Fall 10-27-2014

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Recommended Citation
Elitsur Y, Preston DL. Helicobacter-pylori Negative Gastritis in Children—A New Clinical Enigma. Diseases. 2014;2:301-307. http://dx.doi.org/10.3390/diseases2040301

Diseases **2014**, *2*, 301-307; doi:10.3390/diseases2040301

OPEN ACCESS

diseases

ISSN 2079-9721

www.mdpi.com/journal/diseases/

Review

Helicobacter-pylori Negative Gastritis in Children—A New Clinical Enigma

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External Editor: Marina de Bernard

Received: 21 August 2014; in revised form: 11 October 2014 / Accepted: 13 October 2014 / Published: 27 October 2014

Abstract: The decrease in the prevalence of *Helicobacter pylori* (Hp) infection in children in the world gave rise to a new pathological finding termed as Hp-negative gastritis. Unfortunately, the term "Hp-negative gastritis" has not been identified as a pathological process and has the status of a "second cousin"; in most publications it was never mentioned as a subject to be dealt with, but was "left over" data that was never the topic of the manuscripts' discussions. Only recently has the topic captured the attention of the pathologists who described this phenomenon in adults, yet the pathological and/or clinical spectrum or significance of this phenomenon has not been adequately investigated. In the current manuscript we describe Hp-negative gastritis in children, summarize its clinical prevalence and touch upon the possible etiology, pathology, and/or therapeutic implication. Overall, this review has concluded that Hp-negative gastritis is a pathological phenomenon in children that needs further investigation, and to date, as the title suggests, is a new clinical enigma that needs to be considered.

Keywords: Hp-gastritis; Hp-negative gastritis; children; gastritis

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1. Introduction

Gastritis is a common finding in children who undergo diagnostic upper endoscopy. Although multiple etiologies have been associated with gastritis, in most pediatric cases the etiology of gastritis is unknown (idiopathic). Indeed, various diseases can be associated with gastritis including: *Helicobacter pylori* (Hp) organism, inflammatory bowel disease, allergic gastroenteritis, and others; but those comprise only the minority of the etiologies for gastritis. In the last 3 decades, the *Helicobacter pylori* organism has been the focus of gastritis in children, and many reports have shown that this bacterium is the etiology for moderate to severe gastritis [1]. However, the rate of the Hp-associated gastritis in children has been declining in recent years, especially in the developed countries [2–4]. The decline of the Hp infection rate in children in our practice was previously reported, demonstrating an infection rate between 3%–7% [5,6]. In the present manuscript, we will discuss the Hp-negative gastritis defined as an "idiopathic" gastritis, a condition that involves mucosal inflammation without Hp organism or other known etiologies.

2. Definition of Gastritis

Before the rate of Hp-negative gastritis is discussed, it is important to define the framework of gastritis. Until the Sydney criteria were published, gastritis was defined loosely by the practicing pathologist without any standardization. In 1991, a group of pathologists gathered and produced an important document described as "the Sydney criteria" [7]. A few years later (1994) the document was revised and the histological standard for "gastritis" was established [8]. In this document the various forms of gastritis were described and the pathologists' language became standardized. As in many clinical guidelines, the documentation provided a practical guideline but not all pathologists follow those recommendations in their routine practices. Accordingly, when discussing the rate of Hp-negative gastritis in our medical community, we need to make sure that the local pathologists follow those guidelines. Indeed, our experience suggests that unless the report is a prospective clinical study that included "Sydney Criteria" in the methodology, the description of gastritis may not be standardized or accurate. The average rate of Hp-negative gastritis reported from our center throughout the years showed that when pathology standardization is part of the prospective studies, the rate of Hp-negative gastritis was lower compared to the rate reported in the retrospective studies [mean rate (%): 37% *vs.* 54%, respectively] [9]. The histopathology of Hp-associated gastritis has been well described and its association with gastric cancer, gastric pathology and/or mucosal immune changes associated with it was documented [10]. Nevertheless, as Hp-negative gastritis has not been fully appreciated, there are no specific descriptions for this entity except for a simple description of mild to moderate gastritis characterized by the Sydney criteria. As the interest of this entity increases further pathological details will be forth coming through the efforts of various investigators.

3. Prevalence of Hp-Negative Gastritis (Idiopathic)

The rate of Hp-negative gastritis in children has not been evaluated adequately. In most cases the data are derived from retrospective studies that did not concentrate on this subject and held no direct discussion of this diagnosis. Most of the data is usually an ad hoc analysis calculated from the data

provided in the reports. Moreover, with the declining prevalence of Hp-infection in children in developed countries, the rate of "idiopathic" gastritis is now more evident. For example, we recently reviewed the charts of the first diagnostic upper endoscopic procedures performed in our practice during 2013. A total of 135 procedures were completed and a comprehensive set of biopsies (esophagus, stomach, duodenal bulb, and small intestine) were available in all children. In this cohort, gastritis was identified in 104 (75%) children, of whom 4 (3.8%) children had Hp-associated gastritis, and 10 (9.6%) children had a non-Hp etiology for their gastritis. Finally, a total of 90 (86%) children showed Hp-negative ("idiopathic") gastritis (unpublished data). This data followed our summary report documenting the rate of Hp-negative gastritis in our patient population since the early 1990's [9].

In a recent publication, Kara *et al.* reviewed the histology of children who had upper endoscopy procedures performed. In a total of 358 procedures, 214 (60%) cases had Hp infection and the histological description of those patients was reported. Yet, in a total of 144 children, Hp negative gastritis was detected [11]. Of the Hp-negative patients, 98 children had corpus gastritis and 99 children had antral gastritis. As the focus of the study was Hp infection the histological description for the Hp-negative children was limited.

