

Helicobacter Pylori Infection and Antiphospholipid Antibodies Syndrome: A Case Report and Meta-Analysis of the World Literature

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Introduction

Helicobacter pylori infection is one of the most common chronic infective conditions in the world, present in more than the 50% of the global population [1]. *H. pylori* is a gram-negative helix-shaped bacterium, microaerophilic not sporigen and urease-positive, which colonizes the gastric mucosa, inducing chronic gastritis and peptic ulcer. *H. pylori* infection also concurs to the development of gastric mucosa atrophy, intestinal metaplasia and gastric cancer, such as adenocarcinoma and gastric MALT lymphoma [1-3]. Recent studies have shown that the infection can be related to many extra gastric conditions, such as ischemic heart disease, stroke, neurologic (Alzheimer and Parkinson), endocrine (diabetes mellitus, autoimmune thyroiditis), hematologic (iron deficiency anemia, immune thrombocytopenic purpura), dermatologic (chronic urticaria, acnes rosacea) diseases and infertility [4,5].

The pathogenicity of *H. pylori* is modulated by many virulence factors, in particular the vacuolating cytotoxin VacA and the cytotoxin-associated gene A oncoprotein CagA, which

is expressed by the homologous gene present in the *cag* pathogenicity island. CagA is an important factor even in the development of extra-gastric manifestations, acting through autoimmune or pro-inflammatory pathways [4].

Anti Phospholipid Syndrome (APS) (also known as Hughes syndrome) is an autoimmune disease characterized by hypercoagulability, recurrent miscarriage and arterial and venous thrombosis. Diagnostic criteria of APS include the positivity for circulating levels of LAC (Lupus Anti-Coagulant) antibodies, Anti-b2 glycoprotein-I (IgG and/or IgM isotype) and cardiolipin antiphospholipid antibodies [6, 7]. Recent works underline the possible role of various infections in the etiology of APS including *H. pylori* [7]. The main agents of infection associated with this syndrome are the following: HCV, EBV, VZV, cytomegalovirus, parvovirus B19, HIV, *Salmonella typhi*, *Mycoplasma pneumoniae*, *Mycobacterium leprae* M. tuberculosis, *Streptococcus* spp. and *Staphylococcus* spp., *Borrelia burgdorferi*, *Plasmodium* spp.

Literature Review and Case Analysis – Comparison with our Results

We carried out a meta-analysis according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement guidelines. We searched the medical literature for all publications on *H. pylori* and antiphospholipid

antibody syndrome between January 1983, and October 2013. Searches were performed on Medline, Embase, Clinical Trials, Database of Abstracts of Reviews of Effects (DARE), Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews, Premedline, Healthstar, by using the MeSH heading: "Helicobacter pylori", "H. pylori", "H pylori", "Campylobacter pylori", "C. pylori", "C pylori", "infection", AND ("antibodies, anti phospholipid" OR ("antibodies"[All Fields] AND "antiphospholipid"[All Fields]) OR "antiphospholipid antibodies"[All Fields] OR ("phospholipid"[All Fields] AND "antibody"[All Fields]) OR "phospholipid antibody"[All Fields]).

At the current time, we found only one example in literature supporting the relationship between H. pylori and APS. Cicconi et al. [8], in 2001, reported a case of 33-years old woman, affected by APS and positive for H. pylori infection. In this case, authors found a positive titer for antiphospholipid IgM, related with H. pylori infection confirmed by Urea Breath Test. The patient's symptoms were left sided hemi paresthesias with episodic arms weakness, treated with nimodipine and aspirin for six months without benefits. The antiphospholipid titer decreased after successful H. pylori eradication therapy (clarithromycin 500 mg bid + metronidazole 250 mg bid + omeprazole 20 mg die for seven days), with a gradual symptoms remission.

In April 2003, we observed in our department a 47 year-old woman with a history of recurrent miscarriage (three episodes) and an event of amaurosis. The patient was admitted to our structure for dizziness, nausea and hypotension. Cerebral-CT and MRI showed an obliteration of left basilar artery and PICA, that caused a cerebellar ischemic lesion, with a concomitant severe stenosis of the right basilar artery. The following hematologic tests were performed: ANA, ENA, ANCA, Anti-Mieloperossidase, anti-dsDNA, anti-Chlamydia, CMV, EBV, HSV, HAV, HBV, HCV antibodies, coagulation markers and evaluation of antiphospholipid antibodies (LAC, anti-cardiolipin and Anti-b2 glycoprotein-I). All tests gave

normal results, excepted the following ones: positive LAC titer: aPTT-LA ratio >2 (normal levels <1.2), Platelet Neutralization Procedure >10 (normal values <5), KCT=37 (normal values <15). Tests performed on a serum sample collected six months earlier gave similar results. H. pylori infectious status was determined in serum using commercially available enzyme-linked immunosorbent assays with sensitivity and specificity of 96% (Helicobacter pylori IgG, HpG screen ELISA kit, and Helicobacter pylori CagA kit, provided by Genesis Diagnostics Ltd, Littleport, UK); results were confirmed by home-made Western blotting tests.

The patient was treated since the beginning with warfarin 5 mg, rofecoxib 50 mg and atorvastatin 20 mg; then, we started H. pylori eradication therapy using amoxicillin 1000 mg + clarithromycin 500 mg + omeprazole 20 mg, b.i.d., for ten days, in addition to the base treatment with warfanin, rofecoxib and atorvastatin.

In a subsequent follow-up, an asymptomatic thrombosis of the right popliteal artery occurred in May 2003. In July 2003, LAC titer was reduced (aPTT-LA ratio=1.4). The eradication of infection was verified six months after the end of the treatment by serology, which showed an anti-whole antigen reduction > 50% respect to the titer of the first examination, and by the antigen detection in feces, which gave negative results for three times. In September 2003, the evaluation of APS status gave negative results. Clinical and neurological manifestations disappeared and CT and MRI showed an improvement of the vascular lesions.

Conclusions

According to the results of the meta-analysis on this subject, this is the second case of a possible association between H. pylori infection and APS. We hypothesise those H. pylori infection could concur to determine the development of APS through two possible mechanisms: a phenomenon of antigenic mimicry between bacterial and artery antigens [9] and the chronic stimulation of inflammatory cytokines, which, in

particular, takes place when the infecting organisms express CagA [10, 11]. Before asserting that APS is another extra digestive disease associated with *H. pylori* infection, other studies are needed to confirm these observations. The chronological association of APS improvement and negative LAC titre with eradication of *H. pylori* infection are however suggestive of a role or a concomitant role played by such bacterial chronic infection.

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