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ENDOSCOPIC AND HISTOLOGICAL CORRELATION BETWEEN GASTROESOPHAGEAL REFLUX DISEASE AND FOOD ALERGY

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Abstract: Background - Food allergy (FA) can be defined as an adverse health effect triggered by a specific immune response that occurs upon exposure to a particular food. In some groups of pediatric patients, FA has been related to gastroesophageal reflux, abdominal colic and constipation.

Objective - This study evaluated endoscopic and histopathological findings in gastroesophageal reflux disease (GERD) and FA in a specific pediatric population seen at a private clinic in Goiânia.

Methods - Findings from Upper Digestive Endoscopy (UDE) and histopathological findings from biopsies performed on patients aged zero to eighteen years old were retrospectively evaluated. The diagnosis of GERD was based on endoscopic and histological findings and graded according to Savary-Miller modified classification. The diagnosis of FA was based on histological findings, and the number of intraepithelial eosinophils was compiled.

Results – 474 exams were done, 10 of which were excluded and the remaining 464 (97.9%) comprised our study group. The mean age of the group was 7.7 ± 5.4 years, ranging from 4 months to 18 years of age, with an average of 7 years, 226 of whom (48.7%) were male. Endoscopic and/or histopathological findings of FA were observed in 36/464 (7.8%) of the patients (95% CI ranging from 5.6% to 10.7%). No relationship between the presence of FA and gender was found (p = 0.39). The mean age of patients with FA was 4.7 ± 3.9 years and 8.0 ± 5.5 years in those without allergies (p = 0.0003). GERD was observed in 352/464 patients (75.9%) (95% CI ranging from 71.7% to 79.6%). No relation to gender was observed (p = 0.32). The mean age of patients with GERD was 7.3 ± 5.3 years and 9.1 ± 5.6 years in those without esophagitis (p = 0.003). When the degree of esophagitis was evaluated, 279/352 (79.3%) presented findings compatible with grade I esophagitis, 66/352 (18.8%) grade II, 6/352 (1.7%) grade III and 2 (0.7%) grade IV. No relationship between the presence of GERD and FA was observed: allergy was found in 28/352 (8.0%) patients with GERD and in 8/112 (7.1%) patients without esophagitis (p = 0.8). Likewise, no relationship between the presence of GERD and FA was observed even when we evaluated patients under 5 years of age (18/153 (11.8%) and 5/34 (14.7%), p = 0.6) or under 10 years of age (25/260 (9.6%) and 7 / 72 (9.7%), p = 0.9]. Although the findings of marked esophagitis (grade III and IV) was observed only in patients without FA, this difference was not statistically significant (p = 09).

Conclusion – Our findings show a high prevalence of GERD (75.9%) in a pediatric population at a private clinic in Goiânia. There is an even higher frequency of findings of mild erosive esophagitis. FA was found in 36/464 (7.8%) of these patients. No relationship between GERD and the presence of FA was observed.

Keywords: - Pediatric Digestive Endoscopy; Gastroesophageal reflux disease; Food allergy.

INTRODUCTION

Gastroesophageal reflux (GER) is defined as the retrograde and involuntary flow of gastric contents into the esophagus and can be classified as physiological or pathological[2]. Physiological GER is more common and has a high prevalence in children under one year of age[1], producing regurgitation and, occasionally, vomiting, without compromising the growth and development of the child[2].

In pathological GER or gastroesophageal reflux disease (GERD), there is a wide range of such secondary clinical repercussions as growth deficit or weight loss, irritability, early satiety or food refusal, repetitive and/or chronic lung diseases, sleep disorders, dysphagia or odynophagia, Sandifer's

syndrome (cervical hyperextension, lateral tilt of the head, anemia and esophagitis) and even sudden death[2]. GER can be caused by infections, metabolic and neurological disorders and food allergy (FA)[1].

FA is the abnormal reaction of the body involving immunological mechanisms when food or food additives are ingested[3]. It differs from food intolerance, in which the body develops an abnormal non-immunological reaction of toxic, enzymatic, pharmacological or anaphylactoid nature[3].

