Esophageal eosinophilia in pediatric patients with cerebral palsy
Eosinofilia esofágica em pacientes pediátricos com paralisia cerebral

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ABSTRACT
Objective: To describe the clinical picture, test results, and clinical evolution of patients with cerebral palsy associated with diagnosis of eosinophilic esophagitis, monitored at tertiary centre. Methods: Cross-sectional, retrospective and descriptive study that evaluated the medical records data of pediatric patients with diagnosis of cerebral palsy and eosinophilic esophagitis in a tertiary center of pediatric gastroenterology between August 2005 and August 2013. Results: Seven out of 131 patients with cerebral palsy had the diagnosis of eosinophilic esophagitis. The mean age at diagnosis of eosinophilic esophagitis was 52.3 months and the mean number of eosinophils in esophagus was 35 per high-power field. Symptoms more frequent were recurrent vomiting and disphagia. Endoscopic alterations found were mucosal thickening, vertical lines, mucosal opacification and white plaques. Conclusion: The frequency of eosinophilic esophagitis found was higher than in general pediatric population. The investigation of eosinophilic esophagitis should be done regularly in those patients, once this entity could overlap other gastrointestinal diseases.

Keywords: Cerebral palsy/complications; Eosinophilic esophagitis/etiology; Stomach diseases; Gastroesophageal reflux; Child

INTRODUCTION
Eosinophilic esophagitis (EE) is a disease diagnosed based on clinical and histological parameters. The condition is defined by symptoms of esophageal dysfunction, predominantly eosinophilic inflammation with esophageal biopsy eosinophil count ≥15 per high-power field (hpf), restricted to the esophagus, and unchanged after a 2-month course of proton pump inhibitors (PPI).¹ This entity was first described in the late 1970s by Landers et al.² and presumed as a clinicopathologic entity in 1993, by Attwood et al.³ Despite the large number of publications in recent years, there are still many questions surrounding this pathology. EE is frequently associated with other atopic diseases, such as asthma, allergic rhinitis, atopic dermatitis, and food allergies.¹

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Esophageal eosinophilia is the histological finding of eosinophils in an esophageal biopsy that requires interpretation in the clinical context, since it alone does not set the diagnosis of EE. Other clinical conditions may present with eosinophilia, such as gastroesophageal reflux disease (GERD) and esophageal eosinophilia responsive to PPI.\(^1\)

Cerebral palsy patients often show dysfunction of the gastrointestinal tract, such as swallowing disorder, rumination, GERD, delayed gastric emptying and constipation.\(^4\) GERD occurs in 20 to 90\% of cases depending on the criteria used\(^4\) and swallowing disturbances occur in up to 90\% of cases.\(^5\) All these problems can contribute to feeding difficulties and impaired nutritional status.\(^6\) EE could overlap these very common gastrointestinal disorders in these patients, and might not be suspected of bringing greater loss of nutrition and lower quality of life for that patient.

**OBJECTIVE**
To describe the clinical picture, test results, and clinical evolution of patients with cerebral palsy associated with diagnosis of eosinophilic esophagitis, monitored at tertiary centre.

**METHODS**
This was a cross-sectional, retrospective, and descriptive study performed in the Pediatric Gastroenterology Clinic of Hospital de Clínicas de Universidade Federal de Uberlândia, through records of patients with diagnoses of cerebral palsy and EE, from August 2005 to August 2013. Data were related to age, sex, age at diagnosis, symptoms, endoscopic and pathological changes. Other tests performed such as pHmetry and allergy tests, treatments performed, diet, feeding type, presence or absence of antireflux valve and evolution were collected. This study was approved by the Research Ethics Committee of the organization (protocol number 759/09). Since it is a retrospective study, informed consent was not necessary. The descriptive statistics were used to present the data.

**RESULTS**
In a survey of the medical files of 136 patients with cerebral palsy treated in our clinic, 7 patients with associated EE were found. Of the total, four were male (57\%). The age of the patients at the time of analysis ranged from 70 to 156 months with an average of 104.7 months. Prematurity associated with perinatal asphyxia was the cause of cerebral palsy in four patients (57.1\%), bilirubin encephalopathy in two (28.6\%) patients and in one patient (14.3\%), the cause was not related to the perinatal period but herpetic encephalitis at preschool age.

