The Gut, the Brain and Migraine: When Pills Don't Work

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Introduction

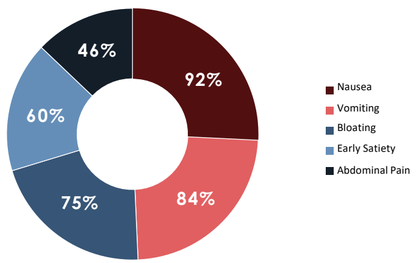
Migraine and Disorders of Gastric Motility

- Migraine is a recurrent headache disorder with moderate or severe headache attacks that are accompanied by nausea, photophobia, and/or phonophobia[1]
- The nausea that accompanies migraine strongly contributes to the burden and disability associated with migraine[2]
- Common gastrointestinal symptoms that present with migraine can include nausea, vomiting, diarrhea, reflux, and constipation[3,4]
- Additional gastrointestinal conditions associated with migraine include inflammatory bowel disease, celiac disease, irritable bowel syndrome, Helicobacter pylori infection, and disorders of gastric motility[5,6]
- The relationship between migraine and gastric motility has important clinical implications in the treatment of migraine, as delayed gastric emptying may affect the absorption of oral migraine treatments[7]

Epidemiology of Disorders of Gastric Motility (**Figure 1**)

- Disorders of gastric motility are part of the spectrum of disorders that include idiopathic gastroparesis and functional dyspepsia. The Rome Foundation recently introduced the term, Disorders of Gut Brain Interaction (DGBI) that includes functional dyspepsia; thus, highlighting the interaction between the brain and gut in these common disorders. Gastroparesis and functional dyspepsia are associated with delayed gastric emptying in the absence of mechanical obstruction[8,9]
- The prevalence is difficult to estimate; however, the prevalence of diagnosed disorders of gastric motility in the United States population has been estimated at 24.2 per 100,000 persons[10,11]
- Major etiologies of disorders of gastric motility are diabetic, post-surgical, and idiopathic; an idiopathic etiology is most common, with females comprising 80% of this diagnosis[12,13]

Figure 1. Common Symptoms Associated With Disorders of Gastric Motility[12]



Methods

- Disorders of gastric motility have long been implicated in association with migraine
- The following key words were used to perform a literature search of EMBASE and PubMED to assess the current state of scientific evidence that exists for linking migraine with disorders of gastric motility: gastric stasis, migraine, autonomic dysfunction

Objectives

- To summarize studies supporting a link between disorders of gastric motility and migraine
- To provide evidence that disorders of gastric motility are also observed outside of migraine attacks during the interictal period
- To present current, unpublished scientific data demonstrating a relationship between migraine and disorders of gastric motility

Results

Table 1. Experimental Studies Assessing Gastric Emptying in Patients With Migraine

Study	N	Subject Group	$T_{1/2}$ (Minutes)*	Detection Method
Boyle 1990[15]	46	People with migraine outside of attack	10.1 ± 5.3	Epigastric impedance
	14	People with migraine during attack	6–<60	
	64	People without migraine-controls	9 ± 5	
Aurora 2006[6]	10	People with migraine–interictal	188.8 ± 100.6	Gastric scintigraphy
	9	People with migraine–ictal	149.9 ± 69.4	
	10	People without migraine-controls	111.8 ± 38.6	
Aurora 2007[16]	1	Person with migraine–interictal	243	Gastric scintigraphy
	1	Person with migraine-spontaneous migraine	124	
	1	Person with migraine–induced migraine	182	
	N/A	Control–normative value	112	
Yu 2012[17]	27	People with migraine without GI symptoms interictally	100.82 ± 23.9	Gastric scintigraphy
	32	Functional dyspepsia patients	125.51 ± 52.6	
	12	Healthy controls	95.23 ± 23.3	
Yalcin 2012[18]	7	People with migraine–interictal	26.29 ± 9.4	Liquid phase gastric scintigraphy
	7	People with migraine–ictal	48.0 ± 18.7	
	7	People without migraine-controls	26.14 ± 95.6	

*$T_{1/2}$, is the time to half gastric emptying; values presented as mean ± standard deviation for all studies with the exception of the Aurora 2007 study.

GI, gastrointestinal; N/A, not available.

