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What is the diagnostic utility of endoscopic scoring systems in children?

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Background/aims: *The aim of this study was to evaluate the consistency of the Savary-Miller, the Hetzel-Dent and the Los Angeles endoscopic classification systems and to compare them with the esophageal histopathology in children.* ***Material and Methods:*** *Children between the ages of 5-17 years who underwent esophagogastroduodenoscopy were included in the study. The endoscopic reports and the still images of the esophagus were reclassified by the same gastroenterologist according to the Savary-Miller, Hetzel-Dent and Los Angeles scoring systems. The esophageal biopsies were also reevaluated by the same pathologist and the consistency between endoscopic and histopathologic esophagitis was evaluated.* ***Results:*** *A total of 113 out of 192 pediatric patients were included in the study. Seventy-three patients (64.6%) had esophagitis according to the Hetzel-Dent classification, whereas only 20 (17.7%) patients were defined as having esophagitis according to the other two classification systems. The consistency between the Savary-Miller and Los Angeles classifications was excellent (κ: 0.92) but the agreement between the Hetzel-Dent and Savary-Miller and between the Hetzel-Dent and Los Angeles classifications were poor. A total of 82 patients (72.6%) had histopathological esophagitis, and there was a weak consistency between all 3 endoscopic scoring systems and the histopathology.* ***Conclusions:*** *Since pediatric patients have milder esophagitis than in adults, the use of endoscopic scoring systems developed for adults seems to be inapplicable for children. The inclusion of minimal endoscopic changes in endoscopic scoring systems by using more sensitive and novel endoscopic techniques would increase the sensitivity of these scoring systems in children.*

Key words: Gastroesophageal reflux, endoscopic esophagitis, endoscopic classification system, children

Endoskopik sınıflama sistemlerinin çocuklardaki tanısal değeri nedir?

Amaç: *Çalışmanın amacı, çocuklarda Savary-Miller, Hetzel-Dent ve Los Angeles endoskopik sınıflama sistemlerinin kendi aralarındaki uyumunu araştırmak ve bunları özofageal histopatoloji verileri ile karşılaştırmaktır.* ***Materyal ve Metot:*** *Özofagogastroduodenoskopi yapılan 5-17 yaş arasındaki çocuklar çalışmaya dahil edildi. Endoskopi raporları ve fotoğrafları, aynı gastroenterolog tarafından, Savary-Miller, Hetzel-Dent ve Los Angeles sınıflamalarına göre yeniden skorlandı. Ayrıca özofageal biyopsiler de aynı patolog tarafından tekrar değerlendirildi, endoskopik ve histopatolojik özofajit arasındaki uyum araştırıldı.* ***Bulgular:*** *Toplam 192 çocuk hastanın 113'ü çalışmaya alındı. Hetzel-Dent sınıflamasına göre 73 hastada (%64.6) özofajit söz konusu iken, diğer iki sınıflama sistemine göre ise sadece 20'şer hastada (%17.7) özofajit tanımlandı. Savary-Miller ve Los Angeles sınıflamaları arasında mükemmel bir uyum (κ: 0.92) varken, Hetzel-Dent-Savary-Miller ve Hetzel-Dent-Los Angeles sınıflamaları arasındaki uyum zayıf düzeydeydi. Toplam 82 hastada (%72.6) histopatolojik özofajit belirlendi, her 3 endoskopik sınıflama sistemi ile histopatolojik sısnıflama arasındaki uyum zayıf seviyede bulundu.* ***Sonuç:*** *Çocuk hastalardaki özofajit erişkinlere göre daha hafif seviyede olduğundan, erişkinler için geliştirilmiş olan endoskopik sınıflama sistemlerinin çocuklarda kullanılması uygun görünmemektedir. Daha hassas ve yeni endoskopik tekniklerin kullanılması devreye girmesi sonucu, minimal endoskopik değişikliklerin endoskopik sınıflama sistemlerine dahil edilmesi ile, çocuklardaki reflü özofajit tanı olasılığı artırılabilir.*

Anahtar kelimeler: Gastroözofageal reflü, endoskopik özofajit, endoskopik sınıflama sistemi, çocuklar

