

PATHOLOGIES ASSOCIATED WITH GASTROESOPHAGEAL REFLUX DISEASE IN CHILDREN

Gabriela Ghiga¹, Eduard Vasile Rosu^{1*}, Claudia Olaru^{2,3}, Nicoleta Gimiga^{2,3}, Oana Maria Rosu², Stefana Maria Moisa^{2,3}, Smaranda Diaconescu^{2,3}

¹. "Sfânta Maria" Clinical Emergency Children's Hospital, Iași, PhD student, "Grigore T. Popa" University of Medicine and Pharmacy, Iași

². "Sfânta Maria" Clinical Emergency Children's Hospital, Iași, Gastroenterology Clinic, Iași

³. "Grigore T. Popa" University of Medicine and Pharmacy, Iași

Corresponding author: Eduard Vasile Rosu rosuedy@yahoo.com

ABSTRACT

Gastroesophageal reflux disease is frequently encountered, yet still underdiagnosed in pediatric pathology. More than two thirds of the pediatric population are diagnosed with gastroesophageal reflux. Various pathologies associated with this disease are listed in the literature. The current article addresses asthma, obesity and dental erosions that are complementary to this condition. A multidisciplinary approach is mandatory for the purpose of optimal therapeutic management.

Key words: GERD, asthma, obesity, dental erosions

INTRODUCTION

Gastroesophageal reflux disease (GERD) is frequently encountered, yet still underdiagnosed in pediatric pathology. Owing to its heterogeneous symptomatology, gastroesophageal reflux has quite a few diagnostic pitfalls, particularly in older infants, children and teenagers, where regurgitation and vomiting – typical of younger babies – are replaced by polymorphic respiratory manifestations. (1) Early detection of the disease and a correct treatment approach prevents the onset of complications and ensures a better quality of life. An undetected reflux that is untreated or insufficiently treated and evolves over a certain period of time can have digestive, respiratory, neurological and nutritional consequences. (2-4)

More than two thirds of the pediatric

population are diagnosed with gastroesophageal reflux. (3) Association with different pathologies sometimes makes it difficult to pinpoint a definitive diagnostic and requires a careful modulation of treatment.

Asthma and GERD

Asthma is known as one of the most frequent pediatric diseases, with an ever-growing prevalence in developed countries. (5) More than 5 million children in the United States have bronchial asthma, this disorder resulting into more than 200,000 hospital admissions and 3.5 million visits with the doctor every year. (6) Children with asthma experience a decrease in their quality of life, as well as a high rate of school absenteeism adding up to more than 14 million school

days annually. Children with asthma, even those deemed to have milder forms, also have a significant risk of death. (7) However, the respiratory symptoms that are indicative of asthma can also pertain to other pathological entities. Of these, gastroesophageal reflux – particularly in children – often leads to symptoms that are consistent with asthma or pneumonia. Children and teenagers with gastroesophageal reflux more frequently present with coughing and other respiratory phenomena aside from the typical esophageal ones, namely pyrosis which occurs in adults.(8) The actual association and the causal relation between asthma and gastroesophageal reflux disease (GERD) have been under debate for some time now. Moreover, studies proved that these two disorders occur simultaneously in a large percentage of individuals, and a series of theories have been postulated in respect of the physiopathological mechanisms for observed association, primarily epidemiological ones. (9)

Up to 75% of adults with asthma report symptoms of gastroesophageal reflux. Moreover, abnormal values of esophageal pH were reported among individuals with asthma in 55% to 83% of adults and 50% to 63% of children. Mathew et al noted that the prevalence of reflux was directly connected to the severity of bronchial asthma symptoms; a study was conducted to measure pH in 68 children with asthma over the course of 24 hours, which showed that the prevalence of reflux was 0% in those with mild intermittent bronchial asthma. In this study, one or more symptoms of reflux were present in 53% of the 15 children with reflux and in 17% of the 53 children without reflux (rate of probability 5.58; $p < 0.05$). (10)

Endoscopic explorations identified esophagitis in 44% of children with reflux and in 9% of those without reflux (OR–odds ratio: 8.53; $p < 0.05$). Thomas et al conducted

a radionuclide scintigraphy in 126 children 6 months to 6 years of age for which the usual anti-asthma medication failed to alleviate the symptoms of bronchial asthma. Overall, 26% of the children were diagnosed with gastroesophageal reflux, with a higher prevalence noted in those with preexisting symptoms of reflux (10/26; 38.5%) compared to those having no reflux symptoms (23/100, 23%). (11)

Alternatively, the series of epidemiological cases showed that the relative risk of pulmonary diseases, including asthma, is increased among people with GERD. For instance, Ruhl and Everhart discovered that people with gastroesophageal reflux have a risk that is approximately 2 times higher for asthma (RR–relative risk: 2.0; 95%CI: 1.0-3.7), bronchitis (RR:2.1; 95% CI:1.4-2.9) and pneumonia (RR: 1.4; 95% CI: 1.1-1.8). (12)

Asthma is a disease caused by the chronic inflammation of airways, where, in addition to the increased secretion of mucus in the airways and smooth muscle hyperresponsiveness, a critical part is played by a number of inflammatory cells, including eosinophils, mast cells, epithelial cells, macrophages and T lymphocytes. These different types of cells secrete a wide variety of inflammation mediators (for instance chemokines, cytokines).