Patients with cerebral palsy presenting gastrointestinal symptoms underwent esophagogastroduodenoscopy (EGD) with biopsies. All patients had suggestive endoscopic changes in the examination that detected esophageal eosinophilia on histologic analyses. The age of detection of esophageal eosinophilia in patients ranged from 23 to 112 months, with a mean of 52.3 months. The number of eosinophils in the esophagus at diagnosis ranged from 20 to 50 eosinophils/hpf with an average of 35 eosinophils. The clinical cases are summarized in table 1. The symptoms presented by patients are shown in table 2, the changes found in endoscopies are described in table 3, and the results of immunologic tests are described in table 4.
Table 1. Clinical data of pediatric patients with cerebral palsy and suspicion of eosinophilic esophagitis

| Data/patients          | Case 1 | Case 2 | Case 3 | Case 4 | Case 5 | Case 6 | Case 7 |
|------------------------|--------|--------|--------|--------|--------|--------|--------|
| Antireflux valve       | NA     | Nissen | NA     | NA     | Nissen | Nissen | Nissen |
| Clinic/pathologic response to PPI | Absent | Absent | Absent | Present | Absent | Absent | Present |
| Diet                   | Amino acid-based formula, extensively hydrolysed formula, and complementary feeding | NA     | Amino acid-based formula, extensively hydrolysed formula, and complementary feeding | NA     | Egg exclusion | Free diet | Free diet | Amino acid-based formula and complementary feeding. Egg exclusion |
| Pre-diagnosis drugs    | PPI and cisapride | PPI and cisapride | PPI and cisapride | PPI and cisapride | PPI and cisapride | PPI and cisapride | PPI and cisapride |
| Post-diagnosis drugs   | PPI | Fluticasone | Fluticasone | PPI | Fluticasone | Fluticasone | Budesonide |

m: month; Eos/hpf: eosinophils per high-power field; RI: reflux index; NA: not applicable; GTM: gastrostomy; PPI: proton pump inhibitor.

Case 1
LSS, 6-year-old male, presented vomiting, low weight gain and dysphagia since infancy with no clinical response to drug treatment of GERD. The patient underwent an endoscopic gastrostomy at 12 months of age, with no improvement of symptoms. The endoscopy showed distal mucosa pallor, thickening with granulations, and furrows. A biopsy showed eosinophilia restricted to the esophagus (32 eosinophils/hpf), which persisted after a course of high-dose PPI for over 8 weeks (>50 eosinophils/hpf). A skin prick test for main food allergens was negative. An elemental diet was undertaken with clinical improvement, but no histological resolution was observed. The patient was considered inappropriate for the treatment with inhaled corticosteroids (swallowed) due to his severe swallowing disorder.

Case 2
RCL, 10-year-old female who presented low weight gain from birth, associated with abdominal pain and frequent vomiting between 12 and 24 months, with no improvement with GERD treatment. At 24 months of age, she received nasogastric feeding with partial improvement of weight gain. After the age of 5, she had several EGDs with biopsies detecting esophageal eosinophilia and rare eosinophils in the duodenal mucosa with use of PPI at low doses. At 8 years of age, she received a course of PPI at high doses for longer than 8 weeks and maintained esophageal eosinophilia (25 to 50 eosinophils/hpf). The endoscopy showed mucosal hyperemia and distal erosion. She also tried to use corticosteroids (swallowed), but it was discontinued due to a swallowing disorder. The oesophageal pH-monitoring (pH-metry) result was suggestive of GERD. Allergy tests were negative. The patient underwent...
gastrostomy and antireflux surgery at 9 years of age with total regression of clinical manifestations and histological eosinophilia.

**Case 3**

LALS, 13-year-old male, with gastrostomy from age 6 years due to a swallowing disorder, chronic abdominal pain and vomiting. At age 9 years, he underwent an EGD with histological examination that detected esophageal eosinophilia (>50 eosinophils/hpf) and frequent eosinophils in the duodenal mucosa. The results of the EGD were not available. He had a course of PPI with an approximate dose of 2mg/kg/day and inhaled corticosteroids (swallowed) with persistent eosinophilia. He showed reduction of vomiting with PPI, and improvement of pain after excluding cow’s milk from his diet. He had negative skin prick tests. Some time later, he returned with abdominal pain and had an elemental diet initiated, showing good clinical and histological response (absence of eosinophils on endoscopy). He is maintaining clinical remission after reintroduction of cow’s milk in the diet.

