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SHORT COMMUNICATION

Fludrocortisone improves nausea in children with orthostatic intolerance (OI)

John E. Fortunato · Hossam A. Shaltout · Megan M. Larkin · Peter C. Rowe · Debra I. Diz · Kenneth L. Koch

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Abstract
Introduction/Results In 17 patients, chronic idiopathic nausea was associated with orthostatic intolerance (OI) by abnormal tilt table tests (88%) or gastric dysrhythmias (71%). After fludrocortisone treatment, there was >26% nausea improvement in 71%, 1–25% in 6%, and no improvement in 24%. In six subjects, EGGs repeated after >50% nausea improvement all remained to be abnormal, suggesting nausea is independent of gastric dysrhythmias.
Conclusion Association of EGG abnormalities and OI in this subset of nausea patients suggests a generalized disturbance of autonomic regulation.

J. E. Fortunato (✉) · M. M. Larkin
Department of Pediatrics, Division of Pediatric Gastroenterology and Nutrition, Wake Forest University School of Medicine, Wake Forest University Medical Center Blvd, 27101 Winston-Salem, NC, USA
e-mail: jfortuna@wfubmc.edu

H. A. Shaltout · D. I. Diz
Hypertension and Vascular Disease Center, Wake Forest University School of Medicine, Winston-Salem, NC, USA

H. A. Shaltout
Department of Pharmacology, School of Pharmacy, Alexandria University, Alexandria, Egypt

P. C. Rowe
Department of Pediatrics, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

K. L. Koch
Department of Internal Medicine, Section on Gastroenterology, Wake Forest University School of Medicine, Winston-Salem, NC, USA

Keywords Fludrocortisone acetate chronic idiopathic nausea · Orthostatic intolerance (OI) · Postural orthostatic tachycardia syndrome (POTS) · Neurally mediated hypotension (NMH) · Electrogastrography · Tilt table testing

Introduction

Patients with nausea represent a heterogeneous population encompassing both organic diseases, such as mucosal inflammation or metabolic disorders and functional gastrointestinal disorders, referred to as chronic idiopathic nausea. Because the mechanism of chronic idiopathic nausea is not understood, treatments have been empirical and less effective than desired [1]. Electrogastrography has been used to determine if symptoms such as nausea and vomiting are associated with abnormal gastric rhythms that disrupt normal gastric peristalsis [2].

The aim of this retrospective study was to determine if children with chronic idiopathic nausea and orthostatic intolerance (OI) by tilt-table test demonstrated abnormal gastric myoelectrical activity by EGG. We also sought to examine the effect of treating OI with fludrocortisone on the severity of nausea symptoms and persistence of EGG abnormalities.

Methods

From a retrospective chart review of 33 pediatric patients at Wake Forest University who underwent EGG recordings from July 2008 to June 2009 for unexplained nausea, 17 subjects were selected with symptoms of dizziness or lightheadedness, OI by tilt table test, and treated with

fludrocortisone for OI for a minimum of 4 weeks. The study was approved by the Wake Forest University Institutional Review Board. All patients had undergone EGD with biopsies before EGG recording.

Tilt-table

Each subject was positioned supine for 15 min before the tilt test began (0–70° upright for up to 45 min). Heart rate and blood pressure were recorded every 2 min, and symptoms every 5 min after upright tilt until brought back to the supine position.

Postural orthostatic tachycardia syndrome (POTS) was defined as a heart rate greater than 120 bpm or a 30-bpm increase from baseline (lowest heart rate during 15 min supine period) in the first 10 min of upright tilt, sustained for >2 min, together with reproduction of orthostatic symptoms. Neurally mediated hypotension (NMH) was defined as a 25 mmHg decrease in systolic blood pressure from baseline (systolic blood pressure during 15 min

