Chronic Idiopathic Nausea of Childhood

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Objectives To compare children with primary, chronic idiopathic nausea to those with secondary nausea associated with functional abdominal pain.

Study design Retrospective chart review of 45 children with a primary complaint of chronic nausea several times per week. Comparisons were made to prospectively collected data on 49 children with functional abdominal pain and comorbid nausea.

Results The majority of those affected were adolescent Caucasian females. Subjects with chronic nausea had a more severe presentation with daily 88% (vs 26%) and constant 60% (vs 10%) nausea ($P < .001$), one-half with peak morning intensity. In the chronic nausea group, 62% had migraines, and 71% (vs 22%) had familial migraines ($P < .001$), 36% had postural tachycardia syndrome and 27% cyclic vomiting syndrome. Both groups suffered comorbid symptoms (anxiety, dizziness, fatigue, and sleep problems). The chronic nausea cohort underwent extensive, negative medical evaluations.

Conclusions Chronic idiopathic nausea of childhood is a poorly described symptom. Patients with primary (vs secondary) chronic nausea were more likely Caucasian, older adolescent females with severe, daily nausea and comorbid conditions such as anxiety, dizziness, and fatigue as well as significantly more migraine features. Chronic nausea is a major, disabling symptom that requires increased recognition as a separate functional entity. Future studies may need to focus on comorbid conditions including migraine and dysautonomia. *(J Pediatr 2014;164:1104-9)*.

Chronic nausea is a poorly characterized symptom in children. Nausea is defined as an extremely unpleasant sensation that often precedes vomiting but may occur as an isolated symptom.[1] A variety of stimuli such as toxins, mucosal injury, visceral pain, inflammation, drugs, motion, memories, and emotions may trigger nausea. Although nausea is a highly subjective sensation, animal studies and human studies on motion sickness define certain physiological correlates.[1,2] Some of these include autonomic arousal, endocrine changes, gastrointestinal (GI) dysmotility, and gastric dysrhythmias. Functional magnetic resonance imaging (fMRI) studies describe the neurobiology of motion-induced nausea and shed some light on the complex, neural pathways of nausea.[3] Still, functional nausea is only described as a clinical symptom without a distinct, underlying physiologic mechanism.

Adult chronic idiopathic nausea is defined as bothersome nausea, occurring several times per week, typically not associated with vomiting and without any identifiable organic cause.[4] Adult 2006 Rome III criteria classify chronic idiopathic nausea under the category of functional nausea and vomiting disorders along with functional vomiting and cyclic vomiting syndrome (CVS).[5] Prior to 2006, adult Rome II criteria categorized nausea as a symptom of dyspepsia. The pediatric Rome III criteria do not recognize chronic idiopathic nausea as a separate category even though children often experience refractory nausea that becomes their primary, debilitating complaint.

We recently demonstrated that childhood nausea frequently occurs as a secondary complaint with other pain-associated, functional gastrointestinal disorders (FGIDs) such as functional dyspepsia, irritable bowel syndrome, abdominal migraine (AM), and functional abdominal pain (FAP).[6] Of the pain-associated FGIDs, only AM includes nausea as supporting diagnostic criterion, but like CVS, the associated nausea is usually confined to the discrete episode of pain or vomiting rather than that occurring on a chronic, daily basis. Similarly, chronic nausea is a common complaint in children with postural tachycardia syndrome (POTS).[7,8] Nausea as a secondary complaint associated with FGIDs is likely to go unrecognized and under investigated.

There is a knowledge gap regarding proper work-up and treatment options for children with nausea.[9] We hypothesized that children with primary chronic nausea suffer more frequent and severe symptoms that impact daily functioning, have more

5-HT_3	5-hydroxytryptamine	FGIDs	Functional gastrointestinal disorders
AM	Abdominal migraine	FHx	Family history
AP	Abdominal pain	GI	Gastrointestinal
CHW	Children's Hospital of Wisconsin	MRI	Magnetic resonance imaging
CT	Computed tomography	PMHx	Personal history
CVS	Cyclic vomiting syndrome	POTS	Postural tachycardia syndrome
FAP	Functional abdominal pain		

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comorbid illnesses, and undergo more extensive diagnostic testing compared with those with secondary nausea. We aimed to describe the demographics, clinical presentation, comorbid disorders, diagnostic work-up, and treatment response in children with primary chronic nausea and compare them with children with FAP who have nausea as a secondary complaint.

