallbladder mucosal layer (Zhou et al., 2013).

Furthermore, the effect of *H. pylori* infection has also been seen in skin diseases. In a study by Federman et al. that examined patients that have chronic idiopathic urticaria, *H. pylori* was found in 30.9% of the total patients affected (Federman et al., 2003). Furthermore, in another study, almost 63.6% of patients with chronic idiopathic urticaria has been in complete remission after eradication of *H. pylori* treatment given (Campanati et al., 2013).

The effect of *H. pylori* towards skin can also be seen in patients with acne rosacea. In a study by Argenziano et al. in patients with rosacea, almost 81% of their patients have harboured *H. pylori* infection (Argenziano et al., 2003). This study has been supported by El-Khalawany et al. in which they observed improvement of rosacea if patient underwent *H. pylori* eradication treatment (El-Khalawany et al., 2012).

The *H. pylori* infection was also studied in relations to neurodegenerative diseases such as in Alzheimer diseases. A study by Kountouras et al. has found that improvement in cognitive function in Alzheimer diseases has been seen in patients that underwent *H. pylori* eradication therapy (Kountouras et al., 2009). Other study that supported such finding has found a strong association of *H. pylori* seropositive with poorer cognitive functions amongst the elderly (Beydoun et al., 2013).

Further study of the effect of *H. pylori* infection towards the lungs has also come into shed when Tsang et al. has found an association of bronchiectasis with *H. pylori* infection. He has found that almost 76% of patients with bronchiectasis has a seropositive for *H. pylori* infection if compared to control (Tsang et al., 1998). In fact, in patients with chronic obstructive pulmonary diseases (COPD), a study have found that COPD patients have higher seroprevalence if compared to controls (Prónai et al., 2004).

1.4 Ocular Manifestation of Helicobacter Pylori Infection

H. pylori was also believed to cause several diseases of the ocular. There were few studies that have shown the role of *H. pylori* in affecting the eyelid and causing anterior blepharitis. Saccà et al. has found that patients with blepharitis were more common to have superimposed *H. pylori* infection if compared to controls (30.6% vs 13.4%). Furthermore,

between the control and *H. pylori* infection, blepharitis in seropositive *H. pylori* was seen to be more severe but responded well to eradication treatment (Saccà et al., 2006). Even though the team was quite sceptical in defining the association of blepharitis and *H. pylori*, the data had suggested that *H. pylori* might play a role in the severity of the diseases itself.

Another structure of the eye that can be affected by *H. pylori* is the uveal tissue. Anterior uveitis, which is a term to describe the inflammation of the anterior aspect of the uveal tissue, was found to also caused by *H. pylori*. A study by Otasevic et al. has found the role of *H. pylori* in causing not only acute anterior uveitis, but also chronic spondyloarthropaties. In their study, seropositive *H. pylori* was seen higher in patients with acute anterior uveitis (at least 66.7% of patients in anterior uveitis) if compared to controls (26.7%) (Otasevic et al., 2006)

Other two most studied diseases of the ocular in *H. pylori* are glaucoma and CSCR. Below are the pathogenesis of *H. pylori* in both of the diseases.

1.4.1 Glaucoma

The role of *H. pylori* in the pathogenesis of primary open angle glaucoma (POAG) has been proposed by Kountouras et al. and Izotti et al. in which both of the teams explained regarding the role of ROS that can induce chronic oxidative stress towards the trabecular meshwork (TM) (Izzotti et al., 2009; Kountouras et al., 2011). These chronic systemic oxidative stress secondary to the continuous release of ROS by PMN will induce the expression of inflammatory mediators and oxidative tissue damage to the TM. This condition will result in the changes of the extracellular matrix and cytoskeleton of the TM

cell and also inducing cell decay (Babizhayev, 2016). Subsequently, the aqueous outflow will be affected and resulting in increasing intraocular pressure.

Other proposed pathogenesis of the role of *H. pylori* is by the direct invasion of the bacterium itself towards the TM that can caused subclinical inflammation and subsequently inducing cross mimicry between endothelium and *H. pylori* antigen. This was evidenced by the findings of Zavos and Kountouras that have shown a direct invasion of *H. pylori* into the TM (Zavos and Kountouras, 2012). They reported the existence of *H. pylori* through iris and TM tissue cultures in POAG patient that underwent trabeculectomy. This evidence has further shed light in the role of *H. pylori* in glaucoma.

