Review Article

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Gastro-Esophageal Reflux Disease in Healthy Older Children and Adolescents

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Gastro-esophageal reflux disease (GERD) in otherwise healthy older children and adolescents is commonly encountered in pediatric clinics and poses a complex treatment problem involving changes of diets and lifestyle. After an initial history taking and a physical examination, typical symptoms of GERD in older children and adolescent are initially treated with the trials of acid suppressants. With an increase of severe cases, more and more GERD children have been evaluated with endoscopy, which helps to delineate an erosive esophagitis from a non-erosive reflux disease as they are presumed to have different pathogenesis. For the pediatric patients without a significant underlying disease, a reflux esophagitis can be treated adequately with acid suppressants. Recently, the rapid increase of children who are taking anti-reflux medication has brought up a serious alarm among pediatricians. Some at risk pediatric patients with recurrent and/or chronic GERD have been linked to adulthood GERD. In this paper, pediatric GERD with and without erosive esophagitis was reviewed along with treatment options and issues specifically for the otherwise healthy older children and adolescents in the primary clinics or the secondary hospitals. **(Pediatr Gastroenterol Hepatol Nutr 2012; 15: 220~228)**

Key Words: Gastroesophageal reflux, Child, Adolescents

INTRODUCTION

Gastro-esophageal reflux disease (GERD) in otherwise healthy older children and adolescents is a significant source of morbidity [1-3]. There have been only a few studies for the prevalence of GERD in Korean pediatric population [4-6]. Older children and adolescent spend extended hours of sitting at desk at school and home while cramming with their subjects. Thus, these children seem to develop obesity or adult-like GERD symptoms. Even though the pediatric GERD symptoms are considerably different from those in adults, a global consensus is that neurologically intact older children and adolescents can be diagnosed and initiated with the similar treatments used for typical adults' reflux symptoms like

heartburn and regurgitation [7,8]. Meanwhile, children have been reported to have more of epigastric pain and regurgitation including extra-esophageal symptom (ex: cough) [4-6,9]. These GERD symptoms interfere with daily activities in about 30% of pediatric patients [4]. Both non-erosive reflux disease (NERD) and erosive esophagitis (EE) present very similar symptoms that pediatric GERD diagnosis can be challenging in the absence of multiple diagnostic studies like endoscopy, esophageal pH monitoring, and/or esophageal multi-luminal impedance measurement (pH-MII) in primary pediatric clinics. The prognosis of GERD in healthy children is positive after treatment [10]. The children with risk factors, especially hiatal hernia, asthma, or a strong family history of GERD may develop a recurrent and chronic GERD later in their life [11-15]. Therefore, an early detection and proper treatment of GERD in those at-risk children lead to fewer complications, possibly preventing a development of subsequent adult GERD. As for treatment, proton pump inhibitors (PPIs) have been known to be efficacious and safe for pediatric GERD. Recently, PPIs and antacid have been overly used up to several folds higher than before in children with GERD. Unfortunately there has also been an increase of children treated with acid suppressants who developed adverse events related to drugs (ex: community-acquired pneumonia or gastroenteritis) [16]. Thus, it is imperative that pediatricians should have a better understanding of pediatric GERD and be cognizant of the side-effects of the medications. In this paper, GERD was reviewed with subtypes of EE/NERDs and treatments' issues in otherwise healthy older children and adolescents.

PREVALENCE

The prevalence of GERD in children varies according to age and country. In USA, 5-8.2% in children in ages of 10 to 17 years was diagnosed with weekly GERD symptoms [3]. 12.4% in children performed endoscopy was diagnosed with EE [11]. While in UK, 10.9/1,000 persons per year for the period of

2000 and 2005 have reported to have a newly diagnosed reflux esophagitis [15]. In adult studies, the prevalence of GERD (ex: weekly heartburn or acid regurgitation) in Asia has been known to be less (5%) than Western countries (20%). Meanwhile, Korean adult patients with erosive reflux esophagitis visiting a secondary or tertiary hospital were reported to have its prevalence rate of 11.8% [17]. In Korean children with upper abdominal pain, EE was reported to be 5.7% in 1992 [5] and 19.9% in 2008, respectively [6]. Other GERD children's complaints were mostly epigastric pain and regurgitation (over 60%). Heartburn was reported to be 18.6% in EE children and 2.9% in NERD children [4]. The frequency of EE seemed to be similar to that of NERD in GERD children [9,18].

About 39-42% of GERD children and adolescents (ages of 6 to 17 years) had either a history of gastro-esophageal reflux (GER) in infancy and/or a strong family history of GER [13]. Generally speaking, childhood GERD often continues to develop into adulthood GERD, indicating that this is a life-long disease which may even turn into Barret's esophagus, ulcer, and/or stricture [19].