Methods

Participants included pediatric patients, ages 8-18 years, followed in the outpatient Pediatric Neurogastroenterology Clinic at Children's Hospital of Wisconsin (CHW), between March 2006 and April 2012. The human research Institutional Review Board at CHW approved this study. Eligibility criteria for the chronic nausea group included a primary complaint of chronic nausea, occurring several times per week for a minimum of 2 months. Forty-five subjects met the inclusion criteria for the chronic nausea group, and we retrospectively reviewed the medical records of these after excluding 2 patients with a documented organic etiology. Inclusion criteria for the abdominal pain (AP) comparison group were as follows: a primary complaint of AP for a minimum of 2 months with nausea as part of their illness (secondary complaint). Forty-nine subjects met the inclusion criteria for the AP group after excluding 4 patients with an organic etiology. For comparison, we categorized patients as having daily nausea or constant nausea (continuous nausea throughout the day vs episodic) in both the chronic nausea and AP groups. Exclusion criteria for both groups were as follows: patients with developmental delay or a neurologic disorder, patients on a medication that could cause nausea, and those with a documented disorder that could explain the nausea and/or AP (ie, *Helicobacter pylori* gastritis, celiac disease, eosinophilic esophagitis/gastroenteritis, and inflammatory bowel disease).

We retrospectively collected data on demographics, medical history, laboratory work, diagnostic imaging, endoscopic biopsies, and treatment response from systematic chart reviews of both groups.

In both groups, prospective data from nonvalidated, parent-reported questionnaires were available on sleep and anxiety. The specific questions addressing sleep problems included: does your child have difficulties falling asleep at night and/or frequent night-time awakenings. If the parent answered yes to 1 or both of these questions, the child was considered to have sleep problems as perceived by the parent. We asked the following questions as a measure of anxiety: (1) Is your child anxious? and/or (2) Does your child worry about grades, schoolwork, or new situations? Prospectively collected (nonvalidated) clinical intake questionnaires were also reviewed on the 49 patients with FAP and nausea as a secondary complaint (AP group). These parent-reported questionnaires incorporated specific questions on nausea frequency, related GI symptoms, comorbid symptoms, family history (FHx), and school absence (reported as number of school days missed because of symptoms over the 2 months prior to evaluation). An average of 2 or more days per month of missed school was considered to adversely affect school performance. For the chronic nausea group, retrospective data was collected from a standardized checklist that includes the symptoms reported in this study such as nausea frequency, co-morbid symptoms, and school absence (number of school days missed in the past month because of symptoms). Two or more missed days was considered to adversely affect school.

Laboratory evaluation was defined as screening (ie, complete blood cell count, electrolytes, hepatic transaminases, lipase, celiac screen) or extensive (ie, metabolic or endocrine serum tests). Laboratory values were considered normal or abnormal based on norms established by CHW laboratory. Results of diagnostic imaging evaluation were collected for all subjects. Abdominal ultrasound and upper GI contrast study were performed in a high percentage of subjects in both groups. Therefore, any additional imaging study performed was defined as extensive.

Treatment response to common first-line medications in patients with nausea and/or AP, such as proton pump inhibitors and 5-hydroxytryptamine (5-HT_3) antagonists (ondansetron) were analyzed in the chronic nausea group. We also analyzed response to amitriptyline, another frequently used medication in patients with pain-associated FGIDs.[10] Although it is standard to document nausea treatment response for the chronic nausea group in our clinic, it is not for the AP group, whose primary symptom was AP. In the chronic nausea cohort, response to each drug was assessed by the clinic physician at the initial (if tried prior to referral) and at each of subsequent visits after interviewing the patient and parent. Drug response was graded and defined as some (at least 25%-50% symptom reduction) or good (>50% improvement) and documented in the clinic note.

To compare 2 groups, a Mann–Whitney U test was performed for continuous variables and χ^2 analysis or Fisher exact test was used for categorical variables. Median, IQR, and frequencies were reported for comparisons. Statistical analysis was performed with SPSS (SPSS Inc, Chicago, Illinois); SAS (SAS Institute, Cary, North Carolina); and StatXact (SAS Institute). An unadjusted P value of $<.05$ was considered significant.

Results

The median age of symptom onset was not different between the 2 groups. However, in the chronic nausea cohort, the median age of presentation was higher than in the AP cohort: 15 (12.5-16.0) years versus 12 (10.0-15.0) years (**Table I**), representing a delay in time to GI consultation.

Clinical Characteristics

The number of subjects complaining of daily nausea and constant nausea were much higher in the chronic nausea