Furthermore, *H. pylori* infection was not only affecting the TM, but it is also capable to induce retinal ganglion cell death through apoptosis and leading to glaucomatous changes. In glaucomatous optic neuropathy, high oxidative stress is a known factor in pathogenesis of glaucoma changes (Chrysostomou et al., 2013; Saccà et al., 2007). Among patients with *H. pylori* infection, high levels of ROS and circulating peroxides were believed to be an important apoptotic signals that can leads to glaucoma (Izzotti et al., 2009). These oxidative stress (ROS and peroxides) were believed to induced mitogen-activated protein kinase (MAPK), TNF-α and interferon gamma which are precursor for apoptotic process that can leads to optic nerve head (ONH) degeneration (Izzotti et al., 2009; Winter-Vann and Johnson, 2007). Furthermore, ROS also able to induce extracellular glutamate within the ganglion cells and inducing excitotoxicity leading to cell death (Epstein et al., 1994). All of these pathogenesis proposed by the studies may leads to ONH and retinal nerve fibre layer (RNFL) damage.

1.4.2 Central Serous Chorioretinopathy

Central serous chorioretinopathy is a diseases characterized by a serous detachment of the neurosensory retina in the macula area (Giusti, 2004; Mateo-Montoya and Mauget-Faÿse, 2014). Patients with CSCR may presented with blurring of vision, positive scotoma, micropsia, metamorphosia and impaired colour vision due to the alteration of the macula anatomical configuration by fluid accumulation (Giusti, 2004). Even though CSCR has a favourable outcome in most of the patients, in a small percentage of the patients, CSCR can be persistent and resulted in permanent visual loss. There were no effective treatment available for the patients and this is due to the lack of precise knowledge of its pathogenesis and causative factors.

Evidence of the role of *H. pylori* in developing CSCR was first described by Giusti in his case report. He have found that the recurrence of CSCR in a 43 years old gentleman were associated with the seropositive of *H. pylori* infection. He also observed that the thickness of the macula area showed significant improvement after the successful eradication of *H. pylori* infection (Giusti, 2004). For this reason, a prospective study of 16 patients with CSCR has been done by Mauget et al to search for the causative link of *H. pylori* and CSCR. Interestingly, the study showed a significantly higher prevalence of *H. pylori* was detected in patients with CSCR (Mauget-Faÿsse et al., 2002). A similar findings has been found by Asensio et al which found that seropositive of *H. pylori* was higher in CSCR patients if compared to controls (Asensio-Sánchez et al., 2008).

The proposed pathogenesis for *H. pylori* in developing CSCR has been described by multiple authors with the basic principle of choriocapilaries damage and accumulation of subretinal fluid in the macula area. Cotticelli et al. proposed that *H. pylori* itself will lead to sustained release of cytokines and vasoactives that can alter the endothelial cells of choriocapilaries under the macula (Cotticelli et al., 2006). Other pathogenesis of CSCR suggested by Franceschi et al. discusses about the role of anti-CagA antibodies interaction with the host (Franceschi et al., 2002). In this case, anti-CagA antibodies possessed a cross mimicry with the vascular wall antigens which then can lead to endothelial dysfunction and leakage. Further microangiopathy and occlusion within the choroidal microcirculation will lead to the decompensation of retinal pigment epithelium and subsequently progression towards developing CSCR (Giusti, 2004).

1.5 Rationale of the Study

This study was intended to search for the association of *H. pylori* infection in developing extra gastric manifestation, particularly in the ONH, RNFL and macula. Furthermore, since almost half of Asian populations were estimated to have *H. pylori* infection, it is imperative for us to determine the effects of *H. pylori* in developing glaucoma or CSCR (Eusebi et al., 2014).

While glaucoma is the second leading cause of blindness in the world, its aetiology is still unclear. Recent studies were only able to detect the risk factors for developing glaucoma. The most common modifiable risk factor for glaucoma is elevated intraocular pressure (IOP) (Distelhorst and Hughes, 2003). However, even with the control of IOP to a specific target, the progression of ONH and RNFL damage still continue and thus jeopardizing the patients' vision. Recent evidences have shown that RNFL changes in glaucoma were caused not only by a single factor, but occurred in multifactorial. Such factors that are known to cause RNFL damage are impaired ocular blood flow, oxidative stress, cytokines and autoimmune mechanism (Chrysostomou et al., 2013; Hohenstein-Blaul et al., 2016; Kokubun et al., 2018; Tezel, 2006). In recent studies, such evidences has been proposed by Izzotti et al and Kountouras et al. that emphasize on the high level of oxidative stress in *H. pylori* infection, that may leads not only TM damage, but also ONH and RNFL damage (Izzotti et al., 2009; Kountouras et al., 2011).