MECHANISM

GER is a physiologic result of the transient relaxation of the lower esophageal sphincter (TLESR) which is often triggered by gastric distension after meal, nasogastric tube, right lateral position, small volumes of liquid meal, etc. When the esophageal protective mechanism is altered, then pathologic GER will show troublesome symptoms during TLESRs, which can be manifested in different reflux types. It has not been clear what underlying mechanism causes which GERD type [12,18,20,21]. GERD ranges from NERD to severe EE depending on the pH value: severe GERD has a higher acid level ($pH < 4$) and liquid reflux, while NERD has nonacid ($pH > 7$), weak acid level ($4 < pH < 7$), bile, or gas in refluxate which enhances their perception of reflux. There is no significant difference in acid secretory capacity but pathologic esophageal acid exposure and sensi-

tivity to acid exposure is different between EE and NERD [20]. Mixed reflux with acid and bile is the predominant form in children with reflux esophagitis but the rates of pathological acid reflux in EE is significantly higher than that of NERD [18,22,23]. The other following factors are also considered for GERD: delayed gastric emptying, decreased esophageal clearance, hypotonic lower esophageal sphincter, visceral neural pathway dysfunction, sustained esophageal contraction, and/or abnormal tissue resistance [15,24]. One of the risk factor is a hiatal hernia which comes with a greater TLESRs frequency depending on its size [21]. This hiatal hernia occurred in 17-39% of children with GERD who had required a long-term treatment [11,12,25]. Its incidence was higher in EE (7.7%) than in NERD (2.5%). Timing of each TLESR was important as the reflux occurred throughout the postprandial period in GERD adults with large hiatal hernia in recumbent (right lateral) or sitting posture [21]. In patients with small hiatal hernia and healthy volunteers, most acidic TLESRs occurred during the first postprandial hour [21]. Acid pocket (pH 1.6) of unbuffered gastric juice area extending 2 cm below the lower esophageal sphincter might have been a postulated factor in adult GERD patients with a hiatal hernia. But acid pocket of hiatal hernia could not answer clearly about acidic reflux in GERD adults and it also needs to be proven in GERD children [20,21].

Nonacid reflux occurs significantly during meal and postprandial period (within 2 hours) in GERD children. Nonacid reflux decrease to the one-third level from initial reflux, but acidic reflux decrease to the two-third level of initial reflux beyond postprandial (after < 2 hours) in GERD children [23].

HABITUAL RISK FACTORS

In children and adolescents, their lifestyles associated with heartburn have to be addressed. Korean children with GERD had their diet related to overeating, eating late at night, drinking soda, eating salty, spicy, or greasy foods, though they were rated not to be obese [4]. A history of small for gestational age or preterm may been linked to an esophageal adenocarcinoma later [26]. Other factors include history of chronic respiratory disorder such as child or teen-aged wheezer or adolescent onset asthma [14,27]. Moderate obese (16%) and extreme obese children (32%) are likely to have more GERD comparing to normal weight children [12].

DIAGNOSIS

Though there is no golden standard for the GERD test battery yet, a combination of tests is generally required in order to properly diagnose GERD. The initial stage assessment should involve a thorough history taking with a physical examination, and an empirical trial (2 weeks) of PPI or histamine-2 receptor antagonist (H2RA). This initial assessment and treatment trial would be sufficient for children with typical symptoms of GERD like regurgitation or heartburn [8,28]. However, GERD in children manifests differently from that in adults. The GERD in children often accompany regurgitation, vomiting, abdominal pain, or cough and the prevalence and severity of those symptoms are very similar between EE and NERD children. Heartburn specific for GERD (2.7-58%) was less in children and adolescents than that in adults, but it was higher in EE children (18.9%) than in NERD (2.9%) [4,6,9]. Thus, clinicians would have a difficult time to objectively assess the severity of esophagitis based on presenting symptoms.

An empirical trial of acid suppressants as a diagnostic test/treatment has been clinically useful in GERD children in the absence of any alarming signs such as failure to thrive or dysphagia [7,8]. A 2-week course of acid suppression with PPIs or H2RAs has not been proven conclusive though.