In Brazil, the most prevalent FA in the pediatric age group is related to cow's milk. Studies report that it is found in 0.3% to 7.5% of children, and 82% manifest symptoms in the first four months of life[1]. It can affect different target organs, determining cutaneous (30 to 50%), respiratory (20 to 30%), gastrointestinal (50 to 60%) and systemic allergies[1].

Although FA and GER are clinical entities of great prevalence in the pediatric age group and some authors suggest a relationship between the two, few studies correlate them, especially in our midst. Therefore, this study aims to correlate endoscopic and histopathological findings of GERD and FA in a given pediatric population seen at a private clinic in Goiânia.

METHODOLOGY

Findings from Upper Digestive Endoscopy (UDE) performed at the Instituto do Aparelho Digestivo de Goiânia as well as histopathological findings from biopsies performed on patients aged up to eighteen years old were retrospectively evaluated.

Data regarding identification (name, sex and age), endoscopic findings and biopsy results, and mainly information regarding the diagnostic criteria of FA were collected from endoscopic records.

The diagnosis of GERD was based on endoscopic and histological findings and graded according to Savary-Miller modified classification[15].

The diagnosis of FA was based on histological findings, and the number of intraepithelial eosinophils was compiled, and this was defined through the evidence of a number greater than or equal to 10 eosinophils per field of high power magnification[4].

All patients aged between zero and eighteen years old submitted to UDE and in whom esophageal, gastric and duodenal biopsies were collected were included in the study.

The EpiInfo 7.1.0.6 program (Centers for Disease Control Epidemiology Program Office, Atlanta, Georgia) was used for statistical analysis. Student's t-test was used to compare the measurements between two independent samples. The correlation between categorical variables was tested through the chi-square test of association, with correction by the Yates Test or (Two-tailed) Fisher's Exact Test when these were found appropriate. The results found were expressed as mean ± standard deviations (SD) and the level of significance used in all tests was set at 5%.

The research protocol was evaluated and approved by the Human Research Ethics Committee of the General Hospital of Goiânia.

RESULTS

474 consecutive exams performed on children aged under or equal to 18 years old were evaluated, 10 of which were excluded from our analysis owing to our inability to fully evaluate the endoscopic and/or histopathological exams. The remaining 464 (97.9%) made up our study group.

The mean age of the group was 7.7 ± 5.4 years old, ranging from 4 months to 18 years old, with an average of 7 years of age, 226 of which (48.7%) were males.

Endoscopic and/or histopathological findings of FA were observed in 36/464 (7.8%) of the patients (95% CI ranging from 5.6% to

10.7%). No relationship between the presence of FA and sex (p = 0.39) was observed. The mean age of patients with FA was 4.7 ± 3.9 years old and 8.0 ± 5.5 years old in those without allergy (p = 0.0003) (Table 1).

Endoscopic findings of GERD were observed in 352/464 (75.9%) of the patients (95% CI ranging from 71.7% to 79.6%). No relationship between the presence of GERD and sex (p = 0.32) was found. The mean age of GERD patients was 7.3 ± 5.3 years old and 9.1 ± 5.6 years old in those without esophagitis (p = 0.003) (Table 2). When the degree of esophagitis was evaluated according to the modified Savary-Miler classification[15], we found that 279/352 (79.3%) presented findings compatible with grade I esophagitis, 66 (18.8%) grade II, 6 (1.7%) grade III and 2 0.7%) grade IV (figure 1).

No relationship between the presence of GERD and FA was observed; allergy was observed in 28/352 (8.0%) patients with GERD and in 8/112 (7.1%) patients without esophagitis (p = 0.8). Likewise, no relationship between GERD and FA was observed even when we separately evaluated patients under 5 years of age [18/153 (11.8%) and 5/34 (14.7%) respectively, p = 0.6, or with less than 10 years of age [25/260 (9.6%) and 7/72 (9.7%), p = 0.9]. Although findings of marked esophagitis (grade III and IV) were only observed in patients without FA, this difference was not statistically significant (p = 0.9) (Table 1).

