Arch Gastroenterol Res. 2025;6(1):22-29.

Archives of Gastroenterology Research Original Research

Abdominal Migraine in Children and Adolescents at a Single Tertiary Pediatric Gastroenterology Center: A Twelve-year Experience on Clinical and Therapeutic Findings

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Received date: March 25, 2025, **Accepted date:** May 14, 2025

Citation: Hachem AS, de Assis Carvalho M, Hercos GN, Dias JT, de Jesus CDF, Machado NC. Abdominal Migraine in Children and Adolescents at a Single Tertiary Pediatric Gastroenterology Center: A Twelve-year Experience on Clinical and Therapeutic Findings. Arch Gastroenterol Res. 2025;6(1):22-29.

Abstract

Background: Abdominal migraine (AM) may be underdiagnosed and represent a substantial problem for children and their families.

Aim: Evaluate the clinical characteristics and the response to prophylactic therapy with Cyproheptadine in children and adolescents with AM.

Methods: Observational, retrospective cohort single-center study in consecutive cases of children and adolescents, referred for initial evaluation of chronic abdominal pain at the Pediatric Gastroenterology Outpatient Clinic. Inclusion criteria: Age between 4 and 17 years; Diagnosis of AM defined from structured questionnaires according to three consensus criteria (Rome III, Rome IV criteria, and The International Classification of Headache Disorders). Exclusion criteria: mild symptoms lasting less than one hour and not interfering with daily activities, burning pain, symptoms suggestive of organic disease, or persistence of symptoms between attacks, chronic organic diseases that compromise growth and development include inflammatory bowel disease, celiac disease, and cystic fibrosis. The diagnosis was reviewed during the minimum 6-month follow-up.

Results: One hundred forty-seven consecutive patients were diagnosed with AM during the twelve-year study and experienced periodic attacks of abdominal pain, a high proportion in the midline, and intervals of complete absence of symptoms. The most frequently associated symptoms with pain attacks were headache and vomiting. The medians of ages at first visit (8.8 years), age at onset of symptoms (6.5 years), and duration of symptoms (18 months). Positive history of migraine in the mother and family members were 27% and 25%, respectively. Cyproheptadine was the first choice in 81 patients, with appropriate treatment performed in 65 patients and complete resolution in 80%.

Conclusions: The current study confirms that a comprehensive history, physical examination, and thoughtful diagnostic criteria are robust for well-defining AM. The findings also reaffirm that prophylactic therapy with Cyproheptadine is highly effective and safe for managing AM in children and adolescents, reassuring the medical community and families of affected children.

Keywords: Abdominal migraine, Chronic abdominal pain, Functional abdominal pain disorders, Cyproheptadine, Prophylactic therapy, Rome IV criteria

Abbreviations: FGIDs: Functional Gastrointestinal Disorders; FAPDs: Functional Abdominal Pain Disorders

Introduction

Gastrointestinal complaints in children and adolescents are common reasons for medical consultation. Indeed, a population-based study showed that 60% of school-age children presented at least one gastroenterological symptom and that 10% of all children complained of abdominal pain weekly [1]. In addition, 5 to 22% of children and adolescents report weekly episodes of abdominal pain [2]. Chronic abdominal pain is classified as organic or functional abdominal pain disorder (FAPD) [3,4]. The latter, with an estimated pooled global prevalence of 11.7% [5], comprises four conditions: functional dyspepsia, irritable bowel syndrome, abdominal migraine, and unspecified functional abdominal pain.

Abdominal migraine (AM), a disorder of gut-brain interaction, is defined according to the Rome III criteria [6] and revised in Rome IV criteria [7]; it also has specific diagnostic criteria according to the International Classification of Headache [8,9]. Despite well-defined diagnostic criteria, AM remains a lesser-known entity and may be underdiagnosed by general pediatricians and gastroenterologists [10]. This underdiagnosis represents a significant issue for children and their families. Therefore, improving the diagnostic accuracy of the disease is crucial, as it can guide clinicians in choosing the appropriate approach for these patients, potentially leading to better patient care.