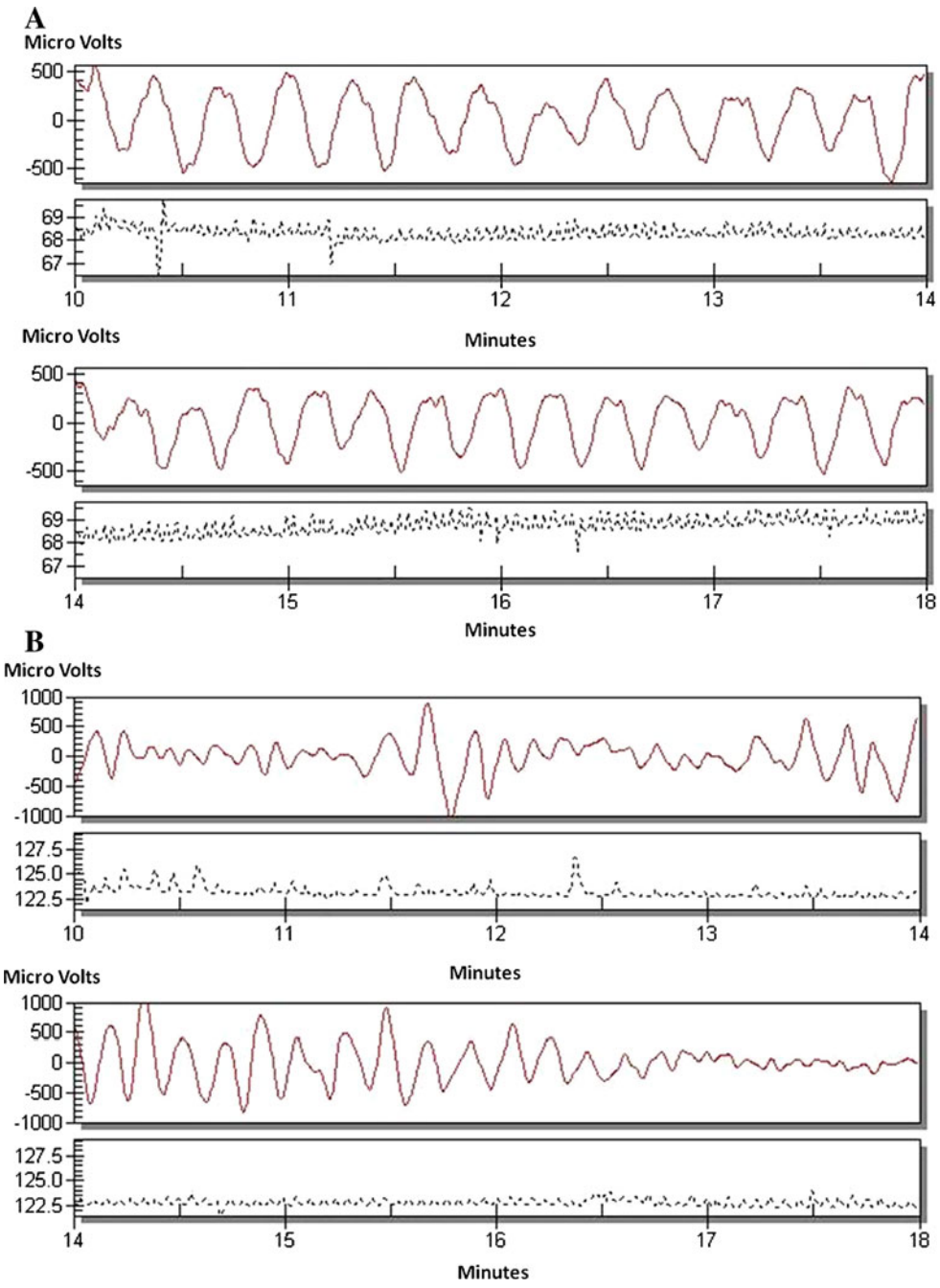

Fig. 1 Representative example of a subject with a normal electrogastrogram (EGG) with gastric waves ranging in frequency from 2.5 to 3.75 cpm (**a**) and a subject with tachygastria with gastric waves ranging from 3.75 to 10 cpm (**b**). The *upper* tracing in each row represents the EGG, while the *lower* tracing in each row corresponds to a patient's respirations

supine period) sustained for >2 min, without an associated increase in heart rate, and associated with reproduction of orthostatic symptoms.

EGG with water load test

EGG was performed and recordings obtained as described [3]. Frequencies were defined as bradygastria (1.0–2.5 cpm), normal (2.5–3.75 cpm), and tachygastria (3.75–10 cpm), and duodenal or respiratory frequencies (10–15 cpm) and reported as normal or abnormal (tachygastria, bradygastria, or mixed dysrhythmia). An example of a subject from the series with a normal EGG and an EGG demonstrating tachygastria is shown in Fig. 1.

