Gut brain interaction in Headache

박 정 욱
가톨릭의대

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CONTENTS

- Gastrointestinal symptom in Headache and migraine
- GI symptoms in migraine : Functional dyspepsia or Structural lesion ?
- Association GI disorder and Migraine : H pyroli. Irritable bowel syndrome, GI motility disorder
- Pathophysiologic relation between GUT and migraine
- Episodic GI syndrome and Migraine

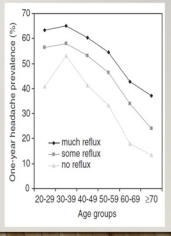
Cephalalgia. 2008 Feb;28(2):144-51.

COMORBIDITY OF HEADACHE AND GI COMPLAINTS : HEAD HUNT STUDY

- Higher prevalence of headache : individuals with reflux (OR 2.4) , diarrhea (OR 2.4), constipation (OR 2.1) , nausea (OR 3.2)
- No difference between migraine and non migraine headache
- The association is increased with headache frequency

Table 3 Prevalence odds ratio (OR) of different gastrointestinal complaints (dependent variables) related to headache frequency and compared with headache-free subjects

		Reflux symptoms (n = 47 046)		Diarrhoea (n = 45 453)		Constipation (n = 46 203)		Nausea (n = 45 478)	
Variables	Total	No.	OR* (95% CI)	No.	OR* (95% CI)	No.	OR* (95% CI)	No.	OR* (95% CI)
Headache-free	32 965	8215	1.0 (ref.)	3806	1.0 (ref.)	5711	1.0 (ref.)	2262	1.0 (ref.)
Migraine									
<7 days/month	4 361	1450	1.7 (1.5, 1.8)	921	1.8 (1.7, 2.0)	1094	1.6 (1.5, 1.7)	1013	3.4 (3.1, 3.7)
7–14 days/month	1 125	469	2.3 (2.0, 2.6)	280	2.0 (1.8, 2.4)	380	2.1 (1.8, 2.4)	375	4.6 (4.0, 5.3)
>14 days/month	350	165	2.6 (2.1, 3.3)	106	2.7 (2.0, 3.3)	131	2.4 (1.9, 3.1)	144	6.7 (5.2, 8.5)



Headache. 2013;53(1):93-103.
Cephalalgia. 2006;26(5):506-10.

GI SYMPTOM AND MIGRAINE

- About ¾ of migraineurs have associated with Nausea, ½ with high frequency
- 30% were associated with vomiting
- High prevalence of migraine in individuals with nausea (OR 3.2 95%CI: 2.6-3.8)
- The association is not related to NSAID usage
- Frequency of nausea is related to typical migraine feature headache

Unilaterality OR 1.4 Pulsatility OR 2.8 Severe intensity OR 2.7

Aggrev by activity OR 4.75 Photophobia OR 2.7 Phonophobia OR 1.7

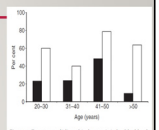


Figure 1 Frequency of idiopathic dyspepsia in healthy blood donors (■) and migraine patients (□) in different age groups.

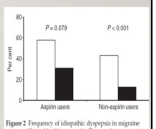


Figure 2 Frequency of idiopathic dyspepsia in migraine patients (□) and healthy controls (■) according to aspirin intake.

GASTROINTESTINAL SYMPTOMS IN MIGRAINE

FUNCTIONAL DYSPEPSIA OR STRUCTURAL LESION ?

ARE GI SYMPTOMS RELATED TO FUNCTIONAL ?

- 24 hour pH meter test of the gastroesophageal tract/ morphologically with esophagogastroduodenoscopy → mostly normal

Migraine prevalence in control individuals and subgroups of patients

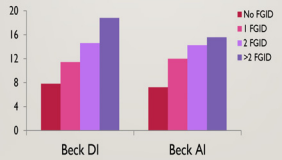
	n	%
Control	310	11
Pt with reflux-like dyspepsia	106	8
ulcer-like dyspepsia	122	7
dysmotility-like dyspepsia	118	23

Endoscopy. 2005;37(7):622-5.
Headache 1996; 36(7):442-5.

Park JW Gut and Liver, 2013, 7(6): 668-674

ARE GI SYMPTOMS RELATED TO FUNCTIONAL ?

Functional GI disorders	Number	prevalence
Functional dyspepsia	26/109	23.9%
Functional Nausea/vomiting disorders	27/109	24.8%



Sohn JH, Front Neurol. 2017 Oct 3;8:526

ARE GI SYMPTOMS RELATED TO STRUCTURAL?

- Gastroesophageal reflux disorder and Gastric ulcer were more prevalent in the migraine group, compared with controls ($p < 0.0001$).

