

## Original Article



# Prophylactic Therapy Response in Children with Abdominal Migraine: A Single Centre Experience in Oman

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## ABSTRACT

**Purpose:** Abdominal migraine (AM) is a very common functional gastrointestinal disorder in children. This study reports the clinical features and response of AM to prophylactic treatment in children.

**Methods:** This retrospective study was conducted between January 2010 and December 2019 at the Royal Hospital in the Sultanate of Oman. This study included children aged ≤ 13 years with a diagnosis of AM based on the Rome IV criteria for functional diagnoses. Clinical, demographic, and treatment data were collected.

**Results:** Seventy-four children were identified, of which 43 were eligible for inclusion in this study. The median age at the onset of symptoms was 7 years (range, 2–12 years). The most frequent symptoms were headache (81.4%), nausea (79.1%), and vomiting (72.1%). Of the total cohort, 46.5%, 23.3%, and 6.9% received riboflavin, pizotifen, and propranolol monotherapy, respectively. Combination therapy was also used; 16.3% of children received pizotifen and propranolol, 4.7% received riboflavin and pizotifen, and 2.3% received riboflavin and propranolol. Patients treated with propranolol monotherapy showed 100% clinical improvement and those treated with riboflavin or pizotifen monotherapy showed 90% clinical improvement. Response to combination therapy with pizotifen and propranolol was 71.4%, and with riboflavin and pizotifen was 100%. In addition, treatment response was significantly associated with the presence of vomiting ( $p=0.039$ ).

**Conclusion:** We found a favorable response to various modalities and combination treatments with riboflavin, pizotifen, and propranolol in children with AM. In addition, the presence of vomiting may predict treatment response.

**Keywords:** Abdominal migraine; Abdominal pain; Riboflavin; Pizotifen; Child; Oman

**Conflict of Interest**

The authors have no financial conflicts of interest.

**INTRODUCTION**

Abdominal migraine (AM) is a form of recurrent abdominal pain and a common type of functional gastrointestinal disorder (FGID) as classified by the Rome IV classification [1]. AM is also classified by the International Classification of Headache (ICH) in its second [2] and beta version of the ICH-3 [3] under episodic syndromes that might be associated with cephalic migraine.

In both Rome IV and ICH-3 classifications, AM is defined as the central or midline abdominal pain that is recurrent with moderate-to-severe manifestations, associated with vasomotor symptoms, and characterized by periods of complete absence of symptoms. Both Rome IV and ICH have noted that there may be an absence of any alarming signs and caution regarding alternative diagnoses that may explain abdominal pain. The ICH-3 considers AM a diagnosis of exclusion, while Rome IV considers AM a more definitive diagnosis based on specific criteria [3,4].

The prevalence of AM varies between 1% and 15% [5-7], with a peak prevalence in girls aged 5-7 years and boys aged 7-9 years [6,7]. Family history of cephalic migraine has been reported in 34-90% of children with AM [8]. The management of AM is similar to that of cephalic migraine. Intravenous valproate and nasal sumatriptan have been successfully used in acute attacks. In comparison, pizotifen, cyproheptadine, flunarizine, riboflavin, propranolol, and amitriptyline were used as prophylaxis with variable success [4]. AM is a condition that is not fully understood and is commonly misdiagnosed in children [6].

Aside from Abu-Arafah's [5] study describing the clinical features of AM, no studies have reported the clinical features and outcomes of AM using the most up-to-date medications for children. This study aimed to assess the response of children with AM to prophylactic therapy. This study may improve pediatricians' and physicians' awareness of the current findings related to treatment response to AM.

**MATERIALS AND METHODS****Study design and population**

This retrospective chart review study included children aged  $\leq 13$  years with a confirmed clinical diagnosis of AM who visited the pediatric gastroenterology clinic at the Royal Hospital in Oman between January 2010 and December 2019. Demographic, clinical, laboratory investigations, and treatment data were collected. The initial diagnosis of AM was based on the ICH-2 [2], ICH-3 in 2013, and 2016 Rome IV criteria, which were adapted for the diagnosis of AM. The clinical presentations of the patients were reviewed multiple times and cross-checked and verified against the Rome IV criteria. AM was considered a positive diagnosis if it fulfilled the Rome IV criteria in the absence of alarming signs or other pathologies that explain the pain [1]. Attention was paid to differentiate between functional dyspepsia and AM based on the Rome IV criteria. Children who did not fit the Rome IV criteria or were found to have a different pathology that fully explained the symptoms were excluded from the study.