- Volans et al (1978) provided early evidence for disorders of gastric motility with migraine by observing a delay in aspirin absorption in people with migraine during an attack, but not during the headache-free period[14]
- Then early studies by Boyle et al (1990) also suggested delayed gastric emptying occurs during migraine attacks but not during the interictal period[15]
- More recently, Aurora et al (2006, 2007) demonstrated delay in gastric emptying during visually induced migraines, the headache-free interictal period, and during spontaneous migraine attacks[6,16]
- Yu et al (2012) reported that delayed gastric emptying was present only in subjects with functional dyspepsia compared to those with migraine and controls[17]
- In a smaller study, Yalcin et al (2012) observed delayed ictal but not interictal gastric emptying in people with migraine compared to controls (**Table 1**)[18]

New Evidence for Disorders of Gastric Motility in Patients With Migraine (**Table 2**)

- A recent retrospective study evaluated gastroparesis-like symptoms in patients from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Gastroparesis Clinical Research Consortium[19]
- A total of 711 patients were studied, 516 patients with gastroparesis and 195 patients with chronic unexplained nausea and vomiting (CUNV)[19]
- Migraine was the most commonly reported overlapping comorbidity and associated with gastrointestinal symptoms in patients with gastroparesis[19]
- Patients with migraine headaches also had a more severe gastroparesis cardinal symptom index (GCSI) (odds ratio [OR] 1.24, 95% confidence interval [CI] 1.05-1.45, p=0.009), increased Trait Anxiety (OR 1.16, 95% CI 1.03-1.32, p=0.02), and were less likely to be diabetic (OR=0.67, 95% CI 0.48-0.94, p=0.02) compared to those without migraine headaches. There were no significant differences between the two groups in Beck Depression or State Anxiety[19]

Table 2. Prevalence of Comorbidities in Patients With Gastroparesis or CUNV[19]

	Gastroparesis* (N=516)	CUNV† (N=195)	Total (N=711)	p-value‡	Population Estimates
Severe Abdominal Pain§	237 (45.9%)	66 (33.9%)	303 (42.6%)	0.004	
Migraine Headache	189 (36.6%)	69 (35.4%)	258 (36.3%)	0.79	7.67%
Endometriosis¶	71 (16.6%)	20 (12.5%)	91 (15.5%)	0.25	3.7%
Fibromyalgia	67 (13.0%)	24 (12.3%)	91 (12.8%)	0.90	6.24%
Chronic Fatigue Syndrome	44 (8.5%)	11 (5.6%)	55 (7.7%)	0.27	6.0%
Interstitial Cystitis	18 (3.5%)	7 (3.6%)	25 (3.5%)	1.00	0.47%

*Gastroparesis based on delayed gastric emptying scintigraphy >60% retention at 2 hours or >10% retention at 4 hours.

†CUNV is defined as chronic unexplained nausea and vomiting, based on non-delayed gastric emptying scintigraphy.

‡p-values derived from Fisher's exact tests.

§Severe abdominal pain based on a score of 4 (severe) or 5 (very severe) on the patient assessment of upper gastrointestinal symptom severity (PAGI-SYM) questionnaire (scale 0-5).

¶89 males excluded from endometriosis counts.

Conclusion

- The association between disorders of gastric motility and migraine may be underrecognized based on new evidence reporting that 36.6% of patients with gastroparesis have migraine headaches
- Very few studies assessing disorders of gastric motility in patients with migraine have been performed, and little is known about the physiological link between these conditions[20]
- Findings are conflicting on whether disorders of gastric motility occur only during a migraine attack or during the interictal period as well[6,14-16,18]
- These discrepancies may be due to variability in test methodology or migraine phenotype[6,14-16,18]
- Recognition of this comorbidity is important for patients who experience gastrointestinal symptoms and do not have relief from migraine symptoms using an oral abortive treatment[7]
- Route of administration and formulation may have an impact on absorption and efficacy of migraine therapies[7]
- Non-oral routes of administration may positively impact patients with migraine and disorders of gastric motility, and non-invasive, non-oral routes such as nasal are a great alternative

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Sheena K. Aurora and Stephen B. Shrewsbury are full-time employees of Impel NeuroPharma and are stockholders in Impel NeuroPharma. Linda Nguyen serves on an advisory board for Gimeli and consults for Pendulum, Neurogastryx, Ironwood, Eli Lilly, and Alnylam. Nada Hindiyeh serves on advisory boards for Amgen, Eli Lilly, Lundbeck, and Zosano Pharma.

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