**Case 4**

VTS, 8-year-old female, presented low weight gain, vomiting and dysphagia since infancy with partial clinical response to treatment of GERD. She also presented recurrent pneumonia. She underwent gastrostomy at age 2 due to a swallowing disorder. At 8 years of age, she had an EGD that showed a distal mucosa thickening and furrows. The histological analysis detected esophageal eosinophilia (40 eosinophils/hpf), which remitted after a course of PPI with an approximate dose of 2mg/kg/day for 8 weeks (5 eosinophils/hpf) associated with clinical improvement during use. She had hives immediately after eating egg with specific IgE to egg white and egg yolk of 8.58 and 5.24, respectively, and a negative atopy patch test for main food allergens. After discontinuation of PPI and maintenance of an egg-exclusion diet, she showed a relapse of esophageal eosinophilia (70 eosinophils/hpf). The result of pH-metry was suggestive of GERD. She was submitted to gastrostomy with surgical correction of reflux at age 5, with total clinical and histological remission at endoscopy 2 months later (0 eosinophil/hpf).

**Case 5**

CHMM, 5-year-old male, presented severe swallowing disorder with two aspiration pneumonias. The result of pH-metry was suggestive of GERD and EGD, which showed a distal mucosal pallor and thickening. The histological analysis detected esophageal eosinophilia (33 eosinophils/hpf) at the age of 2. A course of PPI with dose of 2mg/kg/day was prescribed for more than 8 weeks, but maintained esophageal eosinophilia (>20 eosinophils/hpf). Allergy skin tests were negative. He was treated with inhaled corticosteroids (swallowed) and PPI at low doses, showing clinical and histological remission at a later endoscopy. At 4 years of age, he was submitted to gastrostomy with surgical correction of reflux that resulted in clinical improvement.

**Case 6**

ISR, 7-year-old female who presented vomiting, abdominal pain and distension from 2 months of age with partial clinical response to PPI and use of an elemental diet. She developed hives and vomiting after ingestion of cow’s milk and egg with specific IgE to cow’s milk, egg white and egg yolk of 1.26Ku/L, 9.99Ku/L and 5.54Ku/L, respectively. A food allergy was confirmed by oral challenge. She underwent an atopy patch test for main food allergens, which was negative. At 2 years of age, the EGD showed distal mucosal thinning with white granulations. Esophageal eosinophilia was detected (>30 eosinophils/hpf), which persisted after a course of PPI in a dose of <2mg/kg/day and an elemental diet (22 eosinophils/hpf). The result of pH-metry was suggestive of GERD. She was submitted to gastrostomy with surgical correction of reflux at age 5, with total clinical and histological remission at endoscopy.
the new endoscopy with biopsies after the procedure showed a recurrence of esophageal eosinophilia only in distal third (20 eosinophils/hpf), he started viscous budesonide with improvement of eosinophilia.

DISCUSSION

Esophageal eosinophilia is a histological finding that should be interpreted in the clinical setting. More than one disease could be involved in this tissue inflammation. In an isolated esophageal eosinophilia finding, three main conditions must be suspected: GERD, PPI-responsive esophageal eosinophilia, and eosinophilic esophagitis. The evaluation of patients with cerebral palsy and esophageal eosinophilia should be performed carefully to establish if a diagnosis of EE is appropriate or not. A misdiagnosis or a delayed diagnosis could impede the patient’s adequate treatment, and therefore, a better quality of life. On the other hand, an over diagnosis could add another disease to the patient’s history, also interfering in his and his family’s quality of life.

All patients in this study had symptoms related to esophageal dysfunction and esophageal eosinophilic inflammation with at least 15 eosinophils/hpf, which are initial criteria for the diagnosis of eosinophilic esophagitis. However, not all patients met the other criteria for the diagnosis of this entity.

