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

Tawfiq Taki Al Lawati 1, Omar I. Saadah 1,2, Ruwaina al Riyami 1, and Zuwaina al Yarubi 1

1Department of Child Health, The Royal Hospital, Muscat, Oman
2Department of Pediatrics, Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia
3Pediatric Gastroenterology Unit, Department of Pediatrics, King Abdulaziz University Hospital, Jeddah, Saudi Arabia

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
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-Arafeh’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 ≤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),
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), diabética 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.

**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 (%).

**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 (%).
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 3. Bivariate analysis of factors associated with response to treatment

| Variable                      | No response (n=4) | Positive response (n=37) | $p$-value† |
|-------------------------------|-------------------|--------------------------|------------|
| 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†                | 24 (82.8)‡               | 0.200      |
| No                            | 1 (100)‡          | 5 (17.2)‡                |            |
| Nausea                        |                   |                          |            |
| Yes                           | 2 (50.0)          | 32 (88.9)‡               | 0.100      |
| No                            | 2 (50.0)          | 4 (11.1)‡                |            |
| 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)‡               | 0.552      |
| No                            | 1 (25.0)          | 6 (16.7)‡                |            |
| Nocturnal pain                |                   |                          |            |
| Yes                           | 3 (75.0)          | 22 (73.3)‡               | >0.999     |
| No                            | 1 (25.0)          | 8 (26.7)‡                |            |
| Nocturnal vomiting            |                   |                          |            |
| Yes                           | 0†                | 16 (55.2)‡               | 0.113      |
| No                            | 3 (100)‡          | 13 (44.8)‡               |            |
| Pallor                        |                   |                          |            |
| Yes                           | 1 (25.0)          | 10 (47.6)‡               | 0.604      |
| No                            | 3 (75.0)          | 11 (52.4)                |            |
| Feeling fatigue               |                   |                          |            |
| Yes                           | 1 (25.0)          | 23 (76.7)‡               | 0.067      |
| No                            | 3 (75.0)          | 7 (23.3)‡                |            |
| 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 (%).

* $p<0.05$.
† Fisher’s exact test/Student’s t-test.
‡ Different total from the above.

### 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          | 26.9         | 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.

REFERENCES

1. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional disorders: children and adolescents. Gastroenterology 2016. doi: 10.1053/j.gastro.2016.02.015. [Epub ahead of print].
2. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24 Suppl 1:1-960.
3. Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version). Cephalalgia 2013;33:629-808.
4. Angus-Leppan H, Saatci D, Sutcliffe A, Guiloff RJ. Abdominal migraine. BMJ 2018;360:k179.
5. Abu-Arafeh I, Russell G. Prevalence and clinical features of abdominal migraine compared with those of migraine headache. Arch Dis Child 1995;72:413-7.
6. Carson L, Lewis D, Tsou M, McGuire E, Surran B, Miller C, et al. Abdominal migraine: an under-diagnosed cause of recurrent abdominal pain in children. Headache 2011;51:707-12.
7. Saps M, Velasco-Benítez CA, Langshaw AH, Ramírez-Hernández CR. Prevalence of functional gastrointestinal disorders in children and adolescents: comparison between Rome III and Rome IV criteria. J Pediatr 2018;199:212-6.
8. Mortimer MI, Good PA. The VER as a diagnostic marker for childhood abdominal migraine. Headache 1990;30:642-5.
9. Saps M, Nichols-Vinueza DX, Rosen JM, Velasco-Benítez CA. Prevalence of functional gastrointestinal disorders in Colombian school children. J Pediatr 2014;164:542-5.e1.
10. Korterink J, Devanarayana NM, Rajindrajith S, Vlieger A, Benninga MA. Childhood functional abdominal pain: mechanisms and management. Nat Rev Gastroenterol Hepatol 2015;12:159-71.
11. Mani J, Madani S. Pediatric abdominal migraine: current perspectives on a lesser known entity. Pediatric Health Med Ther 2018;9:47-58.
12. Di Lorenzo C, Colletti RB, Lehmann HP, Boyle JT, Gerson WT, Hyams JS, et al. Chronic abdominal pain in children: a technical report of the American Academy of Pediatrics and the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2005;40:249-61.
13. Covellier JC, Lépine A. Childhood periodic syndromes. Pediatr Neurol 2010;42:141.
14. Condo M, Posar A, Arbizzani A, Parmeggiani A. Riboflavin prophylaxis in pediatric and adolescent migraine. J Headache Pain 2009;10:361-5.
15. Schoenen J, Jacquy J, Lenaerts M. Effectiveness of high-dose riboflavin in migraine prophylaxis. A randomized controlled trial. Neurology 1998;50:466-70.
16. Barbiroli B, Montagna P, Cortelli P, Funicello R, Iotti S, Monari L, et al. Abnormal brain and muscle energy metabolism shown by 31P magnetic resonance spectroscopy in patients affected by migraine with aura. Neurology 1992;42:1209-14. PUBMED | CROSSREF

17. Montagna P, Cortelli P, Monari L, Pierangeli G, Parchi P, Lodi R, et al. 31P-magnetic resonance spectroscopy in migraine without aura. Neurology 1994;44:666-9. PUBMED | CROSSREF

18. Symon DN, Russell G. Double blind placebo controlled trial of pizotifen syrup in the treatment of abdominal migraine. Arch Dis Child 1995;72:48-50. PUBMED | CROSSREF

19. Worawattanakul M, Rhoads JM, Lichtman SN, Ulshen MH. Abdominal migraine: prophylactic treatment and follow-up. J Pediatr Gastroenterol Nutr 1999;28:37-40. PUBMED | CROSSREF