Results

Patient demographics, symptoms, and EGD and UGI test results are shown in Table 1. The median age (range) was 14 years (11–17 years) and predominantly female (71%), with the duration of nausea and dizziness of 12 months (1–156 months) at the time of presentation. Nausea was the predominant symptom in all patients; however, abdominal pain, constipation, and vomiting were noted in 88, 53, and 47% of patients, respectively. Syncope was reported in 3 of 17 patients. EGD biopsy findings included either normal histopathology or mild, non-specific inflammatory changes, not considered the likely cause of the nausea. UGI was performed in seven patients, and all were normal.

Fifteen out of 17 patients had abnormal tilt-table testing. Two patients did not meet criteria for POTS or NMH, but had borderline 29 bpm increase in heart rate from baseline and lightheadedness during the tilt. All 17 were started on fludrocortisone (0.1–0.2 mg/day for a minimum of 4 weeks). Of the 15 abnormal tilt-table studies, the most prevalent diagnosis was POTS ($n = 13$), followed by co-existing POTS/NMH ($n = 5$), and then NMH alone ($n = 2$) (Fig. 2a). Gastric slow waves or pacesetter potentials coordinate normal 3 cycle per minute (cpm) gastric peristaltic contractions [3]. In contrast, gastric dysrhythmias are defined by abnormally rapid or slow gastric electrical events, respectively, termed tachygastrias and bradygastrias. Twelve out of 17 patients (71%) had abnormal EGGs of which the majority demonstrated mixed dysrhythmias (Fig. 2b). The median volume (range) of water consumed until patients perceived their stomachs as "full" was 525 ml (100–800 ml). Of the 16 patients with nausea not associated with dizziness (tilt table test not performed) from the original chart review of 33, 77% had abnormal EGG results.

The median (range) duration of follow-up after starting fludrocortisone was 11 weeks (4–54 weeks). On follow-up after 4 weeks of treatment, there was no nausea improvement in 4 patients (24%), 1–25% improvement in one patient (6%), 26–50% improvement in one patient (6%), and greater than 50% improvement in 11 patients (65%) (Fig. 2c), with little change in severity of symptoms at subsequent visits. Of the four subjects with no improvement, one patient had decreased nausea with beta-blocker

Table 1 Patient demographics, symptoms, and results of previous GI examinations

Patient	Sex	Age	Duration of symptoms (mos)	Additional symptoms	EGD	UGI
1	F	16	2	A	Normal	
2	M	12	12	V, C	Normal	
3	F	12	6	C	Normal	
4	F	14	5	A, V	Mild esophagitis	Normal
5	M	17	36	A, V, C	Normal	Normal
6	M	11	24	A, V	Normal	
7	M	14	3	A, C	Normal	Normal
8	M	16	12	A, C, S	Normal	Normal
9	F	17	156	A, V, S	Normal	
10	F	16	24	A	Normal	
11	F	12	36	A, V	Normal	
12	F	17	1	A, V	Mild gastritis	
13	F	13	6	A, V, C	Mild gastritis	Normal
14	F	14	36	A	Normal	Normal
15	F	13	24	A, C	Normal	Normal
16	F	17	12	A, C, S	Mild gastritis	
17	F	14	6	A, C	Mild gastritis	