DISCUSSION

FA can be defined as an adverse health effect triggered by a specific immune response that occurs on exposure to a determinate food[11]. Such response may occur within minutes or hours after food intake and consists of a mediated IgE reaction, also called immediate hypersensitivity. This, when present in genetically predisposed individuals, leads to the excessive production of IgE-specific antibodies to a particular food due to failure in the development or the breakdown of the oral tolerance mechanism[5].

The diagnosis of FA is based on a minute clinical history, associated with physical examination data, and may be complemented by allergy testing[6]. Types of allergy tests include subcutaneous tests, serological tests and oral challenge tests[5]. Faced with strong clinical evidence, a cutaneous test (Prick Test) can be performed as it offers affordable cost, easy execution, quick interpretation of the result in addition to allowing the analysis of several foods simultaneously. However, its positivity only indicates sensitization to an allergen and not necessarily a clinically important reactivity accompanied by clinical symptoms, that is, some people may test positive and still tolerate the antigen in the diet[5].

Four decades ago, pediatricians began to observe that a number of children did not respond well to standard GERD treatment and by investigating this subgroup better, they observed that these children were allergic to cow's milk. They found that the esophageal mucosa of these patients had a greater number of eosinophils than patients with GERD without allergy. The exclusion of cow's milk, in general, solved the clinical problem. On this occasion, pathologists also noticed that in some cases of esophagitis, the mucosa presented with an exuberant infiltrate of eosinophils[16].

Diseases characterized by the participation of IgE-mediated reactions are characterized by an infiltration of the esophagus, stomach and/or intestinal wall with eosinophils, basal cell hyperplasia, papilla elongation, absence of vasculitis and presence of peripheral eosinophilia in 50% of patients[17]. Although unspecific, eosinophils counts may offer a clue towards the diagnosis, provided that the presence of intestinal parasitosis is excluded and the atopic state of the patient is taken

into account[18]. Endoscopy and biopsy are important for the diagnosis of gastrointestinal manifestations mediated by cellular immunity or mixed mechanism[19].

In some groups of pediatric patients, FA has been related to GER, abdominal colic and constipation[7]. The clinical presentation of FA is compatible with GERD, with abdominal pain, vomiting, regurgitation, dysphagia, irritability and impaction, without improvement with antireflux therapy[5]. These findings are consistent with the study by Forget and Arends[8], which recommends that allergy to cow's milk should be suspected and adequately investigated in case of intractable reflux. According to Semeniuk et al[9], GERD can be caused only by FA in younger children; in older children, however, GERD can coexist with food intolerance.

The association between GERD and FA has been found in some studies[8,9,11,12,13,20]. Forget[8] prospectively evaluated a small group of children with recurrent vomiting and found enteropathy associated with an increase in the number of IgE-producing plasma cells in intestinal biopsy in 20% of the children evaluated. Semeniuk et al[9] observed the presence of GERD and/or reflux esophagitis, through 24-hour pHmetry, in 18.8% of 735 children[9]. In another study by Semeniuk[20], including 138 children with GERD through a 24-hour pHmetry study, 44.9% had GER secondary to FA. Our study found a lower frequency of FA (7.8%).

In the present study we found endoscopic evidence of GERD in 352 (75.9%) of the children. Such high prevalence is probably due to a selection bias, since in our population endoscopic examination is usually requested by gastro-pediatricians and indicated for children clinically more symptomatic, unlike the adult population, with whom we are generally more liberal in the indication of UDE. In fact, similarly to our study, Vieira et al[14], when evaluating 167 infants with less than one year of age in whom GERD was suspected, reported that 42.5% had findings of esophagitis at endoscopy (with a diagnostic criterion that included non-erosive lesions) and 83.2% of histological esophagitis[14].

The main mechanism that relates GERD in patients with FA has still been poorly explained. Ravelli et al[10] showed that the challenge with cow's milk in infants allergic to milk proteins leads to a delay in gastric emptying, triggering the extension of the muscles of the stomach wall, activation of afferent fibers of the vagus nerve and hyper-relaxation of the lower esophageal sphincter (LES). Kaczmarski et al[11,12] associated the harmful role of some foods (cow's milk, soybean, citrus fruits and others) with endoscopic findings in the mucosa of the esophagus and stomach. Hill et al[12] concluded that 6% of young patients with cow's milk allergy had clinical symptoms of acid GER. Substantially higher values of this association have already been found by other authors, such as Kaczmarski et al[11,12,], who have reported figures as high as 44.9%. In the present study we did not observe a relationship between the presence of GERD and FA. Allergy was observed in 28/352 (8.0%) patients with GERD and in 8/112 (7.1%) patients without esophagitis ($p = 0.8$).