INTRODUCTION

Gastroesophageal reflux disease (GERD) is a common disease occurring in 7-20% of the adult population (1-3). The prevalence of symptoms which suggest GERD in children was reported to be

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2-7%, and that is likely to increase with advancing age (4). The diagnosis of GERD is often established on the basis of the symptoms of heartburn and regurgitation in adults (5,6). However, children have variable and non-specific symptoms closely related to age. As the severity of reflux symptoms are not related directly with esophageal mucosal injury and does not reflect the degree of mucosal injury, endoscopy is considered to be an important tool to evaluate the esophageal damage caused by GERD, not only in adults, but also in children. Since the assessment of endoscopic esophagitis is often subjective, multiple scoring systems have been developed for adult patients, including the Savary-Miller (SM) classification, the Hetzel-Dent (HD) classification, and the Los Angeles (LA) classification (Table 1). They provide a more objective and reliable description of macroscopic lesions observed in the esophagus during endoscopy (7-9). These classification systems also provide an estimation of the severity of reflux esophagitis, allowing for better management strategies and prognosis estimates. An ideal classification system should be simple, easy to perform, and reproducible, with the capability of evaluating lesions and complications. Currently there are conflicting results as to the validity and reproducibility of classification systems used for reflux esophagitis in adults (9-13). Since operator experience is an important component of endoscopy, visible mucosal breaks or erosions in the esophageal mucosa are considered the most reliable endoscopic sign of GERD, whereas minimal mucosal changes such as erythema, hyperemia or friability are not reliable endoscopic signs in adult patients (9,11,14-16). Considering the typically shorter duration of GERD in children compared to adults, a mucosal break is a definitive but less commonly seen endoscopic sign of reflux esophagitis in pediatrics. Though no specific classification system has been developed for the assessment of esophagitis in children, the HD classification has been the most commonly used one in pediatric studies (17-19). The LA classification is also widely used in adults as well as in children (9).

The diagnostic yield of endoscopy can be increased by obtaining multiple biopsies with accurate orientation from the major anatomic landmarks of the esophagus. However, sampling error secondary to the patchy distribution of the inflammation in GERD, lack of standardization of biopsy location, and tissue processing and interpretation of morphometric parameters decrease the validity of histopathology as a diagnostic tool in GERD (20-22). Hence, the specificity of histopathologic examination of the esophageal biopsies ranges widely between 27-78% in adults (23). A study which included a very well-defined population of GERD patients and controls demonstrated a high sensitivity (84%) in all GERD patients compared to a high specificity (85%) in controls (23). The authors

Table 1. The three different endoscopic classification system.

Savary-Miller classification (1977)	
Grade 1	Single or isolated erosive lesion(s), oval or linear, but affecting only one longitudinal fold.
Grade 2	Multiple erosive lesions, non-circumferential, affecting more than one longitudinal fold with or without confluence.
Grade 3	Circumferential erosive lesions.
Grade 4	Chronic lesions: ulcer(s), stricture(s) and/or short esophagus, Barrett esophagus. Alone or associated with lesions of grades 1 to 3.
Hetzel-Dent classification (1988)	
Grade 0	No mucosal abnormalities.
Grade 1	No macroscopic lesions but erythema, hyperemia, or mucosal friability
Grade 2	Superficial erosions involving <10% of mucosal surface of the last 5 cm of esophageal squamous mucosa.
Grade 3	Superficial erosions or ulceration involving 10% to 50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa
Grade 4	Deep peptide ulceration anywhere in the esophagus or confluent erosion of >50% of the mucosal surface of the last 5 cm of esophageal squamous mucosa
Modified Los Angeles classification (1999)	
Grade A	One (or more) mucosal break no longer than 5 mm that does not extend between the tops of two mucosal folds.
Grade B	One (or more) mucosal break more than 5 mm long that does not extend between the tops of two mucosal folds.
Grade C	One (or more) mucosal break that is continuous between the tops of 2 or more mucosal folds but involves <75% of the circumference.
Grade D	One (or more) mucosal break that involves at least 75% of the esophageal circumference.

concluded that histology is an accurate and reliable tool for detection of microscopic inflammatory changes in adult patients with GERD, and can play an important role in diagnosis of reflux esophagitis. The interpretation of major markers of microscopic esophagitis, namely basal cell hyperplasia, papillary elongation and dilatation of intercellular spaces in adults with GERD is still controversial (20,21,24). These histological changes were considered as neither specific nor sensitive for pediatric reflux esophagitis in most recently published guidelines (25).