If their symptoms persist, then an endoscopy should be considered especially for the cases of suspected esophagitis. Endoscopy has proven to be a valuable procedure in children with a persistent symptom like a suspected esophagitis. This procedure has low sensitivity (41%) and specificity (77%) as for the diagnostic tool of GERD [6]. The endo-

scopic findings of EE show mostly mild grade lesions with patchy distribution according to the Los Angeles Classification: 52% of GERD children (ages of 12-17) showed grade A esophageal lesions of EE (mucosal break ≤ 5 mm) and 39% of them showed grade B (mucosal break ≥ 5 mm) [9,25]. For NERD, the endoscopic results show either normal condition or minimal changes, grade M (e.g., erythema and/or whitish turbidity) but histological changes were compatible to GERD [25]. There were no defined histological distinction between EE and NERD. The dilation of intercellular spaces (DIS) could be an important histological marker of EE in children as DIS occurs even after a brief exposure of the esophageal mucosa to a small amount of bile acids. DIS can revert to normal after the resolution of heartburn with PPI [25]. EE and NERD are spectrums of GERD in children.

MANAGEMENT

The goal of acute therapy is to have a complete relief of any painful symptoms, to enjoy an improved quality of life, and to resolve possible esophagitis. For a long-term therapy, its goal is to achieve a complete relief of the symptoms and to heal esophagitis with a minimal dose medication within a short time frame. Undoubtedly, any recommendations should be tailored for each patient with GERD [29]. The efficacy of a therapy is monitored by the degree of symptom relief without a routine endoscopic follow-up. Endoscopic monitoring is needed in cases of atypical or persistent symptoms or signs after an adequate recommended therapy, higher grade EE, or esophageal stricture at presentation.

Non pharmacological interventions

GERD in older children and adolescents should be initially managed with their lifestyle modifications while avoiding any triggering substances (ex: tomatoes, chocolate, juice, caffeine, carbonated beverages, and/or alcohol). Other lifestyle changes include prohibiting smoking around children and a late-night eating habit. It has been known to benefit from raising head of the bed, or lying down on the left side. A having small but frequent meals or chewing sugarless or bicarbonate containing gum may decrease reflux [3,4,7,8,12,30].

Pharmacological therapy

A study showed that primary care pediatricians routinely prescribed antacid (49.2%), H2RAs (23.3%), PPIs (22%), or prokinetics (7.5%): 10% of those doctors prescribed four more drugs for their patients. The pediatricians applied a *step-up* approach (24.7%) more than a *step-down* approach (9.8%) when treating GERD in adolescents in Europe [29]. The *step-up* approach begins with H2RA, and monitors its progress, then switches to PPI, if the response remains inadequate. In contrast, the *step-down* approach begins with a PPI treatment, and then switches to H2RA. A choice between the *step-down* vs. the *step-up* therapy is up to a physician's discretion.

1. Drugs for GERD

1) Antacids, alginate and sucralfate: An antacid is the most popular over-the-counter medication for GERD. Antacid (ex: magnesium and aluminum hydroxide, or calcium carbonate) acts by neutralizing acid in the stomach. Alginate-based formulas contain sodium or potassium bicarbonate. They provide a rapid but transient, short-term relief of mild or sporadic GERD symptoms (ex: postprandial heartburn) as a rescue medication. There is little evidence yet for the long term usage in children because of the side effects. Sucralfate is a mucosal protectant which works by blocking diffusion of gastric acid and pepsin across the esophageal mucosa. They can be on-demand used more commonly for NERD, but not for severe symptoms or EE.

2) Prokinetics: Currently there are no sufficient evidences to justify a routine use of prokinetics for treating GERD in children [7,8]. A role of gastric emptying for GER has been controversial. A high dose of domperidone in adults has been related to a higher risk of sudden cardiac death. In addition, metoclopramide has been linked to lactorrhea, or ex-

trapyramidal signs. Recently new prokinetics with reduced side effects are coming into the market, but they have not yet shown enough applicable evidences for children. Targeting on TLESRs of pathogenic mechanism of GER, baclofen appears to decrease the frequency of TLESRs, but it is usually saved for the patients with neurological impairment.

3) H2RAs: H2RAs work to inhibit the interaction of histamine in the parietal cells. They are generally recommended for mild to moderate EE or on-demand use for reflux symptoms for about 1-3 months of period [29]. The H2RAs have shown fast effectiveness that occurs within 30 minutes of intake. The H2RAs control the basal rate of acid during fasting or nocturnal acid breakthrough. However, they have also been known to develop fairly rapid tachyphylaxis 9 days to 6 weeks post-administration by 1st pass metabolism and therefore may not be adequate for long-term use [31]. Meanwhile, ranitidine has an excellent safety record. Its effect does not depend on meal but it is less effective to suppress meal induced acid secretion. Its effect is affected by antacid. A study of critically ill children in pediatric intensive care unit showed that ranitidine (1±0.24 mg/kg q 8 hours) maintained the pH 4.4±1.6 for about 60% of time. This effect of Ranitidine was similar to that of once a day PPI [32].