The current study aims to characterize the demographic, clinical, and anthropometric characteristics and assess the response to prophylactic therapy with Cyproheptadine in children and adolescents with AM. So, the findings from our study at a tertiary referral center are expected to contribute to the field of pediatric gastroenterology, providing knowledge and insights into this condition that can directly be applied in clinical practice. The hypothesis is that Brazilian children with AM treated at a specialized Pediatric Gastroenterology Outpatient Clinic are similar to children in international studies regarding clinical presentation and that their symptoms have improved with the prophylactic treatment adopted.

Methods

Study design, setting, and selection of participants

This observational, retrospective cohort single-center study, included consecutive cases of children and adolescents referred from the Brazilian Public Health System (SUS) for initial evaluation of chronic abdominal pain at the Pediatric Gastroenterology Outpatient Clinic of Botucatu Medical School. The study spanned from January 2008 to December 2019. The available infrastructure includes an outpatient clinic with weekly practice, care standardization, and regular clinical follow-up, ensuring the reliability of the study.

Inclusion criteria: Age between 4 and 17 years; well-defined AM diagnosis from structured questionnaires according to all three consensus criteria: the Rome III criteria [6] for individuals between 2008 and 2016 and the Rome IV criteria [7] for those between 2016 and 2019. The International Classification of Headache Disorders [8,9] was applied to all patients. The diagnosis was reviewed during the minimum 6-month follow-up.

Exclusion criteria: Mild symptoms not interfering with daily activities, burning pain, symptoms suggestive of organic disease, attacks lasting less than one hour, or persistence of symptoms between attacks [11]. Also, systemic chronic organic diseases that compromise growth and development, including inflammatory bowel disease, celiac disease, and cystic fibrosis.

Clinical Research Ethics Committees (protocol CAAE: 20287119.2.0000.5411) approved this study.

Data collection

Data were meticulously collected, coded, and stored in a database of Excel spreadsheets (Microsoft, Redmond, Washington). Parents/caregivers and patients answered all the clinical questions during the visits, ensuring comprehensive data collection. The questionnaire covered relevant aspects, including sociodemographics (age, gender, position of the child in the family; parents' age and education; caregiver's marital status, birth conditions, number of rooms, people and children in the household, and history of migraine in the family), clinical features, and laboratory variables (blood cell count, C-reactive protein, urinalysis, stool for ova & parasites. Additional tests were completed at the researcher's discretion.

Anthropometric data

At the first visit, experienced pediatric nurses played a crucial role in obtaining anthropometric measurements of body weight (kilograms), measured with the child standing on an electronic scale, and height (centimeters) using an adjustable stadiometer, according to the World Health Organization guidelines [12]. BMI (kg/m^2) and *z* score were evaluated according to WHO AnthroPlus [13,14]. The child was classified as obese (*z* score >2), overweight (*z* score between 1 and 2), normal BMI (*z* score between −2 and +1), and underweight (*z* score <−2). All data were adjusted for sex and age [15] and stratified into obesity/overweight and Normal BMI.

Follow-up and treatment

Two experienced pediatric gastroenterologists (MAC, NCM) reviewed the clinical presentations of the patients at various times and determined the patients' final diagnoses. Cyproheptadine was the primary prophylactic treatment choice for pain crises. The prophylactic medications were prescribed as follows: Cyproheptadine (0.25–1.5 mg/kg per day, typically to 2–4 mg nightly); Amitriptyline (0.5–1 mg/kg/day at

bedtime); Flunarizine (7.5 mg/day); Propranolol (2–4 mg/kg/day, up to 10–20 mg BID or TID) [16-19]. Nonpharmacological therapy included explaining and encouraging the child and parents to avoid triggers (emotional excitement, altered sleep patterns, prolonged fasting, stress, foods that could be implicated, or other symptoms) and behavioral therapy when needed [20-22]. The therapeutic response was assessed at follow-up visits over the next six months. The clinical response was classified as complete resolution (disappearance of pain crises) or non-response (crises unchanged in frequency, intensity, or duration), requiring amitryptiline as a second choice.

Statistical analysis

Data were analyzed with GraphPad Prism version 8.4.0 for Windows (GraphPad Software, San Diego, California, USA, www.graphpad.com). Normality data was assessed using the Kolmogorov-Smirnov test to define parametric and non-parametric data distribution. Categorical variables were expressed as numbers and percentages (%) and examined with Fisher's exact test. All continuous variables were expressed as the median and interquartile range (25^{th}—75^{th} percentile) and 95% Confidence Interval of the Median and analyzed with The Mann-Whitney test. All tests were two-sided, and $p<0.05$ was statistically significant.