To our knowledge, the diagnostic validity of endoscopic scoring systems in children has not yet been investigated methodologically. Therefore the aim of this study was to evaluate the consistency of three different endoscopic scoring systems, and to compare them with the esophageal histopathology in children.

MATERIALS and METHODS

Patients

Children between the ages of 5-17 who underwent esophagogastroduodenoscopy (EGD) between January 2006 and December 2009 were included in the study. Before endoscopy, informed consent was obtained from the parents, or patients themselves where appropriate, in accordance with the Declaration of Helsinki. Patients who had complaints related to GERD, such as vomiting, epigastric pain, pyrosis, regurgitation, retrosternal pain, dysphagia, and persistent wheezing were considered eligible for the study. Children who were younger than five years old or with a recent history of non-steroidal anti-inflammatory drugs, proton pump inhibitors, H_2-receptor antagonists, or antibiotics use were excluded from the study. Children having severe chronic co-morbidities like diabetes mellitus, renal disease, neurological disease, or those suffering from gastrointestinal disorders such as celiac disease, inflammatory bowel disease, corrosive esophagitis, and upper gastrointestinal bleeding were also excluded.

Endoscopic and histologic assessment

The endoscopic records of all patients were retrieved and reevaluated by the same gastroenterologist. Those reports, describing the mucosal and vascular details, and the still images of the esophagus were further classified according to the SM, HD and LA scoring systems (Table 1). The three scoring system reports were then categorized as normal, mild-moderate, and severe to allow a reliable comparison between them. Grade 1-2 of the SM classification was considered as the mild-moderate group and grade 3-4 as the severe group. Grade 1-3 of the HD classification was considered to be the mild-moderate group with grade 4 representing the severe group. Finally, grade A, B, and C of the LA classification comprised the mild-moderate group while grade D made up the severe group (Table 2).

During endoscopy, three esophageal biopsy samples were obtained from a 3-4 cm proximal segment of the esophagogastric junction for conventional histopathological examination. Additional biopsy samples were obtained from the antrum, corpus, and distal duodenum as well. All esophageal thin plates were reevaluated by the same gastrointestinal pathologist who was blind to the clinical and laboratory findings of the patients as well as to the previous pathological reports. The histopathological diagnosis of esophagitis was based on the criteria described by Vandenplas and the GERD Working Group of the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) (Table 3) (26). The children who had grade 1a, 1b, 1c and grade 2 esophagitis were grouped as having mild to moderate esophagitis, and those who had polymorphonuclear infiltration with epithelial defect and more severe histopathological findings, such as ulceration and columnar metaplasia, were grouped as having severe esophagitis (Table 2). Patients were divided into two subgroups by age (those over 11 years old and those under 11) to determine the frequency of endoscopic and histopathological esophagitis along with how it related to severity and age.

Table 2. The categorization of the endoscopic and histopathologic scoring systems as normal, mild-moderate, and severe

	Normal	Mild-moderate	Severe
Savary-Miller	Grade 0	Grade 1-2	Grade 3-4
Hetzel-Dent	Grade 0	Grade 1-2-3	Grade 4
Los Angeles	Grade 0	Grade A,B,C	Grade D
Histopathology	Grade 0	Grade 1-2	Grade 3-4-5

Table 3. Criteria for the diagnosis of GER and esophagitis on endoscopic biopsies (ESPGHAN).

Grade	Histologic criteria	Clinical Diagnosis
0	Normal	Normal
1a	Basal zone hyperplasia	
1b	Elongated stromal papillae	Reflux
1c	Vascular ingrowth	
2	Polymorphonuclear cells in the epithelium, lamina propria or both	Esophagitis
3	Polymorphs with epithelial defect	Esophagitis
4	Ulceration	Esophagitis
5	Aberrant columnar epithelium	Esophagitis

Table 4. The distribution of esophagitis according to the Los Angeles (LA), Savary-Miller (SM) and Hetzel-Dent (HD) endoscopic classification systems and the consistency between them.