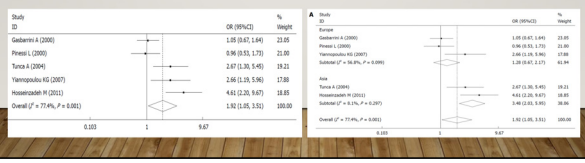
TABLE 3 | Comparison of physician-diagnosed GI disorders between the headache groups and controls.

GI disorder diagnosis	Migraine[a,c] (*N* = 168)		TTH[a,c] (*N* = 168)		Control[a,b] (*N* = 336)		*p*-Value[1]	*p*-Value[2]
	N	%	*N*	%	*N*	%		
GERD	45	26.79	20	11.90	36	10.71	<0.0001	<0.0001
Gastritis	85	50.60	103	61.31	207	61.61		
Gastric ulcer	20	11.90	20	11.90	19	5.65		
IBS	3	1.79	4	2.38	2	0.60		
FGID	6	3.57	17	10.12	25	7.44		
Liver disease	0	0.00	0	0.00	21	6.25		
Etc.	9	5.36	4	2.38	26	7.74		

GASTROINTESTINAL DISORDER & MIGRAINE

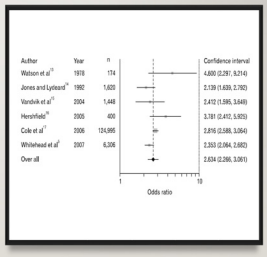
HELICOBACTER PYLORI AND MIGRAINE

- Infection rate of H. pylori is higher in migraine (45% vs 33%)
- CagA-positive strains and Asian > Europeans
- pathogen strain CagA positive especially in MWA 41% vs Control 17%
- migraine attack improved after eradication treatment
- No clinical difference between cononized and non clonoized migraine patients



IRRITABLE BOWEL SYNDROME AND MIGRAINE

- IBS common in female, younger, psychiatric comorbidity
- 35-50% of patients reported have chronic headache
- Migraine prevalence is higher in IBS patients (25%-50% vs s 4%-19% OR 2.66)



GASTROPRESIS AND MIGRAINE

- Gastroparesis : delayed emptying of the stomach in the absence of mechanical obstruction, and its clinical manifestations include nausea, vomiting
- GA is female predominance, 1/3 were remained idiopathic
- In migraine, concerns on the absorption of analgesics and the effect on the therapeutic efficacy related to gastric stasis

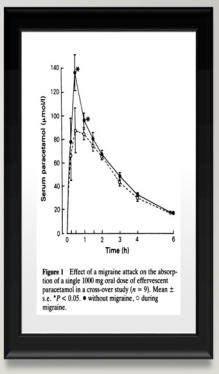


Figure 1 Effect of a migraine attack on the absorption of a single 1000 mg oral dose of effervescent paracetamol in a cross-over study ($n = 9$). Mean ± s.e. *$P < 0.05$. ● without migraine, ○ during migraine.

Gastroenterology. 2004;127(5):1592-622.
Br J Clin Pharmacol. 1984;18(6):867-71.

GASTROPRESIS AND MIGRAINE

- Interictal period : normal or delayed gastric emptying time
  Ictal period : delayed
- delay times were significantly correlated with the intensity of headache, nausea and photophobia
- suggesting an alteration in enteric autonomic function ?

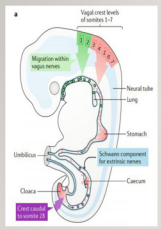
Summary of gastric emptying studies in migraineurs.

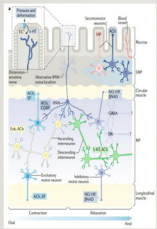
		Time to half emptying
Method of detection	Headache group	$t_{1/2}$ (min)
Epigastric impedance (33)	• Mild attack	< 30
	• Moderate or severe attack	> 30
	• Control	9 ± 5
Gastric scintigraphy (42)	• Interictal	188 8
	• Ictal	148 9
	• Controls	111 8
Gastric scintigraphy (43)	• Interictal	243
	• Spontaneous migraine	124
	• Induced migraine	182
	• Control	112

Br J Clin Pharmacol. 1990;30(3):405-9.
Cephalalgia. 2013;33(6):408-15.
Headache. 2007;47(10):1443-6.
Headache. 2006;46(1):57-63.

PATHOPHYSIOLOGIC RELATION BETWEEN GUT AND MIGRAINE

ANATOMICAL ASPECT : BRAIN AND GUT



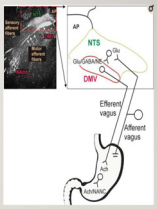


- Enteric nervous system is derived from neural crest cells and secretes similar neurotransmitters including acetylcholine, dopamine, serotonin, and CGRP

Nat Rev Neurosci. 2018;19(9):552-65.