A indicates abdominal pain, *V* vomiting, *C* constipation, *S* syncope

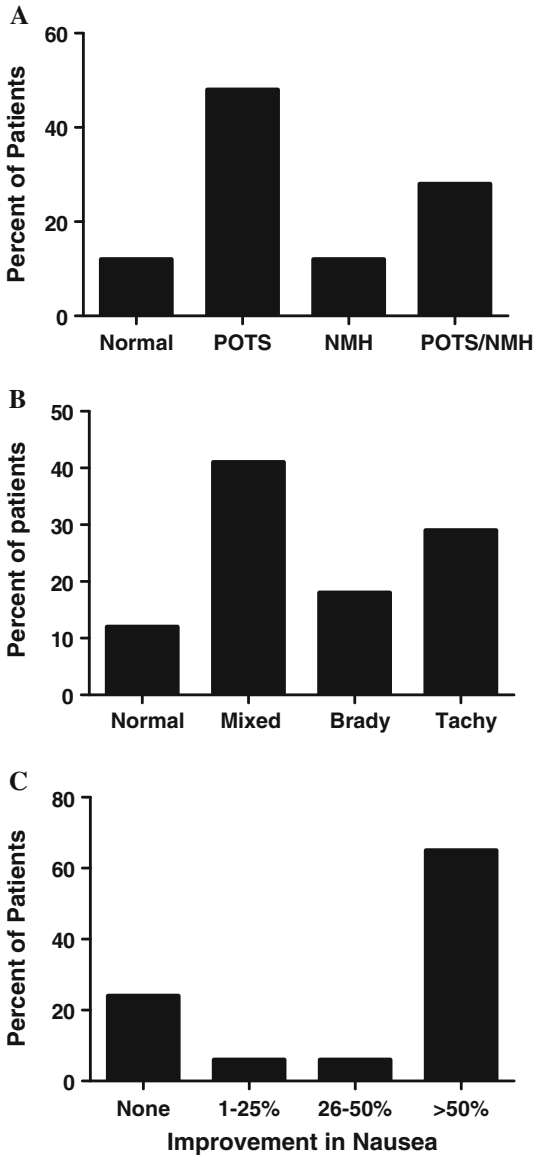

Fig. 2 **a** Tilt table findings among patients with chronic idiopathic nausea. The majority of patients met criteria for POTS with nearly half of those meeting criteria for NMH as well. Only two patients had findings consistent with NMH alone. **b** EGG rhythms in chronic idiopathic nausea patients. The most common gastric dysrhythmia observed was a mixed pattern followed by tachygastria, then bradygastria. **c** Improvement in nausea after 4 weeks of fludrocortisone. Most subjects described some improvement in nausea. Four patients demonstrated no improvement, 1 patient showed improvement between 1 and 25%, one patient showed between 26 and 50%, and 11 patients with >50%

therapy. One patient who described >50% decrease in nausea severity after the initial visit subsequently developed worsening nausea requiring the addition of a beta-blocker, which successfully relieved the nausea. Of the 11 patients who reported >50% decrease in nausea severity, repeated EGG was performed in six. All six EGGs remained to be abnormal.

Discussion

The etiology of chronic idiopathic nausea is not well defined, and consequently, neither is the treatment. We described a group of patients with chronic idiopathic nausea and OI in whom there was symptomatic improvement of nausea when the OI was treated with fludrocortisone acetate. The majority of patients also demonstrated gastric dysrhythmias that were not corrected with therapy for OI. These subjects may represent a new phenotype of "pediatric nausea" not previously identified: OI associated gastric dysrhythmias and nausea.

Since 65% of OI patients demonstrated >50% improvement in nausea after treatment with fludrocortisone, screening for OI symptoms may represent an important component of gastroenterology evaluations. Our results are consistent with those of Sullivan et al. [4] in which 78% of pediatric patients with upper gastrointestinal symptoms (including abdominal pain and nausea) and OI experienced complete resolution of gastrointestinal symptoms when NMH or POTS was treated. A recent study suggested that the diagnostic criteria for OI/POTS in adults may be inadequate for children and that an increase in heart rate greater than 45 bpm may be a more appropriate cutoff to define POTS [5]. However, symptomatic improvement of nausea was achieved with OI treatment in our study using the adult criteria. This underscores the need to better define both the EGG and autonomic characteristics of pediatric patients with nausea and OI.

The high percentage of abnormal EGGs (71%) coexisting with OI raises the possibility that autonomic dysregulation may underlie both abnormalities, a concept supported by a demonstration that EGG changes accompany tilt table testing in children with POTS versus those without POTS [6]. Interestingly, in our study, patients with nausea alone without symptoms of OI also had a high percentage of abnormal EGGs (77%) possible representing a different mechanism for nausea. These patients did not undergo tilt table testing, leaving diagnosis of POTS or NMH remains to be unclear. Furthermore, gastric dysrhythmias did not correct after fludrocortisone despite improvement in nausea, although correction of the OI after treatment was not confirmed by repeated tilt table testing.

In conclusion, evidence that OI is associated with chronic idiopathic nausea and gastric dysrhythmia may reflect common neurogenic or autonomic nervous system origins. While this may reflect a unique link between autonomic regulation and gastric function, the study is limited by incomplete data collection attributed in large part to its retrospective nature. Thus, the authors are currently conducting a prospective study to examine the relationship between OI and chronic idiopathic nausea. In particular, the observation that correction of nausea is

independent of correction of gastric dysrhythmias requires further confirmation of these relationships. Importantly, the observation that fludrocortisone reduced nausea in OI patients supports the need for a future randomized, placebo-controlled trial to determine the possibility of its use as a management tool for these patients.

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