Grade	LA*	SM*	HD*
Normal	93/113 (82.3%)	93/113 (82.3%)	40/113 (35.4%)
Mild - Moderate	18/113 (15.9%)	15/113 (13.3%)	68/113 (60.2%)
Severe	2/113 (1.8%)	5/113 (4.4%)	5/113 (4.4%)

* LA vs HD: κ=0.19, LA vs SM: κ=0.92, SM vs HD: κ=0.25

Statistical Methods

The Number Cruncher Statistical System (NCSS) 2007 and Power Analysis and Sample Size (PASS) 2008 Statistical Software (Utah, USA) were used for data analysis and statistical evaluations. Descriptive statistics were calculated for all variables. McNemar's test and Cohen's kappa index were used to measure agreement between variables. A general rule, applied in many working fields, indicates that the concordance is excellent if Kappa ≥0.80, good if Kappa ≥0.60, moderate if Kappa ≥0.40, and poor if Kappa ≥0.20. Values of Kappa <0.20 indicate a very poor concordance. Diagnostic screening tests were used to calculate sensitivity and specificity. Statistical significance level was selected as $p < 0.05$.

RESULTS

A total of 192 pediatric patients who had a clinical diagnosis of suspected reflux esophagitis were recruited from the outpatient clinic of the Department of Pediatric Gastroenterology in our university hospital. A total of 113 patients were enrolled in the study whereas the remaining 79 patients were excluded because they were younger than 5 years or had at least one of the exclusion criteria that was explained previously.

The mean age of the study group was 10.8±3.4 with children ranging from 5-17 years old. Endoscopic findings were normal in 93 out of 113 (82.3%) children according to the SM and LA classifications whereas only 40 out of 113 (35.4%) had a normal esophagus according to the HD classification. According to the HD classification, esophagitis was found in 73 out of 113 (64.6%) patients. Sixty-eight (93.2%) of them had mild-moderate and 5 (6.8%) had severe esophagitis. When the SM classification was used to assess the presence of endoscopic esophagitis, there was mild-moderate esophagitis in 15 patients (75.0%) and severe esophagitis in 5 (25.0%) of the 20 (17.7%) out of 113 patients. Endoscopic esophagitis was found in 20 patients (17.7%) using the LA classification which was similar to the ratio found by using the SM classification. However, a higher percentage of children had severe esophagitis according to the SM compared to the LA classification (4.4% vs. 1.8%, respectively) (Table 4, Figure 1).

There were no significant differences in the frequency of normal, mild-moderate, and severe esophagitis cases in children younger or older than 11 years of age with the three endoscopic classification systems. When those three classification systems were compared, there was an excellent con-

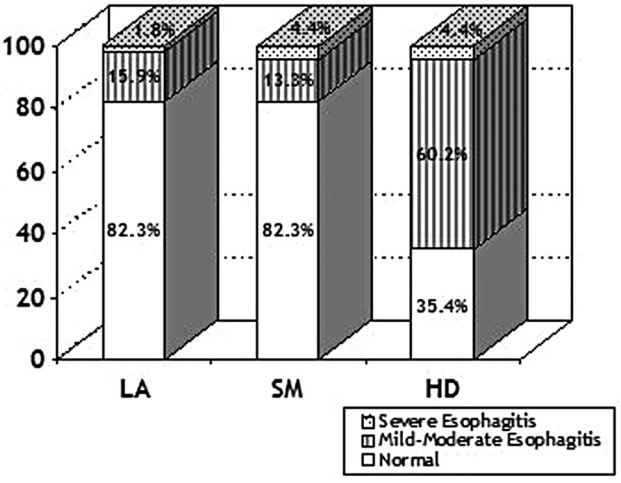

Figure 1. Distribution of endoscopic esophagitis in the study group according to the Los Angeles (LA), Savary-Miller (SM) and Hetzel-Dent (HD) classification.

sistency between only the SM and LA classifications (κ: 0.92). However, the agreement between the HD and SM and between the HD and LA classifications was poor (κ: 0.25 and 0.19, respectively) (Table 4).

