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GASTROENTEROLOGY

Post-infectious gastroparesis: Clinical and electerogastrographic aspects

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Abstract

Aims: Post-infectious gastroparesis (PIGP) is a subgroup of idiopathic gastroparesis. The aim of this study was to identify post-viral gastroparesis and to characterize clinical and electrogastrographic aspects of the disease and their usefulness as a diagnostic tool.

Methods: Patients diagnosed with gastroparesis were defined as PIGP if they had a clear history of an acute viral illness prior to the development of their symptoms. All patients underwent evaluation of gastric emptying and electrogastrography (EGG).

Results: Seven patients met the criteria for diagnosis of PIGP. Patients' age ranged from 3 months to 47 years. A specific virus was identified in two patients (one cytomegalovirus [CMV] and one Epstein-Barr virus [EBV]). EGG was pathological in six out of seven patients. In four out of seven patients, symptoms resolved spontaneously within 4 weeks to 12 months, three patients had improved but were still symptomatic at the time of the writing of this work.

Conclusion: We conclude that post-infectious gastroparesis is an uncommon and often over looked condition. It is self-limiting in most cases. EGG is pathological in most patients.

Introduction

Normal gastric emptying is due to a complex interaction between various regions of the stomach and duodenum. These include a coordinated series of events starting with fundic accommodation of ingested food, antral contractions, pyloric relaxation, and antroduodenal coordination.[1] Interruption of this pathway may lead to altered gastric empting and subsequent disease or symptoms.

Delayed gastric empting in the absence of mechanical obstruction is called gastroparesis. The most common symptoms associated with gastroparesis are nausea and vomiting, but early satiety, abdominal discomfort and bloating may also be present.[1]

Post-viral gastroparesis (PVGP), or post-infectious gastroparesis in cases where a virus is not isolated (PIGP), is regarded as a subgroup of idiopathic gastroparesis. It usually presents with persistent vomiting and weight loss after an acute self-limiting, presumably viral illness.[2,3] By the time the patient comes to clinical attention, the acute illness has often resolved and the causative agent is difficult to detect. Diagnosis is based on the clinical setting, exclusion of other causes for persistent vomiting, and confirmation of delayed gastric emptying. Viruses of the herpes family, gastrointestinal and respiratory viruses have all been implicated in this disease. Patients can remain symptomatic for months or years, and there is no effective treatment at this time.[1–6] While the presentation of gastroparesis and the prolonged symptoms may cause a great deal of consternation and the performance of a large battery of tests, the disease appears to be self-limiting in the majority of patients. In children the duration tends to be shorter and the disease itself milder. In fact, PIGP may be a common and unrecognized disorder, especially at the milder end of the spectrum of disease. Some patients may have a short duration of symptoms and therefore never reach evaluation. Others might reach evaluation, but will not be diagnosed if gastric emptying is not evaluated.

The precise mechanism causing PVGP is unknown. Two previous studies in small cohorts of children serve as the major source of information on this disease to date. The role of gastric dysrhythmias in gastroparesis, or specifically in PIGP, has not been defined. Electrogastrography (EGG) is a technique that measures slow wave potentials originating from the stomach and analyzes their frequency. These slow wave potentials are the initiators of gastric contractions. Disruption of gastric slow wave rhythm correlates with impaired gastric emptying.[7] Previous studies did not evaluate the EGGs during post-viral gastroparesis.

The aim of this study was to identify patients with post-infectious gastroparesis and to assess clinical symptoms, the course of the disease and electrogastrographic characteristics of this disorder.

Methods

Patients referred to three pediatric or adult gastroenterology outpatient motility clinics for persistent unexplained vomiting were

evaluated for gastroparesis. All patients underwent a detailed interview, which included an evaluation for sudden disease onset and infectious diseases at the time of symptom onset. Patients with a suggestive diagnosis of PIGP were referred for gastric emptying studies by scintigraphy or breath testing and EGG. Patients were defined as PIGP if they had a clear history of an acute infectious illness immediately prior (same week) or during the development of their symptoms, evidence of gastroparesis, had no history of recurrent or persistent vomiting or other gastrointestinal or neurological disease, and daily vomiting for >3 weeks. We chose this cut-off period to avoid confusion with gastroparesis occurring during common incidental gastrointestinal viral infections, which usually resolve within 14 days. Our inclusion criteria required daily vomiting, because this is relatively easy to document as an objective symptom, as opposed to more subjective symptoms such as nausea or satiety. Similarly, resolution required cessation of vomiting.