Cases 1, 2, 3, 5 and 7 showed clinical development and tests consistent with the diagnosis of EE with persistent esophageal eosinophilia after a course of PPI in a dose of 2 mg/kg/day or more for, at least, 8 weeks. The patient in case 2 met the criteria for diagnosis of EE but improved clinically and histologically after gastrostomy and antireflux surgery, leaving doubt about the diagnosis of EE. On the other hand, case 4 showed histological remission after PPI at high doses, as the diagnoses of PPI-responsive esophageal eosinophilia or GERD were more appropriate for this patient. Indeed, considering the result of pH-metry, the diagnosis of GERD is even more appropriate. Furthermore, in case 6 there was not an adequate PPI dose to establish diagnosis of EE. Besides, correlating the result of pH-metry and clinical and histological remission after gastrostomy and antireflux surgery, it would be reasonable to attribute the findings to a case of GERD. In case 7, the exclusion of foods associated with a food allergy together with use of PPI at high doses were performed, and therefore, we do not know which action was responsible for improvement. This patient also had clinical improvement after gastrostomy and antireflux surgery, but again showed esophageal eosinophilia during his evolution, effectively consistent with EE diagnosis.

Eosinophils were described in the duodenal mucosa biopsy in cases 2 and 3 — rare and frequent eosinophils, respectively. The presence of eosinophils in other parts of the gastrointestinal tract beyond the esophagus may occur, and the cutoff for suspicion of eosinophilic gastroenteritis is 20 eosinophils/hpf. However, in both cases, there was no pathological description of the eosinophils count to confirm whether it is a normal or altered number for the duodenal region.

The diagnosis of EE seemed appropriate for cases 1, 2, 3, 5 and 7, but not appropriate in cases 4 and 6.

Recent published studies confirmed that gastrointestinal disorders are a major chronic problem in most children with cerebral palsy or neurodevelopmental disabilities. GERD should be suspected due to its frequency in this population, but other conditions must be suspected also, according to the clinical presentation and evolution. In a previous study before the recognition of EE as a disease, the authors concluded that in neurologically impaired children who are unresponsive to conventional antireflux treatments, a course of a highly restricted diet with an amino acid-based formula may bring an immediate and sustained, endoscopically and histologically proven improvement in long-standing gastrointestinal symptoms and esophagitis. This improvement probably occurred because the diagnosis for these patients could be EE.

Moreover, the frequency of EE in patients with cerebral palsy found in this study was elevated compared to the presence of EE in the general population. In a recent consensus published in 2013, because of the difficulty in performing the exclusion diets and the impact of these diets on the patient’s quality of life, it was suggested that patients received initial treatment with swallowed corticosteroids to control symptoms and inflammation; and if controlling this is not achieved, research into food allergies should be conducted to exclude suspected foods. However, this consensus and other studies maintain the possibility of initial treatment with an elimination diet (elemental, Kagalwalla, or directed) according to the experience of each medical unit. In our view, most patients with cerebral palsy are gastrostomyzed, and this fact makes exclusion diets less traumatic. They receive the feeding through probes, which reduces the impact of poor acceptance. Besides, the high prevalence of swallowing disorders in these patients becomes a problem for the use of swallowed corticosteroids.

Children with cerebral palsy or other neurodevelopmental disabilities with suspected EE should be investigated as normal patients, considering the latest recommendations...
for EE that have received great attention from physicians, which therefore, has resulted in rapidly growing knowledge about this disease.\(^{15-18}\)

Despite the diagnosis of EE, this population has some particularities that should be considered as a result of the new finding of esophageal eosinophilia. In 2008, the literature described cases of anticonvulsivant hypersensitivity syndrome, which shows a severe and unusual reaction to antiepileptic agents that can have esophageal eosinophilia as a component.\(^{19}\) Patients with cerebral palsy usually have chronic use of anticonvulsant drugs, making this diagnosis an important possibility of esophageal eosinophilia.

One of the limitations of this study was its retrospective format, which did not allow data systematization with several procedures and other occurrences in each patient. Another limitation was the selection criteria of patients, which was the result of the diagnostic crossing in an automated system, and did not allow the analysis of the number of patients with cerebral palsy who underwent endoscopy or had other diagnoses confirmed as GERD. Nonetheless, the findings related to EE in this group of patients were relevant in relation to their frequency and novelty.

**CONCLUSION**

The diagnosis of eosinophilic esophagitis is very important in patients with cerebral palsy and should be done carefully, taking into account the regular criteria, since the frequency of eosinophilic esophagitis in patients with cerebral palsy found in this study was elevated, compared with the presence of eosinophilic esophagitis in the general population. Furthermore, the treatment of these patients should also take into account their particularities, including swallowing disorder and alternative feeding means, with the possibility of performing exclusion diets as a reasonable option. Further studies are needed to establish specific diagnosis and treatment in patients with cerebral palsy and esophageal eosinophilia.

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