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# Functional gastrointestinal disorders in migrainous children: efficacy of flunarizine

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The aim of this study was to evaluate the prevalence of functional gastrointestinal disorders (FGIDs) in children with migraine headache and the effects of flunarizine on gastrointestinal manifestations. We studied 50 migrainous children (mean age 8.63 years). The clinical pattern and the diagnosis of FGIDs were obtained from structured questionnaires. All subjects underwent measurement of total gastric emptying time (TGEt) performed by real-time ultrasonography of the gastric antrum at baseline (T0). In the second part of the study, we evaluated 10 migrainous children (mean age 9.8 years) with associated FGIDs. In these 10 patients, repeated TGEt evaluation together with a detailed symptom history was obtained after 1 (T1) and 2 months (T2) of treatment with flunarizine. Control groups were composed of 10 migrainous children without FGIDs (mean age 9.2 years) and nine sex- and age-matched healthy children. Gastrointestinal disorders were present in 70% of the patients. Migrainous children with FGIDs had significantly ($P < 0.01$) more prolonged TGEt than subjects without FGIDs. Prior to therapy, all migrainous children with FGIDs had prolongation of TGEt compared with controls ($P < 0.05$). Patients on flunarizine had a significant decrease in TGEt at both 1 ($P < 0.01$) and 2 months ($P = 0.002$) of therapy. The mean frequency of abdominal pain per month was significantly ($P < 0.001$) reduced at T1 compared with T0. The mean frequency of vomiting per month was significantly decreased at T1 ($P < 0.05$) and even more so at T2 ($P < 0.01$). Finally, the mean frequency of headache per month was significantly reduced only at T2 ($P < 0.05$), whereas the mean duration of headache was significantly decreased at T1 ($P < 0.01$) with no difference between T1 and T2. Most children with migraine report FGIDs, associated with a delayed gastric emptying. Flunarizine decreases the frequency and duration of migrainous episodes as well as the gastrointestinal symptoms. □ *Antimigraine prophylaxis, calcium antagonists, functional gastrointestinal disorders, migraine headache*

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## Introduction

Migraine is the most important cause of headache both in children and adults (1). The International Headache Society (IHS) diagnostic criteria have been recently revised (2). Before puberty migraine prevalence is about 4% (3) and increases with age more rapidly in girls than in boys. The quality of life of children with headache is significantly affected by their health condition, the impact of headaches being similar to that of other chronic illnesses (4).

It has long been recognized that migraine headaches are frequently associated with gastrointestinal symptoms. Among the functional gastrointestinal disorders (FGIDs), cyclic vomiting syndrome (CVS) and abdominal migraine are usually classified as

  

migraine variants or equivalents (5). This relationship is supported by several observations: there is a high prevalence of migraine headache and abdominal pain in paediatric CVS patients, with a higher prevalence of migraine among first-degree relatives of children affected by CVS; migraine headache and CVS share a similar temporal profile of disorder onset and resolution of symptoms; both syndromes share many associated gastrointestinal, sensory and vasomotor symptoms (6).

There is also evidence that the baseline sympathetic tone in children with CVS differs from that of control subjects, in a pattern similar to that found in migraine patients. Rashed et al. (7) have demonstrated that both children with CVS and adults with migraine headache manifest elevated sympathetic tone responses to postural changes. Migraine-type neural and vascular changes have been documented in CVS children, as well as a predominance of sympathetic adrenergic over parasympathetic cholinergic tone (8). Good et al. (9) have reported similar visually evoked responses in children affected with CVS and with migraine.

Therapy for CVS and abdominal migraine focuses on preventing attacks with prophylactic medication. Several studies have shown improvement using propranolol, cyproheptadine and amitriptyline, usually resulting in a ≥50% decrease in the number and/or severity of episodes in CVS patients (10, 11). Pfau et al. have reported that 75% of children with CVS responded to antimigraine medication, as opposed to control children who suffered from chronic vomiting (12). Furthermore, another study has shown that CVS patients who also suffered from migraine improved twice as often (79% vs. 36%) as non-migrainous CVS patients when treated with antimigraine therapy (13). The shared therapeutic response of CVS and migraine implies that closely related neurally mediated pathways are responsible for some or all of the symptomatology of these two disorders.

Flunarizine is a calcium channel blocker which has been shown to reduce attack frequency in migraine headaches (14). It has been used for paediatric migraine prophylaxis and more than one randomized, placebo-controlled, double-blind study has demonstrated its effectiveness (15, 16).