Results

One hundred forty-seven consecutive patients (around 12 per year) were diagnosed with AM during the twelve-year study period **(Figure 1)**. **Table 1** demonstrated a slight predominance in the female sex, medians of ages at first visit (8.8 years), and age at onset of symptoms (6.5 years), and the interval between symptom onset and diagnosis (18 months) with the following percent distribution in months: ≤6 (24%), >6 to ≤12 (22%), and >12 (54%) of patients. A positive family history of Migraine was reported in the mother (27%) and family members (25%).

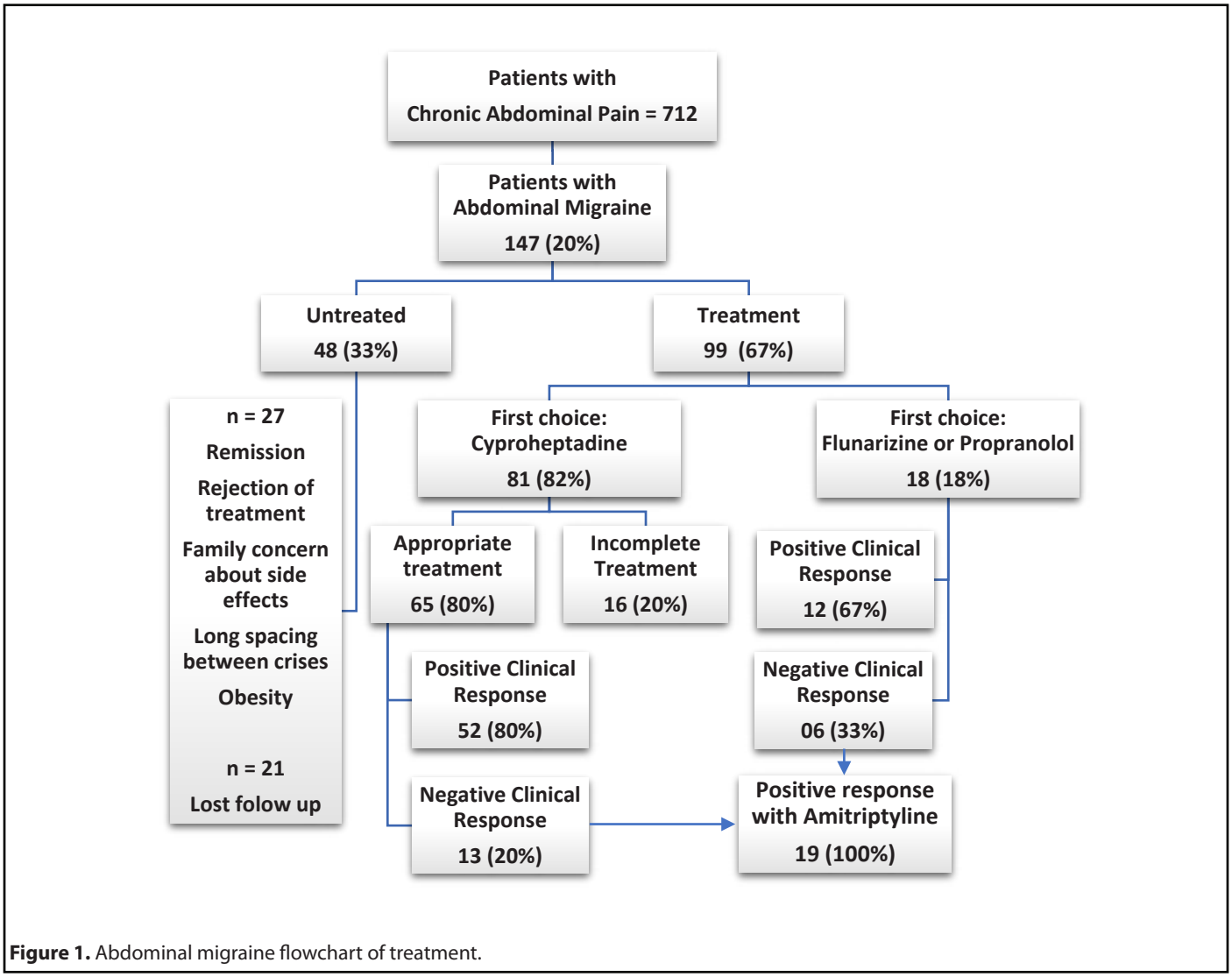

Figure 1. Abdominal migraine flowchart of treatment.