Only children who satisfied the Rome IV diagnostic criteria were included in this study. The Rome IV criteria define AM as "paroxysmal and stereotypical episodes of intense,

acute periumbilical, midline, or diffuse abdominal incapacitating pain as the predominant symptom, lasting at least 1 h and interfering with daily activities. The pain should be associated with at least two of the following: anorexia, nausea, vomiting, headache, photophobia, or pallor, and the episodes should occur at least twice within six months.” [2].

Organic causes of abdominal pain were excluded after appropriate laboratory investigations involving celiac screening, testing for inflammatory markers, taking a complete blood count, serum amylase testing, carrying out a chemistry and metabolic work-up, ultrasound imaging of the abdomen, various cross-sectional imaging modality checks of the abdomen, and brain and upper gastrointestinal endoscopy in selected patients.

This study described the prophylactic effects of pizotifen, propranolol, and riboflavin on AM in children. The medications were prescribed as follows: pizotifen, 1 mg at night; propranolol, 0.5 mg/kg twice daily (max. 10 mg per dose); and riboflavin, 10 mg/kg (max. 300 mg/day). Treatment options were introduced to the family according to the severity of the illness; detailed information about various options was also provided for helping the family in making appropriate treatment choices. Propranolol was avoided in children with asthma or cardiac diseases. Families were advised to have a daily blood pressure check for the child at the nearest health center. Pizotifen was avoided in obese children owing to its stimulatory effect on appetite. Response was assessed at the first follow-up outpatient visit, approximately 2–3 months after treatment. Parental perception was used to assess the treatment response. Treatment response was considered favorable if it led to >50% reduction in the frequency of abdominal pain, as perceived by parents.

### Study aims

The main aim of this study was to assess the clinical response of prophylactic treatment on AM and to examine factors that may be associated with a positive treatment response.

### Statistical analysis

Statistical analyses were performed using SPSS software (version 20.0; IBM Co., Armonk, NY, USA). Descriptive statistics included frequencies and percentages for categorical variables and mean and standard deviation or median and interquartile range for continuous variables, where appropriate. Demographic and clinical data were compared using Fisher's exact test for categorical variables and Student's *t*-test or Mann–Whitney U-test for continuous variables. Statistical significance was set at  $p < 0.05$ .

### Ethical considerations

This study was approved by the ethical research committee of the Royal Hospital (Reference number 24/19) and was conducted in accordance with the Declaration of Helsinki. The patient consent was waived as the study did not involve patients' names or identifications.

## RESULTS

### Baseline characteristics

Of the 74 children initially identified with recurrent abdominal pain, 43 satisfied the diagnostic criteria for AM and 31 were excluded. Exclusion was based on the presence of an identifiable organic etiology and failure to match the diagnostic criteria for AM. The excluded patients were labelled with the following diagnoses: cyclical vomiting ( $n=10$ ), cephalic migraine ( $n=5$ ),

**Table 1.** Baseline characteristics of the study group

Variable	Value (n=43)
Age at presentation (y)	6.8±2.6
Duration of illness (mo)	12 (0–96)
Sex	
Male	26 (60.5)
Female	17 (39.5)
Family history of migraine headache	26 (60.5)
Clinical features	
Nausea	34 (79.1)
Vomiting	31 (72.1)
Nocturnal vomiting	16 (37.2)
Nocturnal abdominal pain	25 (58.1)
Headache	35 (81.4)
Pallor	11 (25.6)
Fatigue	24 (55.8)
Weight (kg)	26.8±9.8
Height (cm)	126.6±16.0
Laboratory investigations	
Hemoglobin (g/dL)	12.2±1.0
Albumin (g/L)	39.2±4.6

Values are presented as mean±standard deviation, median (interquartile range), or number (%).

pancreatitis (n=3), irritable bowel syndrome (n=2), non-specific functional abdominal pain (n=2), *Helicobacter pylori* infection (n=2), hereditary angioedema (n=1), food allergy (n=1), gall stones (n=1), urinary tract infection (n=1), giardiasis (n=1), diabetic ketoacidosis (n=1), and age >13 years (n=1). The median age at presentation was 7 years (range, 2–12 years). Of the total 43 children of the cohort, 60.5% (n=26) were males and 39.5% (n=17) were females. The most frequently associated symptoms, alongside abdominal pain, were headache (81.4%), nausea (79.1%), and vomiting (72.1%). The median duration of illness was 12 months (range, 0–96 months). Family history of migraine headache was present in at least 60.5% children. The baseline characteristics of the patients are shown in **Table 1**.