All patients underwent an evaluation that included detailed history and physical examination, ophthalmic examination, routine blood tests (including a complete blood count, serum glucose, electrolytes, amylase, transaminases, creatinine, blood urea nitrogen [BUN]), a barium swallow with small bowel series, gastroscopy with biopsies, abdominal ultrasound, gastric emptying studies and EGG. Ammonia levels, computed tomography (CT) scans of the abdomen or brain, and spinal fluid analysis were performed in selected patients, as deemed necessary by the treating physicians.

Gastroparesis was evaluated within each center by EGG and gastric scintigraphy or C^{13} octanoic acid breath tests.[8,9] Patients with evidence of peptic disease on endoscopy, persistent hepatitis, prior history of prolonged nausea and vomiting, or previous gastrointestinal surgery were excluded. Virology studies were performed in individual centers prior to referral when the disease was suspected, or by the motility centers when they were involved early in the course of the disease (depending on type of presentation).

Gastric emptying was assessed by either one of two methods. In the first, gastric scintigraphy was performed with a standard meal (or formula for children <2 years-old) mixed with 25–40MBq^{99m}TC colloid. Patients were then imaged on a single head gamma camera (SP-4, Elscint, Haifa, Israel). A low energy all-purpose collimator was used. Patients were scanned in the supine position and in the left anterior oblique position. Static and dynamic studies were obtained immediately after eating and every 1 min for the next 60 min. Time activity curve was than obtained from the region of interest. Scintigraphy was considered abnormal for adults above age 15 years if after 60 min more than 60% of the test meal was retained.[10] For children below 15 years, T1/2 of gastric emptying was 87 min.[11]

The second method involved a 4 h C^{13} octanoic acid breath test using the Oridion Breath ID multitest platform (Oridion Breath ID, Jerusalem, Israel). After an overnight fast, a scrambled egg was made with 5 g of margarine served on two slices of bread. Then 100 mg of octanoic acid was added and homogenized into the yolk moiety of the egg. Egg white was added to it and baked. A 150 mL glass of water was allowed. This test was also used for follow up in patients without resolution or prolonged symptoms in order to verify that symptoms were associated with persistent gastroparesis and not due to somatization or other disorders.[12]

All patients underwent a single channel EGG using an EGG multigram GI edition (Synectic Medical, Copenhagen, Denmark), with analysis by a software program (Electrogastrogram version 6.30, Synectics Medical). The digitized file was analyzed using Fourier transformation, running spectral analysis (RSA) with Fourier transformation, and calculation of the percentage distribution of power in the four frequency ranges described below.

Electrical activity was recorded from two pairs of Ag-AgCl bipolar skin electrodes, the captured signal amplified and digitalized, and running spectral analysis performed. The dominant frequency and power of spectrum were calculated using a sequence of computerized algorithms. Gastric slow wave rhythm in the range of 2.4–3.6 cycles per minute was considered normal. Bradygastria was defined as gastric rhythm of less than 2.4 cycles per minute and tachygastria as a rhythm of 3.7–10 cycles per minute. Gastric arrhythmia was defined as a combination of bradygastria and tachygastria. An EGG was considered abnormal if the slow wave frequency was outside the normal range more than 30% of the time[7,13–15] (see Fig. 1: normal EGG).

Study protocol

All patients stopped medications which could affect gastric motility at least 48 h before examination. After an overnight fast, patients were placed in the supine position for 1 h pre-prandial and 2 h postprandial. The test meal was composed of a sandwich with egg/meat and a glass of orange juice. Artifacts were excluded from the analysis by manual inspection of the computer charts.