CONCLUSION

Our study observed a high prevalence of GERD in a pediatric population at a private clinic in Goiânia, probably reflecting a selection bias, with the majority of cases presenting mild esophagitis at endoscopy. FA was found in 36/464 (7.8%) of these patients. No relationship between GERD and the presence of AA was observed.

STATEMENTS

STATEMENT OF ETHICS

The research protocol was evaluated and approved by the Human Research Ethics Committee of the General Hospital of Goiânia. And the subjects have given their written informed consent.

DISCLOSURE STATEMENT

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Américo de Oliveira Silvério: Research planning, data analysis, review of results and writing of article.

Caroline Filardi Silveira, Francielle Andrade Torres and Lucas Massao Miamae: Research planning, data collect, article writing, review of results and writing of article.

Natália Ribeiro Silvério: Review of results, writing and translation of article

José Eduardo Mekdessi and Sérgio Teruaki Miamae: Conducting examinations, review of results and writing of article.

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Characteristic	Total group	With FA	W/O FA	Value of p
N (%)	464 (100)	36 (7.8)	428 (92.2)	
Mean age ± SD (years)	7.7 ± 5.4	4.7 ± 3.9	8,0 ± 5.5	0.0003
Gender (F/M)	238 / 226	16 / 20	222 / 206	0.4
GERD				
Present n(%)	352 (75.9)	28 (77.8)	324 (75.7)	0.8
Absent n(%)	112 (24.1)	8 (22.2)	104 (24.3)	0.8
Grade I n(%)	279 (60.1)	22 (61.1)	257 (60.1)	0.9
Grade II n(%)	66 (14.2)	6 (16.7)	60 (14.0)	0.9
Grade III n(%)	6 (1.3)	0 (0.0)	6 (1.4)	0.9
Grade IV n(%)	2 (0.4)	0 (0.0)	2 (0.5)	0.9

Table 1 – Demographic characteristics of the population according to the presence of food allergy (FA)

GERD = Gastroesophageal reflux disease

Characteristic	Total group	With GERD	W/O GERD	Value of p
N (%)	464 (100)	352 (75.9)	112 (24.1)	
Mean age ± SD (years)	7.7 ± 5.4	7.3 ± 5.3	9.1 ± 5.6	0.003
Gender (F/M)	238 / 226	176 / 176	62 / 50	0.3
FA				
Present n(%)	36 (7.8)	28 (7.9)	8 (7.1)	0.8
Absent n(%)	428 (92.2)	324 (92.1)	104 (92.9)	0.8

Table 2 – Demographic characteristics of the population according to the presence of gastroesophageal reflux disease (GERD)

FA = Food allergy

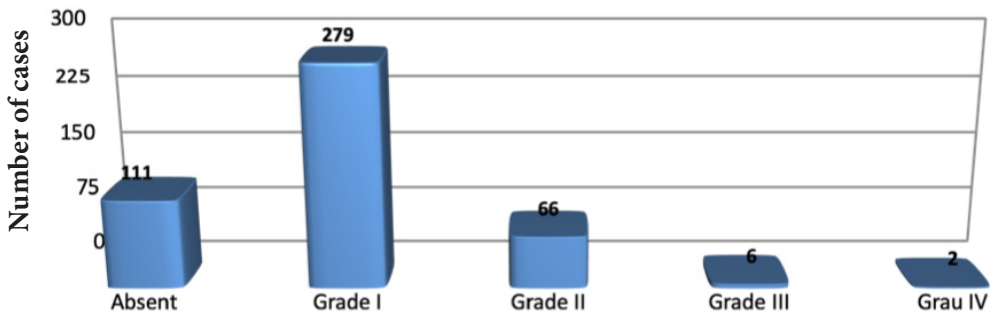

Figure 1- Degree of esophagitis according to modified Savary-Miller classification 15