### Study outcomes

Patients were started on prophylactic treatment with riboflavin, pizotifen, or propranolol, either as monotherapy or as part of a combination therapy (**Table 2**). Of the 20 patients (46.5%) who received riboflavin monotherapy, 18 (90.0%) reported improvement in abdominal pain, 1 patient (5.0%) reported no change, and 1 patient (5.0%) was lost to follow-up. Pizotifen monotherapy was prescribed to 10 patients (23.3%), of whom 9 (90.0%) reported improvement and 1 (10.0%) reported no improvement owing to the lack of compliance. Three patients (6.9%) were started on propranolol monotherapy, with improvement in abdominal pain reported in all three (100%). Combination therapy of pizotifen and propranolol were given to seven patients (16.3%), of whom five (71.4%) improved; one (14.3%) was non-compliant and one patient (14.3%) was lost to follow up.

**Table 2.** Treatment outcomes in children with abdominal migraine

Treatment	Number (n=43)	Outcome		
		Improvement	No improvement	Lost to follow up
Riboflavin monotherapy	20 (46.5)	18 (90.0)	1 (5.0)	1 (5.0)
Pizotifen monotherapy	10 (23.3)	9 (90.0)	1 (10.0)	0
Propranolol monotherapy	3 (7.0)	3 (100)	0	0
Pizotifen+propranolol	7 (16.3)	5 (71.4)	1 (14.3)	1 (14.3)
Riboflavin+pizotifen	2 (4.7)	2 (100)	0	0
Riboflavin+propranolol	1 (2.3)	0	1 (100)	0

Values are presented as number (%).

**Table 3.** Bivariate analysis of factors associated with response to treatment

Variable	No response (n=4)	Positive response (n=37)	p-value <sup>†</sup>
Age at presentation	6.0±2.9	6.8±2.6	0.576
Sex			
Yes	2 (50.0)	23 (62.2)	0.637
No	2 (50.0)	14 (37.8)	
Family history of migraine			
Yes	0 <sup>‡</sup>	24 (82.8) <sup>‡</sup>	0.200
No	1 (100) <sup>‡</sup>	5 (17.2) <sup>‡</sup>	
Nausea			
Yes	2 (50.0)	32 (88.9) <sup>‡</sup>	0.100
No	2 (50.0)	4 (11.1) <sup>‡</sup>	
Vomiting			
Yes	1 (25.0)	30 (81.1)	0.039*
No	3 (75.0)	7 (18.9)	
Headache			
Yes	3 (75.0)	30 (83.3) <sup>‡</sup>	0.552
No	1 (25.0)	6 (16.7) <sup>‡</sup>	
Nocturnal pain			
Yes	3 (75.0)	22 (73.3) <sup>‡</sup>	
No	1 (25.0)	8 (26.7) <sup>‡</sup>	>0.999
Nocturnal vomiting			
Yes	0 <sup>‡</sup>	16 (55.2) <sup>‡</sup>	0.113
No	3 (100) <sup>‡</sup>	13 (44.8) <sup>‡</sup>	
Pallor			
Yes	1 (25.0)	10 (47.6) <sup>‡</sup>	0.604
No	3 (75.0)	11 (52.4) <sup>‡</sup>	
Feeling fatigue			
Yes	1 (25.0)	23 (76.7) <sup>‡</sup>	0.067
No	3 (75.0)	7 (23.3) <sup>‡</sup>	
Hemoglobin (g/dL)	12.7±0.7	12.1±1.0	0.305
Albumin (g/L)	40.0±1.7	39.0±4.8	0.746

Values are presented as mean±standard deviation or number (%).

\* $p<0.05$ .

<sup>†</sup>Fisher's exact test/Student's *t*-test.

<sup>‡</sup>Different total from the above.

Two patients (4.7%) received a combination of riboflavin and pizotifen, and both reported improvement in abdominal pain. One patient (2.3%) had a combination of riboflavin and propranolol and showed no improvement due to the lack of compliance.