Among the three endoscopic classification systems, minimal mucosal changes such as erythema, hyperemia or mucosal friability were included only in the HD classification, and classified as grade 1 esophagitis. Since minimal change in the esophageal mucosa has been considered as unreliable endoscopic sign of esophagitis in the latest pediatric GERD guidelines (25), the analysis was repeated by regarding the children with grade 1 esophagitis according to the HD classification as normal. In this case, 93 (82.3%) patients were considered as normal, 15 (13.3%) patients had mild-moderate and 5 (4.4%) patients had severe esophagitis according to the HD classification. Hence, the consistency between the HD, SM and LA classifications was raised up to an excellent degree with the level of κ: 0.92.

In our study group, 82 (72.6%) patients had varying degrees of histopathological esophagitis. The remaining 31 (27.4%) patients who had symptoms suggestive of clinical reflux had normal histopathologic findings in their esophageal biopsies. Seventy-nine (69.9%) out of 113 children had a mild to moderate degree of histopathological esophagitis, and only three (2.7%) had a severe degree of histopathological esophagitis. There was no significant difference between the patients under and over the age of 11 with respect to the frequency of normal, mild-moderate, and severe histopathological esophagitis.

When the consistency between endoscopic and histopathologic esophagitis was evaluated, a weak consistency was found between the HD classification and the histopathology (κ: 0.327). However, neither the SM nor the LA scoring systems used for assessment of esophagitis were correlated with esophageal histopathology (κ=0.068).

DISCUSSION

Gastroesophageal reflux (GER) which frequently occurs in otherwise healthy infants, refers to reflux without associated complications, and it generally resolves between 1-2 years of age (4,27). GERD is defined by the presence of reflux in combination with associated complications, and usually does not resolve spontaneously (28,29). In clinical practice, it is important to make a distinction between GER and GERD. Since GERD symptoms are usually age-dependent and heterogeneous during childhood, it could be useful for clinicians to be able to assess the severity of esophagitis based on the presenting symptoms (4,27,30). In adults, several studies investigating the relationship between the symptoms and endoscopic findings of GERD reported a poor correlation (31-34).

Though 24-hour ambulatory pH monitoring is an ideal method to reflect the extent of esophageal exposure to acid, it is not considered useful for the diagnosis of erosive esophagitis or the follow-up of healing of esophageal erosion in response to treatment (35,36). Therefore, upper gastrointestinal system (GIS) endoscopy has been commonly used in the diagnosis of GERD (35). The ESPGHAN consensus report revealed that endoscopy is essential in patients with symptoms suggesting esophagitis (37). There is usually no correlation between the severity of an erosion and the severity of symptoms. However, the severity of an erosion is considered helpful in predicting treatment response, relapse, and development of complications (35,38).

Using a valid and reproducible classification system is important in the diagnosis of endoscopic esophagitis. The HD, SM, LA, and MUSE (Metaplasia, Ulcer, Stricture, Erosion) systems have been the most widely used classification systems. According to a study researching the preference of different endoscopic classification systems between 2003 and 2006, the LA classification system

was used in more than half of the studies (56%), and the SM and the HD classifications were used in 36% and 5% of the studies respectively (39). Today, the use of the LA classification has been increasing up to 95% in the North America and 60% in the European and other countries (39). Currently, there is no ideal classification system available for the diagnosis of endoscopic esophagitis in adults. Each classification system has its own advantages and disadvantages. Because minimal changes in the esophagus can cause subjective evaluation results when included in the classification system, the LA classification, the latest of these systems, grades only according to the number and size of erosions and excludes the minimal changes in the esophagus (40). However, great variations in inter- and intraobserver agreement have also been reported in studies done with endoscopic classification systems which excluded minimal changes. Rath et al. (10) found correlation between the LA and MUSE system, but not between the SM and other two classification systems with respect to interobserver agreement. There have been studies reporting moderate to good inter- and intraobserver agreement with the LA classification (13,17) as well as studies reporting insufficient agreement and a need for modification (11,12).