Our study was designed to determine the prevalence of FGIDs in children with migraine headaches, to define clinical characteristics of migrainous children with and without associated FGIDs, and to evaluate the effect of flunarizine on gastrointestinal symptoms and gastric emptying time in migrainous children.

## Methods

The first part of the study involved the evaluation of 50 consecutive patients referred to our clinic for migraine (mean age $8.63 \pm 2.8$ years, 21 males). Migraine was defined according to the ICHD-II criteria (2).

Questions were posed concerning migraine onset, family history, total number of episodes, frequency and duration of attacks, intervals between episodes, prodromal symptoms, precipitating and alleviating factors and associated symptoms.

For each consecutive migrainous patient, a structured questionnaire was completed which recorded symptoms and signs needed to satisfy the paediatric Rome II criteria for the following disorders: functional dyspepsia, irritable bowel syndrome, functional abdominal pain, abdominal migraine and CVS (17, 18). Furthermore, functional vomiting was diagnosed according to the adult FGID criteria (17), with the aim to include all subjects complaining of a history of recurrent but not cyclic vomiting, not explained by abnormalities of the gut or central nervous system, metabolic or biochemical disease.

Measurement of gastric emptying time was performed by real time ultrasonography (US) of the gastric antrum after ingestion of a mixed solid-liquid meal (19). All subjects were examined using a 5-MHz linear probe applied to the epigastrium, with minimal abdominal compression. Baseline scans were performed on an empty stomach and follow-up measurements were performed at 30 and 60 min, then at 15-min intervals until emptying was complete. The gastric emptying time was calculated by measuring the cross section of the gastric antrum at the sagittal plane passing through the superior mesenteric vein. The antral cross-sectional area, elliptical in shape, was calculated by the following formula: $\text{Area} = \pi \times \text{longitudinal diameter} \times \text{antero-posterior (AP) diameter}/4$ (20) and the stomach was considered empty when the cross-sectional area returned to baseline and persisted unchanged for at least 30 min. Total gastric emptying time (TGEt) was calculated in relation to the start of the meal.

In the second part of the study, we evaluated 10 migrainous children with associated FGID diagnoses (mean age $9.8 \pm 1.9$ years, seven males). Subjects were selected from our migrainous children who had indications of preventive treatment according to the American Academy of Neurology (AAN) Guidelines (21, 22). These children with migraine received flunarizine 5 mg, as a single daily dose, orally for a period of 2 months. A detailed symptom history was recorded and a general physical and

neurological examination performed at baseline. During the study, children's caregivers kept a weekly symptoms diary and recorded: number and duration of migraine attacks, frequency of gastrointestinal symptoms and presence of side-effects. All patients were evaluated at 1 and 2 months and the symptoms diary was checked and collected. As controls we chose a group of 10 migrainous children without FGIDs (mean age 9.2 ± 1.8 years, six males) and nine healthy children (mean age 8.6 ± 1.7 years, five males). All children underwent US measurements of gastric emptying time at baseline, 1 and 2 months. Controls were not in treatment with antimigraine prophylaxis.

Informed consent to participate in the study was obtained from parents of all patients and the experimental design was approved by our institutional review board.

### *Statistical analysis*

Continuous variables are shown as mean ± SD. The unpaired *t*-test and one-way ANOVA with the Bonferroni test for multiple comparisons were used, as appropriate. Repeated measures ANOVA was applied for the analysis of data at different times of observation (T0, T1 and T2) with the Bonferroni test for the post hoc test. Categoric variables were analysed using the $\chi^2$ test.

All analyses were performed with SPSS software, ver. 13.1 (SPSS Inc., Chicago, IL, USA).

## Results

FGIDs were present in 35 (70%) of the 50 migraine patients; specifically, 35% reported functional abdominal pain and 35% reported functional vomiting. None of the patients responded to the diagnostic criteria for functional dyspepsia, irritable bowel syndrome, abdominal migraine or CVS. Clinical criteria for definition of functional vomiting and functional abdominal pain are summarized in Table 1. A family history of migraine was reported in 84% of the study population. At baseline, the mean ± SD duration and frequency (number of episodes/month) of migraine attacks were 8.7 ± 10.6 h and 5.4 ± 1.41, respectively.

TGEt was significantly prolonged ($P < 0.01$) in children with migraine and associated FGIDs when compared with children with migraine alone (mean ± SD: 183.57 ± 35.12 vs. 122 ± 37.01, $P < 0.05$). The presence of specific triggers was not significantly different between the two groups, nor was the alleviating factor of sleep.