Table 1. Baseline characteristics of children, adolescents, and parents with abdominal migraine.		
	Median (IQR)	**95% Confidence interval of median**
Sex: Female/Total n (%Female)	83/147 (56)	
Birth order, 1st child, n (%)	53 (36)	
Age of mothers, years	32 (28–37)	(31–34)
Age of fathers, years	36 (31–40)	(35–37)
Crowding index, co-residents per room	0.9 (0.7–1.2)	(0.8–1.0)
Age at diagnosis, months	106 (82–128)	(99–113)
Age at symptom onset, months	78 (49–108)	(70–84)
Time interval between symptom onset and the diagnosis, months	18 (6–36)	(12–24)
Body Mass Index, BMI z score	0.39 (-0.4–1.3)	(0.1–0.6)
Overweight /Obesity, BMI z score >1, n (%)		
Overweight	16 (11)	
Obesity	25 (17)	
Family history of migraine, n (%)		
Mother	40 (27)	
Others	38 (25)	

Table 2 shows the clinical characteristics of children and adolescents. All patients had periodic attacks of abdominal pain and intervals of complete absence of symptoms. The coexistence of midline abdominal pain + vomiting + headache was prevalent and occurred in 47% of the patients. The symptoms most frequently associated with abdominal pain attacks in decreasing frequency were headache (69%), vomiting (64%), nausea (47%), pallor (39%), and photophobia (34%). Laboratory results are presented in **Table 3**. There was no anemia, abnormal white cell, or eosinophils absolute count. The stool for ova and parasites was positive in four children. The esophagogastroduodenoscopy was normal in all 10 performed.

Table 4 compares clinical variables between the children with and without prophylactic treatment. The prophylactic therapy group's age at the first visit and onset of symptoms was significantly lower ($p<0.05$) than the no prophylactic therapy group. The proportion of children with headaches, vomiting, mothers with headaches, and other family members with headache were significantly higher in the prophylactic therapy group ($p<0.05$).

Table 2. Clinical characteristics of children and adolescents with abdominal migraine.	
	n (%)
Attacks of abdominal pain and completely healthy between attacks	147 (100)
Primary pain location and associated symptoms	
Midline abdominal pain	117 (79)
Midline abdominal pain + headache + vomiting	69 (47)
Midline abdominal pain + headache	27 (18)
Midline abdominal pain + vomiting	21 (14)
Poorly localized abdominal pain	30 (21)
Symptoms during attacks of abdominal pain	
Headache	102 (69)
Vomiting	95 (64)
Nausea	70 (47)

Pallor	58 (39)
Photophobia	51 (34)
Anorexia	43 (29)
Retrosternal pain	12 (08)
Limb pain	10 (07)
History of regular bowel habits	93 (63)

Table 3. Laboratory data of children and adolescents with abdominal migraine.

	Median (IQR)	**95% Confidence interval of median**
Hemoglobin, grams/dL	13.3 (12.7–13.9)	(13.1–13.6)
Mean Cell Volume, MCV, fL	83 (79–85)	(81–83)
Red Cell Distribution Width, RDW, %	13.8 (12.7–14.9)	(13.3–14.2)
White blood cell count, WBC, cells/mcL	7200 (5800–9900)	(6900–7600)
Eosinophils absolute count, cells/mm^3	334 (195–495)	(250–383)
Eosinophil Percent, %	5.1 (2.6–7.8)	(3.8–5.6)
Platelet count (×10^9/l)	306 (264–352)	(294–320)
Mean Platelet Volume, MPV, fL	8.2 (7.7–9.0)	(7.9–8.6)
C-Reactive Protein	0.5 (0.2–0.6)	(0.5–0.5)
Stool for ova and parasites (91 samples), n	04 positive results: 01 Giardia, 01 Ascaris, 01 Enterobius, and 01 Blastocystis	
Esophagogastroduodenoscopy, n (%)	10 (07) all normal	

Table 4. Comparison of clinical characteristics in children and adolescents with abdominal migraine on prophylactic treatment versus no treatment.