The occurrence of erosive esophagitis is less common in young children with GER symptoms than in adults, and it increases with age (41). Despite this basic difference in children and adults with respect to endoscopic esophagitis, the classification systems developed in adults are also being used in children (26,41,42). In our study, we found endoscopic esophagitis in 64.6% of patients according to the HD classification and in 17.7% of patients according to the SM and LA classification, with varying degrees of reflux esophagitis in 72.6% of patients according to histopathological evaluation. In adults, it is estimated that 40–50% of patients with typical reflux symptoms in tertiary centers and only 20–30% in primary care practice have erosive esophagitis (43). Gilger et al. (41) reported the prevalence of erosive esophagitis in 12.4% of 7188 children who underwent an upper GIS endoscopy by investigating case records in the Pediatric Endoscopy Database System- Clinical Outcomes Research Initiative (PEDS-CORI) retrospectively. The authors reported a prevalence of 5.5% erosive esophagitis in children between 0-1 years and 19.6% in children who were at adolescent age (41). The prevalence of erosive esophagitis was 17.7% according to the SM and LA classifications in our study. There were no differences between children who were 5-11 years old and those who were 11-17 years old. The higher prevalence rate of erosive esophagitis compared to the PEDS-CORI study could be explained by a recruitment bias since the subjects were selected from pediatric gastroenterology outpatient clinics, and were considered eligible for endoscopy due to their serious reflux symptoms. Gupta et al. (27) observed erosive esophagitis in 50% of 90 children ages 1-17 years with symptoms suggesting GERD. They concluded that symptoms were not predictive in distinguishing erosive from non-erosive esophagitis. The prevalence of erosive esophagitis in our study group was lower than the rate reported by Gupta et al. However, unconventional endoscopic and histopathological classifications developed by a pharmaceutical company were applied to the patients for the evaluation of esophagitis in their study (27).

A multicentric Italian study demonstrated that reflux symptoms were highly correlated with histologic scoring particularly in children who have a normal esophagus endoscopically (44). Normal endoscopic findings, namely lack of an erosion or mucosal break, do not rule out histopathologic esophagitis. In fact, microscopic esophagitis has been found in one-third of children without any endoscopic lesion in another study done by Biller et al. (45). Furthermore, it has been reported that microscopic changes are more frequent in esophageal biopsy samples obtained from patients with nonerosive reflux disease (NERD) than in the controls (20,23). The treatment of patients with reflux is usually guided by symptoms, but in contrast to adults and adolescents, clinical diagnosis based on a history of heartburn can not be used in infants and small children. At the same time, the presence of a normal esophageal mucosa during endoscopy does not exclude the diagnosis of NERD, and histology may be helpful in these cases. The presence of eosinophilia, elongation of papillae, basal hyperplasia, and dilated intercellular spaces alone or in combination suggesting mild degree of histological esophagitis was declared as nonspecific in the latest guidelines (25). However, children with microscopic esophagitis were the ones who underwent endoscopy because of the severity of their reflux symptoms in this study, and microscopic esophagitis was found in almost three quarters of this population. Nevertheless, most of the patients

were having a mild degree of esophagitis according to the HD classification. Hence, we suggest that minor mucosal changes such as erythema, hyperemia or friability of the esophagus during endoscopy in a child with symptoms suggestive of reflux warrants taking esophageal biopsies.

In conclusion, GERD is less serious in children than in adults and usually causes mild endoscopic findings that are generally accepted as nonspecific for reflux esophagitis, and erosive esophagitis is less common in children than in adults. Systems for endoscopic classification of esophagitis which were developed in adults still have questionable validity in this age group (10-12). Hence it would be misleading to use the same endoscopic classification systems in children. The diagnostic value of minimal endoscopic changes in endoscopic classification and/or the histopathologic examination of carefully obtained esophageal biopsies should be evaluated in well-designed, multicenter studies including children of different age groups with reflux symptoms before denying the minimal endoscopic changes and histologic findings such as eosinophilia, elongation of papillae, basal hyperplasia, and dilated intercellular spaces in evaluation of children with reflux symptoms. However, subjective reporting of the endoscopic findings would be an issue, and this conflict could be eliminated by using more sensitive and novel endoscopic techniques.

Disclosure Statement

The authors declare that no financial or other conflict of interest exists in relation to the content of the article.

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