### Analysis of factors that may influence the treatment response

Bivariate analysis of multiple variables and a positive response to therapy showed an association only with vomiting ( $p=0.039$ ). The association with the fatigue symptom did not reach statistical significance ( $p=0.06$ ) (Table 3). Riboflavin, a drug associated mostly with vomiting, was identified through multivariate analysis, including riboflavin, propranolol, and pizotifen as independent variables (odds ratio=14.4, 95% confidence interval=1.91–108.8,  $p=0.01$ ); therefore, riboflavin has the best treatment response (Table 4).

**Table 4.** Binary logistic regression of drugs related to the occurrence of vomiting in children with abdominal migraine

Variable	OR	95% CI for OR		p-value
		Lower	Upper	
Riboflavin	14.4	1.91	108.8	0.010*
Propranolol	9.6	0.81	112.9	0.073
Pizotifen	4.2	0.61	28.9	0.146

OR: odds ratio, CI: confidence interval.

\* $p<0.05$ .

## DISCUSSION

AM is one of the most common FGIDs in the pediatric age group and occurs in approximately 0.5–4.0% of children with recurrent abdominal pain, with girls generally being affected more commonly than boys [6,9]. The pathophysiology of AM and the entire spectrum of FGIDs are poorly understood. However, it is thought to be related to visceral hypersensitivity, abnormal intestinal motility, gut microbial dysbiosis, and other early-life events [10].

The Rome IV criteria define AM by excluding other possible causes of abdominal pain in children [11]. A timely and correct diagnosis of AM may mitigate stress on the family and medical care providers and limit unnecessary investigation [12]. This study highlights the clinical features of AM in the present cohort of children in Oman and describes their response to prophylactic therapy. The fact that there were only 43 children diagnosed with AM during the 10-year period in the largest tertiary center in this region raises concerns about the possibility of under diagnosis of AM, particularly in this area, and also in general.

While our study was consistent with other studies in terms of age at presentation, it differs with respect to the predominance of boys over girls [13]. Moreover, we noted that >50% of children suffered from abdominal pain at night; thus, waking them from sleep. This issue has not been emphasized in previous studies. In addition, our study found a high prevalence of a family history of migraine in patients with AM.

There are limited data on preventive therapies for AM in children; current treatments mainly involve avoidance of triggers and pharmacotherapy [4]. The choice of a particular prophylactic medication was based on physician discretion, requirements of the individual patient, family preference, and side effects. Riboflavin was the most widely administered therapy, with no significant side effects, and most parents welcomed the idea of food as a medicine. However, the use of riboflavin in children as prophylaxis for AM has not been widely studied. Evidence regarding its use has been extrapolated mostly from adult studies, although a small number of pediatric studies relate to cephalic migraine since AM is a variant of cephalic migraine [14,15]. Indeed, children with AM show similar changes in visual response to those with cephalic migraine [8]. Riboflavin is a precursor for both flavin mononucleotide and adenine dinucleotide, which are involved in mitochondrial functions and are thought to be impaired in patients who suffer from cephalic migraine [16]. The energy metabolism of the brain and muscle, as shown by 31P magnetic resonance spectroscopy, has been shown to be affected in patients that experience migraine aura [17]. In the present study, it was observed that 18 of the 20 patients who received riboflavin as monotherapy and three patients who received it as part of combination therapy showed improvement. To the best of our knowledge, no previous study has examined the use of riboflavin for the treatment of AM symptoms.

Pizotifen is a serotonin inhibitor that has been shown to be effective for the prevention of AM in 70% of patients in a small placebo-controlled trial [18]. Our results are consistent with this finding, reinforcing the use of pizotifen in the management of AM. Propranolol was used in 11.3% of patients, either alone or in combination with other drugs. Our results with propranolol are comparable with those of other studies, reporting around 75% improvement in AM [19].

Broadly, this study demonstrated the effectiveness of riboflavin in the prevention of AM attacks and reinforces earlier studies on the beneficial use of pizotifen and propranolol. Retrospective nature, small sample size, lack of control subjects, and lack of consideration

of the effects of long-term sustained treatment may be the limitations of this study. Future prospective studies should include a larger sample size and a longer follow-up time for the examination of treatment response to overcome these limitations.

The present study on Omani children with AM showed a favorable response to various modalities of prophylactic therapy, including riboflavin, pizotifen, propranolol, and combination therapy, all of which were almost equally effective. The presence of vomiting may predict the treatment response.

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