Clinical, paraclinical, histological and genetic correlations in children with gastritis

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Gastrointestinal pediatric pathology is probably the most frequent reasons for presenting to the general practitioner or pediatrician. Multiple studies performed in time have reached the consensus that children with gastrointestinal pathologies require close monitoring in order to prevent long-term complications, such as the negative impact on growth, but also the risk of neoplasia.

Gastritis represents the inflammation of the gastric mucosa, frequent among children, which is most often used inappropriately in daily practice based only on the clinical symptoms without any histological proof. Depending on the etiology, multiple classifications are available, but there are two wide groups of gastritis, non-Helicobacter pylori (*H. pylori*) mediated and *H. pylori*-induced gastritis. The prevalence of non-*H. pylori* induced gastritis is very difficult to be estimated since most studies did not focused on this topic as main objective. Contrariwise, *H. pylori* infection is probably the most common infection worldwide, which is acquired during the first decades of life and it can persist the entire life if not treated. Therefore, the identification of this pathology during childhood might prevent the delays regarding its eradication and the occurrence of chronic inflammation that might results in gastric cancer during adulthood. The diagnosis of non-*H. pylori* gastritis must be based on anamnesis, clinical exam, laboratory tests, but especially on endoscopic features and histological exam. On the other hand, multiple non-invasive diagnostic tools have been assessed in order to detect *H. pylori* infection, such as serological test, stool antigen, urea breathing test, but upper digestive endoscopy with gastric biopsy and histological exam remain the gold-standard regarding the diagnosis of *H. pylori* induced gastritis. Rapid urease test and culture represent also invasive test for the detection of *H. pylori* infection. The histological exam is the only one that provides details regarding the type and severity of the inflammatory process. The treatment of both non-*H. pylori* and *H. pylori* mediated gastritis involve acid suppression drugs, whereas the appropriate eradication of *H. pylori* infection requires antibiotic treatment.

This research involved pediatric patients with gastrointestinal symptoms and its main objective was to identify the most frequent symptoms in children with gastritis, but also to establish the associations between the clinical picture, laboratory tests, endoscopic features, histological and different genetic features in these children.

Thus, the first study included in this thesis was performed on 137 children and its main objective was to identify the systemic inflammatory status associated to *H. pylori* induced gastritis in children. Thus, the children were divided into two groups: group 1 – the study group comprising 50 children with *H. pylori* induced gastritis, and group 2 – control group including 87 children without pathological modification at the histological exam. We found that our two groups were similar regarding the age and gender distribution. We noticed a higher frequency of *H. pylori* infection in children from rural area ($p=0.008$). The significant symptoms in children with *H. pylori* infection were epigastric pain and loss of appetite ($p=0,035/p=0.038$). Among the assessed laboratory parameters, hemoglobin, leukocytes, lymphocytes, neutrophils, eosinophils, and erythrocyte sedimentation rate were found to present higher levels among the study group. Nevertheless, only leukocyte and neutrophil counts expressed significant

associations with *H. pylori* infection in children (p=0.007/p=0.030). We also assessed the role of neutrophil/lymphocyte ratio in identifying the systemic inflammatory status related to *H. pylori* induced gastritis in our groups. Despite the fact that the value of this ratio was higher among the children with *H. pylori* induced gastritis as compared to control group (1,994±1,459 versus 1,780±1,423), our findings were not statistically significant (p=0.214). Therefore, we concluded that leukocyte and neutrophil counts might represent useful diagnostic tools in detecting the inflammatory status related to *H. pylori* induced gastritis in children. Moreover, neutrophil/lymphocyte ratio is also an important parameter of this low-grade systemic inflammation presenting higher values in children with *H. pylori* infection despite the lack of significantly statistical association. Another important finding of this study was that poor socio-economic level is an important risk factor for *H. pylori* infection in children.

Our second study included 147 children admitted for gastrointestinal symptoms and aimed to identify the associations between TLR4 polymorphisms and *H. pylori* infection in children with gastritis. The children were divided according to the presence of *H. pylori* at the histological exam into 2 groups: group 1 comprising 50 cases with *H. pylori* induced gastritis, and group 2 – 97 children with non-*H. pylori* mediated gastritis. Both, age and gender distribution were similar for our studied groups. We identified significant associations between the poor socio-economic status and *H. pylori* infection (p=0.002), but the frequency of this infection did not differ significantly between children from rural and urban area (p=0.184). The most frequent symptoms encountered in our study were: epigastric pain, abdominal pain, heartburn, nausea, vomiting and loss of appetite. Both gastroesophageal and biliary reflux were more frequent among children with non-*H. pylori* mediated gastritis, but without statistical significance (p=0.943/p=0.212). Regarding the laboratory parameters, only neutrophil count was higher in children with *H. pylori*-induced gastritis, whereas hemoglobin, leukocytes and lymphocytes values did not differ among the two studied groups. The inflammatory biomarkers assessed in this study, erythrocyte sedimentation rate and C-reactive protein presented similar values in the two studied groups (p=0.565/p=0.079). Similarly, we found no significant differences regarding transaminases and serum iron. The results of the rapid urease test were significantly associated with the presence of *H. pylori* infection at the histological exam (p<0.001). The paving stone aspect of the gastric mucosa was also significantly associated with *H. pylori* (p<0.001). assessing the role of *TLR4* rs4986791 and rs4986790, we identified that the variant genotype of both polymorphisms represents a protecting factor against the risk of *H. pylori* infection in children with gastritis, but without statistical signficance (p=0.812/p=0.756). Thus, similarly to the previous study, this study also underlined a significant association between poor socio-economic status and *H. pylori* infection. Moreover, our findings proved that rapid urease test is a useful diagnostic tool in detecting this infection. The paving stone aspect of the gastric mucosa is a significant macroscopic sign of *H. pylori* infection. The variant genotypes of *TLR4* rs4986790 and rs4986791polymorphism acted as protecting factors against *H. pylori* infection, but without statistical significance.

The main original aspect of this thesis is the age of the population since most of the studies reported in the literature that assessed subjects with gastritis involved adult populations. Moreover, the diagnosis of *H. pylori* in both our studies was based on the result of the histological exam. The fact that we assessed the role of innate immunity in the development of *H. pylori* infection, by studying two gene polymorphisms of TLR4 is probably the most important aspect regarding the originality of this research.