The natural history of asthma, irrespective of the age of onset, is one where chronic inflammation can lead to airway remodeling, irreversible airflow obstruction and accelerated decline in lung function. Essentially, the longer the duration of asthma, the higher the risk of irreversible pulmonary lesions and changes. It is a well-known fact that asthma favors gastroesophageal reflux via a variety of mechanisms, including:

-cough-induced increase of intra-abdominal pressure levels that increase the

pressure gradient via the lower esophageal sphincter

-hyperinflation that modifies the relationship between the crural diaphragm and the gastroesophageal junction

-airways obstruction conducive to negative intrathoracic pressure

-specific asthma medications that reduce the pressure of the lower esophageal sphincter.

A few theories were proposed to explain the pathophysiological mechanisms of bronchial asthma induced or exacerbated by gastroesophageal reflux. These include the reflux theory which suggests the direct stimulation of airways inflammation by aspiration of gastric contents or airways' hyperresponsiveness triggered by aspiration of small quantities of acid into the lower airways. The acidity of the reflux, the presence of food allergens and digestive enzymes can favor airways and smooth muscle inflammation, resulting in the increased responsiveness of the bronchial smooth muscle. The foundation of the reflux theory is that the common embryological origins of the respiratory and gastrointestinal systems led to a common innervation in the form of the vagus nerve and thus share the same autonomous reflexes. Therefore, the stimulation of receptors in the distal esophagus by gastric reflux causes a vagal reflex and bronchial constriction. (9)

Obesity and GERD

There is conclusive proof in adults that **obesity** is a risk factor for GER, erosive esophagitis, Barrett's esophagus and esophageal adenocarcinoma. Unlike the abundant literature on adult patients, pediatric data is limited. (13)

In a study conducted in pediatric clinics in Norway, Stordal et al compared the symptoms of GER in 872 children with

asthma and 264 control subjects. They discovered that excess body weight was associated with a higher prevalence of GER symptoms in children aged 7 to 16 years old, with or without asthma (or 1.8, 95% CI 1.2-2.6). (14) Malaty et al assessed children diagnosed with or having symptoms indicative of gastroesophageal reflux disease (GERD) in a pediatric gastroenterology clinic in the USA. The authors reported that these children with GERD were more susceptible of being obese, with a BMI (body mass index) above the BMI reported in the national database on children's nutritional status. (15)

The prevalence of GER symptoms was compared among 236 obese children admitted in specialized clinics and 101 children with normal BMIs admitted in general pediatric clinics in the USA. In this study, every subject was interviewed using a questionnaire for reflux symptoms and a reflux score was thus calculated. Obesity remained the only significant predictor for a high score of reflux symptoms after the control of certain variables, such as age, sex, race and coffee consumption. Also, the score for reflux symptoms increased linearly with the increase in BMI. In a group of children with obesity (IMC > 2.7), 20% of children had a positive score. (15)

Similarly, Teitelbaum et al also found a larger prevalence of obesity among children with GER in a gastroenterology clinic compared to healthy subjects in the control sample. (16)

One possible mechanism for obesity-induced GER includes the extrinsic gastric compression by the surrounding adipose tissue, which leads to an increase in intra-gastric pressures and the subsequent relaxation of the lower esophageal sphincter. Another potential theory is that excess dietary fat could lead to a delay in gastric emptying, which results in gastroesophageal reflux.

It is a well-known fact that childhood

obesity often carries into adulthood. Moreover, childhood gastroesophageal reflux is also likely to carry into adulthood. For this reason, obese children with acid reflux are susceptible to become obese adults with acid reflux and can develop complications, including esophagitis, Barrett's esophagus and even malignancy. Therefore, early diagnosis and swift therapy in obese children with GER are essential in order to prevent long-term morbidity and complications of this disease. Lowering the BMI was shown to improve the symptoms of acid reflux in adults.

Although the pediatric literature is still limited on this topic, weight loss should be an integral part of the management for obese children with gastroesophageal reflux.

Dental erosion and GERD

The high prevalence of gastroesophageal reflux disease in children increases the responsibility of dentists to watch out for this potentially severe state when they see unexplained cases of dental erosion. Although gastroesophageal reflux is a normal physiological event, excessive gastric and duodenal regurgitation, combined with a decrease in the normal protective mechanisms – including inadequate saliva

production – can lead to several esophageal and extraesophageal disorders. (17) Sleep-related reflux is an insidious process, as the supine position favors the proximal migration of gastric contents, and the normal production of saliva is much reduced. Gastric acid easily displaces saliva from dental surfaces, while proteolytic enzymes (pepsin) remove the protective coating on teeth. (18) Although more and more evidence brought forward show the associations between GERD and dental erosion in studies on both animals and humans, there are relatively few controlled clinical studies. The suspicion of an endogenous source of acid associated with observed dental erosion requires additional investigations and a referral to the pediatric gastroenterologist. (19)

Another study compared the presence of dental erosion in children aged 3 to 12 years old with GERD compared to other children in the same age span without GERD. Thus, 98% of the children with GERD (53 of 54) had dental erosion, compared to 19% of the control group (11 of 58). A meta-analysis published in 2013 showed that researchers proved as early as 1937 that GERD is the cause of dental erosion, and there is increasing evidence supporting this statement.