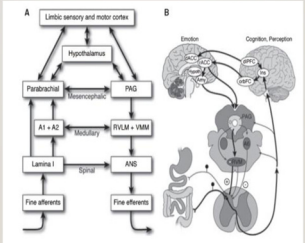
ANATOMICAL ASPECT : BRAIN AND GUT

- Sensory information from the GI tract is transmitted through vagal afferent neurons via glutamatergic synapses to terminate in the nucleus tractus solitaries (NTS).
- 2nd -order neurons integrate synaptic inputs from vagal afferent neurons as well as higher CNS centers involved in autonomic regulation including the caudal ventrolateral medulla and the paraventricular nucleus of the hypothalamus paraventricular nucleus



Ann Rev Physiol. 2006;68:279-305.

ANATOMICAL ASPECT : MIGRAINE AND GI SYMPTOM



AUTONOMIC NERVOUS SYSTEM AND MIGRAINE

- Autonomic nervous system (ANS) dysfunction, which has previously been linked to both headache and GI complaints, might be a common mechanism
- Migraineurs may be prone to ANS hypofunction
- ANS dysfunction may be related to disability in migraine patients :

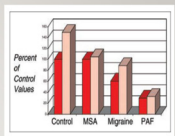


Fig 1.—Schematic summary of plasma norepinephrine levels. MSA indicates multiple system atrophy; PAF, pure autonomic failure.

Table 2.—Most Commonly Reported Clinical Symptoms Related to Postural Changes in Patients with Pure Autonomic Failure, Multiple System Atrophy, and Migraine*

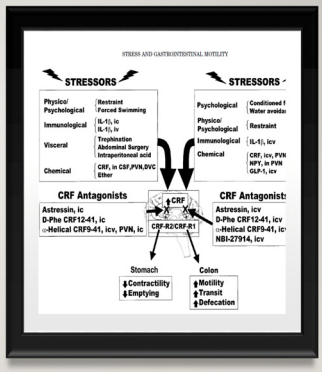
Symptom	Pure Autonomic Failure (n = 32)†	Multiple System Atrophy (n = 40)†	Migraine‡
Syncope	91	45	9
Dizziness/lightheadedness	84	53	70
Suboccipital/paracervical "coat hanger" neck pain	81	53	55
Visual disturbances	75	53	45

Neurology. 2002;58(3):422-7.

Peroutka SJ. Migraine: a chronic sympathetic nervous system disorder. Headache. 2004;44(1):53-64.

THE ROLE OF CRF IN MIGRAINE

- CRF signalling system is activated by stressors (e.g. infections, psychological, energy depletion) and plays an important role in mediating autonomic activation and vagal alterations that impact on gut motility



Neurogastroenterol Motil. 2001 Jun;13(3):229-36.
Am J Physiol. 1997 Jul;273(1 Pt 1):G191-6.

ROLE OF CGRP IN GI MOTILITY

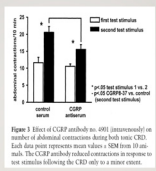


Figure 3 Effect of CGRP antibody no. 4901 (intravenously) on number of abdominal contractions during both tonic CRD. Each data point represents mean values ± SEM from 10 animals. The CGRP antibody reduced contractions in response to test stimulus following the CRD only to a minor extent.

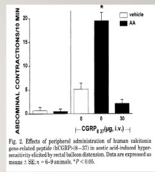


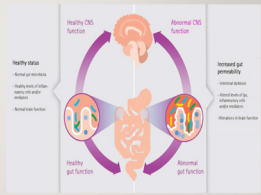
Fig. 2. Effects of peripheral administration of human calcitonin gene-related peptide (hCGRP)-(8–37) in acetic acid-induced hypersensitivity elicited by rectal balloon distention. Data are expressed as means ± SE; n = 6–9 animals. *P < 0.05.

- CGRP is an important neurotransmitter of the inhibitory sensory neuron, and it has been hypothesized that disorders of reservoir functions may result in symptoms of functional dyspepsia

Front in Neurol. 2014. 21

ROLE FOR GUT BARRIER IN MIGRAINE : MICROBIOTA

- IBS and other GI disorder : inflammatory cytokine induced increased permeability
- Increased permeability is related to food stress, exercise
- Gut microbiota can alter neurotransmitter level ; 5HT and CGRP ?