Gastric emptying times of migrainous children with FGIDs treated with flunarizine and of controls are summarized in Fig. 1. Prior to therapy, migrainous children with associated FGIDs had a prolonged TGEt compared with both healthy children and children affected by migraine without FGIDs ($P < 0.05$). When these patients were treated with flunarizine, they demonstrated significant decreases in TGEt at both the 1-month ($P < 0.01$) and 2-month ($P = 0.002$) evaluations. There were no significant differences in gastric emptying times between treated patients and controls at 1 or 2 months.

All patients treated with flunarizine showed a decrease in frequency and duration of migraine attacks (Table 2). A summary of gastrointestinal and headache symptomatology in treated patients is shown in Table 2.

During the study period, subjects treated with flunarizine did not suffer any relevant side-effects.

**Table 1** Clinical criteria for definition of functional abdominal pain and functional vomiting

*Functional abdominal pain*
At least 12 weeks of:
1 Continuous or nearly continuous abdominal pain in a school-aged child or adolescent; and
2 No or only occasional relation of pain to physiological events (e.g. eating, menses or defecation); and
3 Some loss of daily functioning; and
4 The pain is not feigned (e.g. malingering); and
5 The patient has insufficient criteria for other functional gastrointestinal disorders that would explain the abdominal pain.

*Functional vomiting*
At least 12 weeks, which need not to be consecutive, in the preceding 12 months of:
1 Frequent episodes of vomiting, occurring on at least three separate days in a week; and
2 Absence of criteria for an eating disorder, rumination, or major psychiatric disease according to the DSM-IV; and
3 Absence of self-induced and medication-induced vomiting; and
4 Absence of abnormalities in the gut or central nervous system and metabolic diseases to explain the recurrent vomiting

## Discussion

Published studies have shown the prevalence of migraine headache to be between 30 and 80% in children affected by CVS or abdominal migraine (5, 6, 23). However, there are few data on the prevalence of FGIDs in migrainous children. Our study shows a large prevalence of FGIDs of 70% in paediatric patients with a diagnosis of migraine. Among FGIDs, our migrainous children reported two disorders in particular: functional abdominal pain and functional vomiting. Although the latter corresponds to the adult Rome II criteria for FGID, we chose to consider it for the purpose of including all subjects complaining of a history of recurrent vomiting in the absence of organic abnormalities but not corresponding to the diagnostic criteria for CVS. In a recent study we reported that of 9960 patients, newborn to 12 years old, 194 satisfied the Rome criteria for various FGIDs but only three (0.03%) were affected by CVS (18). Furthermore, previous studies have proposed criteria and questionnaires extensively used and validated in adults, to identify FGIDs such as functional dyspepsia and irritable bowel syndrome, in paediatric populations (24–26).

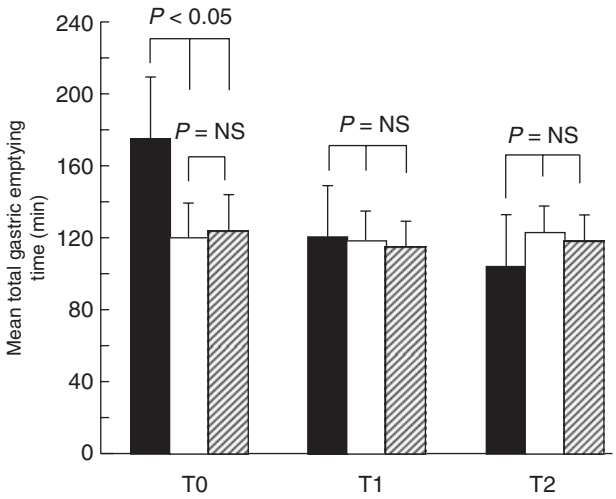


**Figure 1** Total gastric emptying time measured at baseline (T0) and after 1 (T1) and 2 (T2) months of treatment with flunarizine. Migrainous children with functional gastrointestinal disorders (FGIDs): T0 vs. T1, $P < 0.01$; T0 vs. T2, $P = 0.002$; T1 vs. T2, $P$ = NS. ■, Migrainous children with FGIDs; □, controls; hatched, migrainous children without FGIDs.

In our study, FGIDs associated with migraine appear to correlate with a prolonged gastric emptying time. The gastric emptying rate of solids in children is difficult to evaluate because the available methods are either invasive or induce a substantial radiation burden. A good correlation between scintigraphic and US parameters has been found using either liquid or solid meals (27). Hence, in our study the gastric emptying test was performed by means of a real-time US examination, a validated, non-invasive method for studying gastric motility (20, 28).