	Prophylactic therapy n = 99	**No Prophylactic therapy n = 48**	
	Median (IQR)		**p=**
Age at diagnosis, months	101 (73–123)	117 (94–142)	**0.004**
Age at symptom onset, months	72 (48–98)	96 (54–120)	**0.02**
The time interval between symptom onset and the diagnosis, months	15 (6–36)	24 (7–39)	0.42
Midline abdominal pain, n (%)	75 (76)	30 (62)	0.11
Symptoms associated with abdominal pain, n (%)			
Headache	74 (75)	27 (56)	**0.03**
Vomiting	70 (70)	25 (52)	**0.04**
Nausea	46 (46)	24 (50)	0.72
Pallor	38 (38)	20 (41)	0.72
Photophobia	34 (34)	17 (35)	1.0
Anorexia	26 (26)	17 (35)	0.25
Family history of migraine, n (%)			
Mother	33 (33)	07 (14)	**0.01**
Others	32 (32)	06 (12)	**0.009**
Limb pain, n (%)	05 (05)	05 (10)	0.29
History of regular bowel habits, n (%)	65 (66)	28 (58)	0.46

Figure 1 is a flowchart of the evolution of prophylactic therapy, with Cyproheptadine being the first choice in 81 patients. The appropriate treatment was performed in 65 patients, with a remarkable 80% experiencing complete resolution (disappearance of pain crises). There was a minimal recurrence that was improved with the adjustment of the dose of Cyproheptadine. Those with no response (13 patients) and those initially submitted to treatments with flunarizine or propranolol with partial improvement or non-response after 6 months (06 patients) were submitted to amitriptyline prophylaxis, and all had a positive response. During the study, subjects treated with Cyproheptadine did not suffer any relevant side effects. Forty-eight (33%) of the patients were untreated for different conditions: remission of symptoms at the first visit, refusal of treatment because of long spacing between crises, family concern about side effects and preferring treatment only during attacks, and obese/overweight children (n=27), and lost follow-up (n=21).

Discussion

The current study, which evaluated sociodemographic, clinical, and prophylactic therapy with Cyproheptadine in children and adolescents with AM, has yielded significant findings. The main results include: all patients experienced periodic attacks of abdominal pain, with a high proportion in midline and intervals of complete absence of symptoms; the most frequently associated symptoms with abdominal pain attacks were headache (69%) and vomiting (64%). The medians of ages at first visit (8.8 years), age at onset of symptoms (6.5 years), and the interval between symptom onset and the diagnosis of 18 months emphasize the importance of early diagnosis in managing the condition. There was positive family history of migraine in the mother (27%) and family members (25%), higher in the prophylactic therapy group. Age at the first visit and onset of symptoms were significantly lower in this group. Cyproheptadine was the first choice in 81 patients, with appropriate treatment performed in 65 patients and complete resolution in 80%, underscoring the importance of Cyproheptadine in treating AM in children.

Epidemiology

In a recent meta-analysis [5], the estimated global prevalence of AM in children (aged 4-18 years) was 1.7% (95% CI, 1.2%–2.3%). This figure provides a crucial context for understanding the significance of the current study's findings. Before this, data from the USA showed a higher prevalence rate of 9.2% [22], and South American studies ranged between 0.7-5.2% [23-25]. However, the current study's prevalence was 20% among 712 functional abdominal pain patients evaluated for 12 years. This study was performed in a tertiary hospital outpatient clinic, and a patient selection probably occurred **(Figure 1)**.