In most pediatric publications, the data are retrieved from retrospective studies and the analysis is not directed toward Hp-negative gastritis. It is assumed that prospective studies of this topic would be more beneficial and accurate. Nonetheless, even in those reports, the specific analysis of Hp-negative gastritis was not the main topic of the discussion [12–14]. In a recent prospective study, a Chinese group assessed the endoscopic findings of children diagnosed with functional abdominal pain [15]. Only patients who were positive by Rome 3 criteria were included. A total of 80 children were evaluated of whom 5 had significant mucosal findings including duodenitis, gastritis, and mucosal erosion. Seventy-five children showed no significant gastric pathology. Nevertheless, the "non-significant findings" were described by the pathologists as descriptive changes such as: reactive mucosal changes and mild chronic inflammatory cell infiltrates (mild gastritis) [15]. The long term prognosis and the clinical significance of those "non-significant findings" in children have not been elucidated.

The topic of Hp-negative gastritis or the lack of detection of Hp organism in the stomach of adult patients has been raised previously by Yoo *et al.* [16] and had an editorial response by Genta [17]. In those publications, missing Hp organism in the mucosa was attributed to atrophic gastritis/ metaplastic epithelium and to other associated clinical reasons such as: chronic use of proton pump inhibitors (PPI) and antibiotic use. In recent publications, the topic of Hp-negative gastritis in adult patients has been raised by a few investigators. In a prospective analysis of 491 adult patients, Nordenstedt *et al.* evaluated the rate of gastritis and its associated pathology and confounding factors [18]. In this study the authors demonstrated gastritis in 200 (40.7%) patients of whom 41 (20.5%) were Hp-negative. Of the confounding factors, alcohol consumption and smoking were significantly associated with Hp-negative gastritis but not drugs (PPI, NSAID). The authors concluded that the "causes and implications of this entity (Hp-negative gastritis) are unknown and worthy of future studies" [18]. In an editorial that followed this report the author reminded us of the other common reasons for missing the bacterium in the biopsies of adult patients including: sampling error, or chronic use of PPI and antibiotics [19]. A more innovative explanation is suggested by the author, but needs further confirmation and research, involves the gastric microorganisms (GI microbiota) that are now at the forefront of the investigators interest [19]. For the pediatric population (especially the younger age group), some of those reasons are

limited (tobacco use, alcohol, NSAID, or atrophic gastritis), but others could play a role in lack of detection of the bacterium (antibiotic and PPI usage). To better understand this topic, prospective studies will need to consider those factors in their study planning.

4. Hp-Negative Gastritis and the Microbacterium Hypothesis

In the last few decades the human microbiome project was completed and published. Within that project, many uncultivable bacteria that inhabit the normal gastrointestinal tract were reported [20]. Indeed, the project reported that there are up to 1833 uncultivable colonies living in the normal stomach [21]. Previous reports suggested that the local gastric microbiome might interact with the *H. pylori* organism and may influence the development of peptic ulcer disease, or gastric cancer [22]. Other authors documented the possible interaction of the gastric microbiome with different human diseases and warned that "comprehensive knockout" of all microorganisms in the stomach may not be beneficial for the human health [23].

In a recent editorial, Genta *et al.* suggested that the etiology for Hp-negative gastritis in adults may be related to the bacterial flora that inhabits their stomach. Indeed, the current research implicates the gastric microbiome in the pathophysiology of *H. pylori* infection but there is no clear evidence that describes its effect in the development of idiopathic gastritis in adults or children. Moreover, Kato *et al.* investigated the bacterial gastric flora in Hp negative children and adults (10 pts/group). Several microorganism species were detected in the stomach of adult patients but very few in children [24]. Unfortunately, in that report, histological description of the gastric mucosa was not available; thus, the association of the gut flora and idiopathic gastritis could not be assessed. Moreover, the repertoire of the gastric microbiota in children during normal development or during different disease states have not been adequately investigated or published. It is concluded that the gut microbiome may have an important role on the pathophysiology of many human diseases, but its relationship towards idiopathic gastritis, especially in children, has yet to be proven.

In summary, the rate of Hp-negative gastritis has been reported in adults and children. The "frustration" of the pathologists described by Genta *et al.* [19] related to positive gastritis in the absence of Hp organism in the biopsy is well respected. It is assumed that a similar situation is part of the pediatric pathologists' "frustrations" as well. Unfortunately, due to the lack of research, the etiology behind this finding as well as the clinical significance of Hp-negative gastritis has not been elucidated in children. As the term "gastritis" means inflammatory process by definition, many pediatric gastroenterologists in their clinical practice would treat those patients for the inflammation. The lack of correlation between patients' symptoms and idiopathic gastritis [25,26] may suggest that those patients should not be treated. Unfortunately, we are lacking appropriate studies to direct our therapeutic decisions in either direction. Future studies should target the topic of "Hp negative gastritis" (idiopathic) to identify possible pathological factors and prospective clinical studies that should be planned in order to direct physicians to answer the Shakespearian paraphrase: "to treat or not to treat: this is the question".

5. Conclusions

The present manuscript reviews the topic of Hp-negative gastritis in children. With the decreased rate of Hp infection in children around the world it is expected that this condition will increase and become more recognized. Unfortunately, the pathophysiology and the clinical implications of this condition are unknown. As the interest in the gastrointestinal microbiome increases, new etiological factors may be discovered, advancing our knowledge towards solving this enigma.

Author Contributions

Yoram Elitsur MD: Guarantor of the article, study design, manuscript preparation, critical review, final approval of the manuscript. Deborah L Preston BS: Complete chart review, data collection, data analysis, manuscript edits.

Conflicts of Interest

The authors declare no conflict of interest.

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