However, both of the team had use only POAG patients which already have underlying RNFL loss to search for the complication of *H. pylori* infection. Meanwhile, the study of the effects of *H. pylori* infection towards ONH and RNFL per se in patients with no sign

and symptoms of glaucoma is scarce and was only done by Atilgan et al. in their study. Atilgan et al. has search for the possible effects of *H. pylori* infection towards the ONH and RNFL before and after treatment commencement and subsequently comparing it to healthy control. Their result had shown that the defects seen in *H. pylori* infected patients in the ONH and RNFL was persistent even after eradication treatment was started (Atilgan et al., 2017). This has shown as an evidence that the ONH and RNFL damage, similar to glaucoma, were permanent and irreversible. This further emphasize that the study of ONH and RNFL in patients with *H. pylori* infection may leads to timely detection of structural damage and thus can halt the progression of RNFL loss through early intervention. Moreover, since the structural damage that occur in the ONH and RNFL were believed to be affected first before functional damage of visual field defects, this study was also aimed to look for these early damages rather than functional damage (Johnson et al., 2000). In fact, Johnson et al. also emphasised on the important of detecting structural damage in the early stage of glaucoma that can be accurately related to visual field changes . A quantitative measurements by OCT in detecting structural damage means a more accurate approach can be applied in determining early ONH and RNFL damage. Therefore, due to this belief, Zullo et al. called for extensive research for its pathogenesis that should be done in order for better management of glaucoma patients (Zullo et al., 2012). At the same time, this study will also lead to a better understanding of the role of *H. pylori* in glaucomatous optic nerve damage.

On the other hand, the effects of *H. pylori* towards the macula has only been studied in patients whom already had macula thickening. The detection of high seroprevalence of *H. pylori* in CSCR may indicate that a causal link is possible between these two entities. Both of the pathogenesis proposed regarding the role of *H. pylori* in CSCR has emphasized the

effects of *H. pylori* in causing vascular endothelial damage, which can subsequently leads to macula thickening and visual disturbances. Such damage is evidenced by the disruption of the choroidal and choriocapillaries circulation in CSCR patients with *H. pylori* infection. Furthermore, focal occlusion of choroidal microcirculation in CSCR evidenced by non-profuse areas, filling delays of the choroidal and choriocaplillaries, as well as reduced blood flow during fluorescein and indocyanin green angiography had further strengthened the proposed pathogenesis of CSCR in *H. pylori* infection (Horozoglu et al., 2018). Even though CSCR is known to resolve by itself, almost 50% of the patients may develop recurrence (Giusti, 2004). Early detection of macula thickening in patients with *H. pylori* infection may leads to a better prognosis by preventing recurrence as found by Giusti in his case report (Giusti, 2004).

Thus, with rising evidences of relationship of RNFL and ONH damage with *H. pylori* infection which was described by Kountouras et al. and few other similar studies in different populations, as well as relationship of macula thickening in CSCR with *H. pylori* as described by Giusti, the need for thorough evaluation of *H. pylori* role in the eye diseases, mandate an analysis study to be done (Giusti, 2004; Kountouras et al., 2017).

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CHAPTER 2

OBJECTIVES

2.0 General Objectives

To evaluate the optic nerve head parameters and macula thickness in patients with *Helicobacter pylori* infection.

2.1 Specific Objectives

2.1.1

To compare the mean of optic nerve head parameters between patients with *Helicobacter pylori* infections and control.

2.1.2

To compare the mean of retinal nerve fibre layer thickness between patients with *Helicobacter pylori* infections and control.

2.1.3

To compare the mean of macula thickness in patients with *Helicobacter pylori* infections and control.

CHAPTER 3

MANUSCRIPT

Analysis of Optic Nerve Head Parameters, Retinal Nerve Fiber Layers and Macula Thickness in Helicobacter Pylori Infection

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