Diagnosis

The diagnosis of AM was made excluding organic diseases and based on three sets of diagnostic criteria, such as the Rome III-IV criteria and the International Classification of Headache Disorders. The Rome III criteria were released in 2006, and the Rome IV criteria were released in 2016 with minor changes concerning the FAPDs, specifically in the AM. The use of three criteria for diagnosis that remained slightly modified over a long study period, considering that 54% of patients had symptoms more than 12 months before diagnosis, suggests that there may have been a positive influence on the quality of diagnosis throughout the study. In addition, the exclusion criteria for diagnosing comprised persistence of symptoms between attacks that positively reinforce the AM diagnosis. All routine investigations, including endoscopies, were negative, emphasizing the importance of early diagnosis, which permits proper management and avoids unnecessary and extensive investigations, empowering clinicians in their practice [26,27].

AM is observed as a subtype of FAPDs occurring in attacks in children that are unwell with abdominal pain and associated symptoms. However, it is separated by free and entirely healthy intervals of symptoms. These findings were described early [28], even before the publication of the Rome III criteria. In the current study, these stereotypical episodes were obtained in all patients with sudden onset and ending. The pain attacks should be associated with at least two symptoms. Positively, headache is the most prevalent associated symptom, and the triad midline abdominal pain + headache + vomiting was observed in 47% of patients in the current study. Exceptionally, headache is omitted by one classification [29].

The average age at diagnosis of AM is around 10 years, with a maximum incidence of 7 years [10], being very similar to this study. Most studies demonstrated a higher prevalence in girls than boys, differing from the slight predominance of the female sex obtained in this study. Indeed, clinical manifestations were very similar to those published in the literature, reinforcing that the presentation of AM should have little variability worldwide [30]. In addition, a family history of cephalic migraine has been reported in 34–90% of children with AM [31], resembling the result obtained in this study.

Treatment with cyproheptadine

The current therapeutic interventions for FAPD are pharmacological, nonpharmacological, and psychological. Pharmacological therapy is reserved for patients with symptoms severe and frequent enough to interfere with their everyday activities. It should be noted that paroxysmal attacks of moderate to severe midline abdominal pain last for hours. Consequently, the morbidity associated with AM episodes must be considered. The pharmacological agents aimed to minimize visceral pain or alter one pathophysiological mechanism. Cyproheptadine is an antihistaminic agent with a 5-HT receptor antagonist and has been used since 1975 [32,33]. Indeed, prospective, retrospective, and systematic reviews reported partial or complete symptom resolution and effectively prevented AM [18,34-41]. However, these results

could have methodological lacks. The small sample size is the primary failure observed.

In the current study, complete resolution occurs in 80% of the patients with the appropriate treatment. This high percentage is a reason for optimism. The drug is not only practical but also cost-effective and safe. During the study, subjects treated with Cyproheptadine suffered no significant adverse effects, providing reassurance about its safety in pediatric patients. However, it was contraindicated only in a group of obese patients. Flunarizine and propranolol were used in 18 patients, with a positive response in 66%. However, possible side effects have discouraged their use.

Limitations and strengths

The current study has limitations: First, it was conducted at a single tertiary center, affecting the findings' generalizability. Second, it is an observational retrospective cohort study. However, to minimize the errors, two extractors performed a standardized approach with a trainee to collect data on electronic records.

This study had several strengths: First, all children were diagnosed based on three international criteria, and data were collected using a unique form created according to the Rome questionnaire for FGIDs. Second, the diagnosis was established at least 6 months of follow-up, and the organic chronic abdominal pain was systematically evaluated and excluded. Third, due to the great demand, variety of etiological possibilities, complexity, and high cost of excessive and unnecessary investigations, a standard methodology has been adopted to approach children with chronic abdominal pain, providing us with a homogeneous convenience casuistic. Fourth, to our knowledge, this is the first study that evaluated AM in Brazilian children and adolescents.

Conclusions

Our study shows that a comprehensive history and physical examination with thoughtful diagnostic criteria are robust for well-defined AM. Prophylactic therapy with Cyproheptadine, as our study confirms, is highly effective and safe in managing AM in children and adolescents, providing a promising treatment option.

Conflict of Interest

The authors have no conflicts of interest.

Funding Statement

The authors have no financial conflicts of interest.

Author Contributions

Bibliographical Survey (ASH, NCM, JTD, GNH, CDFJ, MAC), Clinical Data Collection (ASH, CDFJ), Drafting of the Manuscript (GNH, NCM, MAC), Critical Revision of the Manuscript (JTD, GNH, MAC, NCM).

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