4) PPIs: PPIs work to selectively and irreversibly block the H+/K+ ATPase in the gastric parietal cells. The dosage of each PPI varies per weight and age as they are rapidly absorbed and metabolized: esomeprazole (0.2-1 mg/kg/day, 1-17 years), omeprazole (0.7-3.5 mg/kg/day, 2-16 years), lansoprazole (0.7-1.44 mg/kg/day, 1-17 years), pantoprazole (0.6-1.2 mg/kg/day) [33-36]. PPI does not develop tachyphylaxis [36]. All kinds of PPIs have similar antisecretory effects. The effects of the metabolizer CYP2C19 polymorphism on PPI in children are known to be similar to those in adults. The CYP2C19 polymorphism occurs in 15-20% in Asian and newborns [33]. Presently the Food and Drug Administration of the USA did not approve PPIs for use in infants younger than 12 months. PPI is acid labile, so it needs to be protected by enteric coating. The intake of PPI 15-30 minutes before the first meal of the day can work effectively by blocking acid pumps, thus alleviating symptoms and healing the esophagus. Its timing of 'before the first meal of the day' is crucial in order to maximize its anti-secretory effect in an empty stomach and to minimize its interaction with foods. The effect of omeprazole or lansoprazole can be reduced by sucralfate. During a critical illness, PPIs could offer an advantage over H2RAs as PPI has been well tolerated without the need for dosing adjustment for renal insufficiency. The healing rate of EE using PPIs has been excellent with intragastric pH over 4.0 for 12-17 hours of a 24-hour period [37]. Antisecretory property (pH>4) of one morning dose PPIs reaches 10-30% (2.5-8 hours) on day 1 and its maximum of 50-75% (12-15 hours) on day 5. Its healing rate in children with EE peaked at 4 weeks with PPIs treatment [38]. Meanwhile, the dose-response curve to PPI plateaued for EE cases, but there was no dose-response plateau for heartburn. The clinical efficacy of the PPI has been related to the degree and duration of acid suppression as well as the length of the treatment. An abrupt withdrawal of PPIs has been reported to cause reflux symptoms. Therefore, it is advised to gradually taper off the medication over 2-4 weeks.

PPI is recommended for severely acute EE, a symptomatic relief of NERD, prevention of nocturnal acid secretion and relevant reflux, and a relief of supra-esophageal symptoms of GERD.

Symptom responses to PPIs in NERD have been 20% less than that in EE. A typical duration of NERD treatment is 4 weeks, and then change to as needed treatment.

The duration of PPI treatment for EE in children has not been well defined. Their endoscopic examinations of EE children showed 84% healing rate including the histological healing rate of 43-75% after 8 weeks of treatment. With 12 weeks or longer treatment, their healing rate was up to 95%. Severe esophagitis of grade C to D with underlying disease required a higher dose or longer duration of PPIs [39,40]. With lansoprazole, the rates of symptom improvement at 8weeks and 16 weeks were 75.7%,

75.7% in EE children and 85%, 85% in NERD children [4]. The decisions for maintenance therapy could be determined by monitoring symptoms at 8 weeks of PPIs in GERD children. Their 16-week therapy outcomes had the same efficacy as that of the 24-week therapy with lansoprazole [4]. Understandably, the clinical efficacy of PPI treatment in EE children can be determined by the degree and duration of acid suppression as well as the length of the treatment.

2. Adverse events of acid suppressant

Generally PPI has been considered to be safe but with a caveat of some safety concerns for a long-term usage. About 1-9% of children with PPI experienced drug related side effects such as diarrhea, headache, abdominal pain, nausea, dizziness, and/or rash. For those patients, the PPI should be switched to other agent. It has been also reported that low acid induced by PPIs may reduce the level of ampicillin, cyanocobalamin, iron, digoxin, or ketoconazole. The decreased gastrin level after a long-term treatment has been reported to recover to its normal range after the termination of PPI. 61% of GERD children were reported to have enterochromaffin cell like hyperplasia for 11 years of treatment, but with no carcinoid changes [34].

19% of NERD children treated with lansoprazole for 8 weeks experienced adverse events with 15 mg dosage, while only 4% of EE patients experienced those events with 30 mg dosage [40]. This lansoprazole is also known to decrease the level of hemoglobin. Omeprazole may cause idiosyncratic, not dose-dependent reaction such as pancreatitis, agranulocytosis, toxic epidermal necrosis, and interstitial nephritis. Overdose of omeprazole can cause flushing, tachycarida, or headache. Both omeprazole and lansoprazole are known to cause possible liver dysfunction. Drug to drug interaction with liver cytochrome P450-CYP2C19 may occur with clarithromycin, benzodiazepine, phenytoin, warfarin, or theophylline.