Gastrointestinal motor abnormalities are common in a variety of FGIDs (29–31). Altered myoelectrical activity of the stomach with a delayed gastric emptying time has been reported in children affected by CVS (32) and has been suggested to play a pathogenic role in functional dyspepsia (33). For this reason, on the basis of a possible link between migraine and FGIDs, we found it of interest to study this parameter in migrainous children. The finding of delayed gastric emptyng in our children affected by migraine and FGIDs could be interpreted as an epiphenomenon, reflecting the overlap between inadequately defined functional syndromes, shared pathophysiology or the activation of physiological interaction at different levels of the brain and gut axis.

Much evidence points to a clinical and pathophysiological link between migraine syndromes and FGIDs, such as CVS, abdominal migraine and others. For example, a positive family history of migraine is present in 72% of paediatric patients with CVS compared with only 14% of children with chronic vomiting (13), while a positive family history is present in 65% of abdominal migraine patients

**Table 2** Gastrointestinal symptoms after 1 and 2 months of treatment with flunarizine

| | Baseline (mean ± SD) | One month (mean ± SD) | Two months (mean ± SD) |
|---|---|---|---|
| Abdominal pain (no. episodes/month) | 4.9 ± 2.9 | 0.71 ± 1.25* | 0.71 ± 1.49 |
| Vomiting (no. episodes/month) | 15.5 ± 11.8 | 1.25 ± 1.89† | 0.8 ± 1.78‡ |
| Headache (no. episodes/month) | 7.1 ± 4.87 | 4 ± 2.62 | 2.18 ± 236† |
| Headache duration (h) | 4.71 ± 2.42 | 1.71 ± 1.6* | 1.5 ± 1.87 |

*$P < 0.001$ compared with baseline; †$P < 0.05$ compared with baseline; ‡$P < 0.01$ compared with baseline.

(23). In our study, almost all patients reported affected family members. Patients with isolated migraine as well as migraine patients with associated FGIDs also share exacerbating and alleviating factors.

In the second part of our study, we evaluated the effects of flunarizine on gastrointestinal symptoms and on gastric emptying time in children with migraine and associated FGIDs. The positive response to flunarizine lends support to the pathophysiological relationship between migraine and FGIDs.

Other antimigraine therapies are effective in CVS: Anderson et al. (11) have demonstrated that both amitriptyline and cyproheptadine are effective prophylactic treatments for CVS, with remission rates of 83–91%. In another study, migraine prophylaxis resulted in complete resolution of cyclic vomiting episodes in 75% of children (12). Abdominal migraine also responds well to migraine prophylactic medications, such as propranolol or cyproheptadine (34).

We chose to study the effects of flunarizine because it has been shown to be effective against migraine in more than one randomized, placebo-controlled, double-blind study and because it has smooth muscle-relaxing properties which may improve symptoms in FGIDs. Flunarizine is a calcium channel blocker which can modulate neurotransmission as well as vascular tone; it has minimal negative inotropic effects, and it also has antihistamine properties (H1). It was introduced into the antimigraine armamentarium because of its modulating effect on vascular tone, as well as its cytoprotective effect against cellular hypoxia (35).

Several pathophysiological pathways are potential candidates in the aetiology of both migraine and FGIDs, are intimately associated with brain–gut interactions and related to voltage-gated calcium channels (36). Recent lines of evidence favour a role for ion channel mutations in the pathogenesis of migraine. For example, four missense mutations of the $\alpha_1$ subunit of the neuronal calcium channel CACNL1A4 have been described in patients affected by hemiplegic migraine and are presumed to cause this syndrome (37, 38). CVS has also been proposed to result from a similar channelopathy (39, 40).

Clinical improvement in our patients with migraine and FGIDs, when treated with flunarizine, may be due to one or more of several mechanisms of action: a calcium channel blocker in a yet undefined channelopathy, an antihistamine on the central afferent pathways, or perhaps peripherally by acting directly to relax smooth muscle either in the vasculature or in the intestinal wall.

Whatever the mechanism, flunarizine treatment in our patients with migraine and FGIDs resulted in marked improvement in gastrointestinal as well as headache symptoms and was also quantifiable as a decrease in total gastric emptying times as measured by US. A larger, randomized, placebo-controlled trial of flunarizine in these syndromes should be the next step.

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