CONCLUSIONS

Gastroesophageal reflux disease has a complex clinical picture. The extra-digestive manifestations require a wide scope approach and the swift commencement of investigations.

A multidisciplinary approach is mandatory for the purpose of optimal therapeutic management (pediatric gastroenterologist, pediatric allergist, pediatric pneumologist, pediatric endocrinologist, pediatric dentist).

REFERENCES

- 1 Ferreira, C., Carvalho, E., Sdepanian, V., Morais, M., Vieira, M. and Silva, L. (2014). Gastroesophageal reflux disease: exaggerations, evidence and clinical practice. *Jornal de Pediatria*, 90(2), pp.105-118.

- 2 Dan Moraru, Marin Burlea, Evelina Moraru, Eugen Cîrdei, Georgeta, Diaconu. *Pediatrie – patologie digestivă, nutrițională și neurologică la copil*. Ed. Fundației Academice AXIS, Iași, 2008, p.100-118. ISBN 978-973-7742-643.
- 3 Diaconescu S, Miron I, Gimiga N, et al. Unusual Endoscopic Findings in Children: Esophageal and Gastric Polyps: Three Cases Report. *Medicine (Baltimore)*. 2016; 95(3):e2539.
- 4 Gimiga N, Olaru C, Diaconescu S, Miron I, Burlea M. Upper gastrointestinal bleeding in children from a hospital center of Northeast Romania. *Minerva Pediatr*. 2016;68:189–95.
- 5 Alvey Smaha D. Asthma emergency care: national guidelines summary. *Heart Lung* 2001; 30:472-4.
- 6 Mannino DM, Homa DM, Akinbami LJ, Moorman JE, Gwynn C, Redd SC. Surveillance for asthma: United States, 1980-1999. *MMWR Surveil Summ* 2002;51:1-13.
- 7 Robertson CF, Rubinfeld AR, Bowes G. Pediatric asthma deaths in Victoria: the mild are at risk. *Pediatr Pulmonol* 1992;13:95-100.
- 8 Ashorn M, Ruuska T, Karikoski R, Laipala P. The natural course of gastroesophageal reflux disease in children. *Scand J Gastroenterol* 2002;37: 638-41.
- 9 Gold, B. (2005). Asthma and gastroesophageal reflux disease in children: Exploring the relationship. *The Journal of Pediatrics*, 146(3), pp.S13-S20.)
- 10 Mathew JL, Mittal SK, Kalra KK, Rajeshwari K, Gondal R. Prevalence and profile of gastroesophageal reflux in children with bronchial asthma. In: Program and abstracts of the American College of Allergy, Asthma and Immunology 2003 Annual Meeting. November 7-12, 2003; New Orleans, La. Abstract 38.
- 11 Thomas EJ, Kumar R, Dasan JB, Kabra SK, Bal CS, Menon S, Malhotra A. Gastroesophageal reflux in asthmatic children not responding to asthma medication: a scintigraphic study in 126 patients with correlation between scintigraphic and clinical findings of reflux. *Clin Imaging* 2003;27:333-6.
- 12 Ruhl CE, Everhart JE. Respiratory complications of gastroesophageal reflux disease (BRGE) in a prospective, population-based study. *Gastroenterology* 1999;116:A92.
- 13 Phatak UP, Pashankar DS. Obesity and gastrointestinal disorders in children. *J Pediatr Gastroenterol Nutr* 2015; 60:441–445.
- 14 Stordal K, Johannesdottir G, Bentsen B, et al. Asthma and overweight are associated with symptoms of gastro-oesophageal reflux. *Acta Paediatr*. 2006;95: 1197–201.
- 15 Malaty H, Fraley JK, Abudayyeh S, et al. Obesity and gastroesophageal reflux disease and gastroesophageal reflux symptoms in children. *Clin Exp Gastroenterol*. 2009;2:31–6.)
- 16 Teitelbaum J, Sinha P, Micale M, et al. Obesity is related to multiple functional abdominal diseases. *J Pediatr*. 2009;154:444–6.
- 17 Gastroesophageal Reflux Disease and Tooth Erosion. Sarbin Ranjitkar, John A. Kaidonis, * and Roger J. Smales. *Int J Dent*. 2012; 2012: 479850.
- 18 Farup C, Kleinman L, Sloan S, et al. The impact of nocturnal symptoms associated with gastroesophageal reflux disease on health-related quality of life. *Archives of Internal Medicine*. 2001;161(1):45–52.
- 19 Oral manifestations of gastroesophageal reflux disease. Ranjitkar S, Smales RJ, Kaidonis JA. *J Gastroenterol Hepatol*. 2012 Jan;27(1):21-7. doi: 10.1111/j.1440-1746.2011.06945.x. Review