The acid suppression could produce unwanted adverse events due to the hyposecretion (pH>4.0) of gastric acid, bacterial modification, and/or altered immune function, which could then lead to multiple infections and malabsorption of nutrients. The children (9-15 months of age) treated with ranitidine and omeprazole for 8 weeks were more subjected to acute gastroenteritis (OR, 3.58; 95% CI, 1.87-6.86) and community acquired pneumonia (OR, 6.39; 95% CI, 1.38-29.7) at the 4 months post-treatment follow-up [16]. Several pediatric studies correlated the acid suppressant increased risks of necrotizing enterocolitis in very low birth weight infants or candidemia, pneumonia, especially beta-hemolytic *Streptococci,* infection /sepsis by *E. Coli* or *K. pneumonia*, urinary tract infection, small bowel bacterial overgrowth, *C. difficile* associated diarrhea, extended hospital stay, or death [41]. In elderly patients, hip/vertebra fracture, long-term Mg depletion, food allergy, decreased vitamin B12, iron, and Ca level were reported [42]. However, it should be noted that these studies made causal associations with limited and inconsistent evidences [16,41,42]. It is a general observation that otherwise healthy older children and adolescents with GERD usually respond well with a short-term (4-8 weeks) treatment of PPIs. Thus, it is not conclusive to predict that GERD children have similar adverse events from a long term usages seen in adults patients.

PROGNOSIS

When given adequate doses, PPIs can safely work to relieve GERD symptoms and heal esophagitis in children. The level of this initial treatment success would then impact its long-term outcome for reflux symptoms and esophagitis. There have been inconsistent findings on long term outcomes. A study showed that a majority of treated GERD children did not have a recurrence [10], while another study showed that 30% of adults were taking either H2RAs or PPIs approximately after a 15-year duration of follow-up of GERD diagnosed at a mean age of 5 years [43]. 7% of treated esophagitis have shown recurrence after 9 month [19]. It appeared that GERD in infancy and childhood might be correlated with a reflux disease later in life [43]. Particularly EE in

children is now believed to develop into a chronic disease [44].

TREATMENT FAILURE

The definition of GERD treatment failure is controversial but it means incomplete or unsatisfactory symptoms in response to a full course of PPIs [38]. Intragastric pH < 2.0 may be a predictor of non-healing. Most GERDs including grade M, A or B, have improved well after a PPI treatment over 4 to 8 weeks, but a considerable number of EE of grade C or D have failed to respond to the treatment. Because of these unsatisfactory outcomes of the GERD treatments, the more flexible dosing in relation to meals and lifestyle should be considered. One of the undeniable factors of these negative outcomes is that patients often do not adhere to the rigorous regimen of prescribed treatment which includes resolute changes of diet and lifestyle. The reasons for a treatment failure have known to be multifactorial [38].

A management of PPIs treatment failure involves multiple steps: 1) stopping of PPIs for 1 week, 2) re-endoscopy, 3) esophageal pH monitoring, or pH-MII, etc. Esophageal pH monitoring can be useful when evaluating the efficacy of antisecretory therapy or to correlate symptoms (ex: cough, chest pain) with acid reflux episodes, to select children with wheezing or respiratory symptoms in whom GER becomes an aggravating factor, and to evaluate the success of pre- and post antireflux surgery. A weakness of esophageal pH monitoring is that it does not have an absolute clinical value due to its limitations of not being able to detect nonacid reflux 2 hours postprandial when GER occurs.

pH-MII can be used to detect acid-, weak acid-, and nonacid-reflux episodes. A significant number of GERs include non-acidic reflux [18,23]. Nonacid-, gas-GER is associated with a respiratory disorder like asthma [45,46]. This method is superior in terms of finding the temporal relationship between the symptoms and GER, when evaluating esophageal bolus transport or, probing the proximal extent of GER episodes. For these with treatment failures, children need to be referred to a pediatric gastroenterologist.

CONCLUSION

There has been an alarming increase of otherwise healthy older children and adolescents presented with gastro-esophageal reflux symptoms in community pediatric clinics. The GERD usually responds well with H2RA and PPI treatments, but in some cases these treatments have been linked to adverse events of pneumonia or gastroenteritis. Therefore, it is imperative that pediatricians should develop an in-depth understanding of the GERD mechanism, an effective dosage and treatment duration of a specific medication, and its side effects of short term/ long-term usage in order to optimally address each patient and to achieve desired therapeutic goals.

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