EPISODIC GI SYNDROME AND MIGRAINE

INFANTILE COLIC, CYCLIC VOMITING SYNDROME, ABDOMINAL MIGRAINE

CVS, ABDOMINAL MIGRAINE AND MIGRAINE

- Migraine headache, abdominal migraine and CVS are functional disorders that seem to be manifestations of a common diathesis
- Their nosological distinction is based on their predominant symptoms: headache in migraine, intense abdominal pain in abdominal migraine, and nausea and vomiting in CVS
- The prevalence of CVS, abdominal migraine and migraine headaches peak at ages 5, 10 and 11 years respectively
- Migraine headaches are reported in 24– 70% of adults with CVS
- autonomic nerve dysfunction was common in adult CVS patients

Journal of pediatric gastroenterology and nutrition. 1995;21(4):454-8.
Boles RG, Adams K, Li BU. 2005;133A(1):71-7.
The Journal of pediatrics. 1999;134(5):567-72.

CVS AND MIGRAINE

- Migraine headaches are reported in 24– 70% of adults with CVS OR: 7.5
- Autonomic nerve dysfunction was common in adult CVS patients
- younger onset age and headache during CVS attacks may have increased risk of migraine development.

Table 2 Summary of abnormalities in autonomic function test observed in 9/21 adult patient with cyclic vomiting syndrome

			Orthostatic test		Parasympathetic function			
Case #	Age	Gender	BP change	HR change	Deep breathing (E/I index)	Valsalva index	Posture index	Sympathic skin response
1	21	F	↓2/7 mmHg	**↑42 beats min⁻¹**	1.37	1.67	1.32	Present
2	44	F	**↓31/9 mmHg**	↑15 beats min⁻¹	**1.14**	1.23	1.07	**Absent**
3	24	M	**↑13/10 mmHg**	↑12 beats min⁻¹	**1.18**	1.93	1.41	**Absent**
4	44	F	**↓28/18 mmHg**	No change	**1.07**	1.51	1.07	**Absent**
5	43	F	↑7/5 mmHg	↑14 beats min⁻¹	**1.10**	1.86	1.17	Present
6	50	F	↓11/2 mmHg	↑15 beats min⁻¹	**1.04**	**1.18**	**1.01**	**Absent**
7	50	F	↓6/2 mmHg	↑24 beats min⁻¹	**1.21**	1.70	**1.02**	**Absent**
8	27	F	↑11/8 mmHg	**↑35 beats min⁻¹**	1.58	1.59	1.18	**Absent**
9	19	F	↑15/7 mmHg	↑16 beats min⁻¹	1.43	1.73	1.50	**Absent**

CVS AND MIGRAINE IN ADULT POPULATION

APPLICATION OF ROME III CRITERIA FOR CVS

Park JW Gut and Liver, 2013, 7(6): 668-674

Table 2. Prevalence of Functional Gastrointestinal Symptoms in 10 Migraine Patients

Disorder	Value
Functional gastroduodenal disorders	46 (42.2)
FD	26 (23.9)
Nausea and vomiting disorders	27 (24.8)
CIN	13 (11.9)
Functional vomiting	5 (4.6)
CVS	9 (8.3)

INFANTILE COLIC AND MIGRAINE

Neurology. 2012 Sep 25; 79(13): 1392–1396.
JAMA. 2013 Apr 17;309(15):1607-12

- Infantile colic : early life of migraine headache ?
- Maternal history of migraine : 2.6 time higher of LR of infantile colic
- Child with migraine headache more likely to have experience of colic than control :

Table 3. Multivariable Odds Ratios of Primary Headaches by Primary Source for Infantile Colic Diagnosis

	Outcome, OR (95% CI)			
	According to Parent Interview		According to Health Booklet	
	Migraine	Tension-Type Headache	Migraine	Tension-Type Headache
Presence of infantile colic	6.61 (4.38–10.00)	1.46 (0.82–2.32)	6.68 (4.40–10.13)	1.48 (0.80–2.36)
Primary headache in first-degree relatives	6.64 (4.30–10.25)	0.65 (2.34–5.71)	6.98 (4.50–10.81)	3.84 (2.45–6.02)
Mixed formula feeding	1.65 (1.09–2.48)	2.23 (1.44–3.44)	1.66 (1.10–2.51)	2.25 (1.45–3.49)
Gestational age at birth (per 1 week)	1.04 (0.93–1.15)	1.23 (1.07–1.41)	1.05 (0.94–1.16)	1.24 (1.10–1.43)
Infantile colic in first-degree relatives	1.10 (0.65–1.88)	1.37 (0.77–2.44)	1.04 (0.61–1.78)	1.29 (0.72–2.32)

SUMMARY

- About ¾ of migraineurs have associated with Nausea, ½ with high frequency
- The association of GI symptom is increased with headache frequency and related to typical migraine features
- Functional dyspepsia or structural lesion ? : still inconclusive
- Migraine is related to H pylori infection, IBS, and Gastroparesis
- Contribution of Enteric nervous system and autonomic dysfunction in migraine
- CVS, abdominal migraine and Migraine headache may seem to be manifestations of a common diathesis