Results

Patient data

During the study period, 15 patients referred for persistent unexplained vomiting were evaluated for suspected post-infectious gastroparesis. Three patients with normal gastric emptying studies were excluded. In another two patients symptoms resolved before gastric emptying was carried out. One was an 18-year-old patient with 3 months of daily vomiting starting during serologically documented Epstein-Barr virus (EBV) related infectious mononucleosis, and the other was a 63-year-old woman with 1 week duration of 'flu like' symptoms and persistent vomiting that lasted 1 month after the infectious symptoms had resolved. An additional patient with persistent vomiting after an episode of vomiting and diarrhea lasting 1 week was excluded because a neuromuscular disorder was also present. Another patient was a 63-year-old male who had a kidney transplant. A year later he developed cytomegalovirus (CMV) infection which was confirmed by the finding of inclusion bodies in esophageal biopsy. The patient had persistent vomiting for a year since the infection, despite appropriate anti-viral therapy and negative consequent biopsies. Gastric scintigraphy failed due to persistent vomiting and the patient was therefore excluded. A 19-year-old patient had persistent vomiting for 12 months after an acute episode of gastroenteritis, and this patient was also excluded because gastric scintigraphy failed due to vomiting.

The seven remaining patients had a history of an acute infectious illness antedating or occurring with their symptoms. Patients' entry data, as well as precipitating disease, duration of symptoms and motility investigation are presented in Table 1.

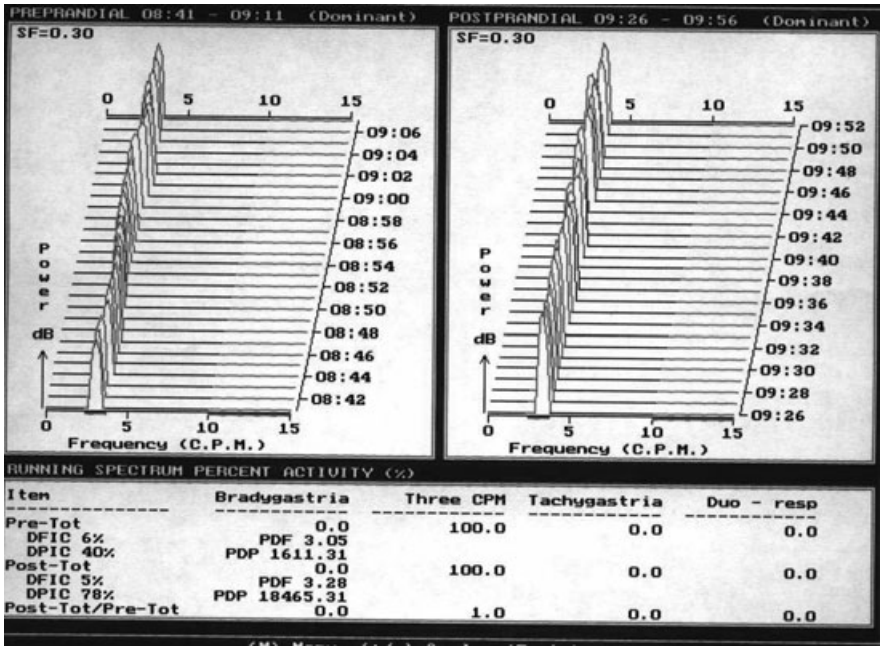

Figure 1 Normal electrogastrography.

Table 1 Patients' data

Patient	Age	Sex	Acute illness	Duration of symptoms	Gastric emptying scintigraphy or octanoic acid BT (T 1/2)
1	5 months	F	CMV	4 weeks	120 min
2	14 years	M	'Flu like'	12 months	158 min
3	10 years	M	'Flu like'	12 months	91 min
4	19 years	F	Sore throat, EBV	12 months	166 min
5	14 years	M	Vomiting and diarrhea	13 months	176 min
6	47 years	F	'Flu like'	18 months (active)	80 min
7	15 years	F	'Flu like'	10 months (active)	110 min

CMV, cytomegalovirus; EBV, Epstein-Barr virus.

Viral etiology was identified in two cases (one CMV and one EBV) during the acute illness. Patient 1 was an infant with fever and transient elevation of transaminases, accompanied by positive serology for acute CMV infection. Transaminases normalized almost immediately, however, she developed severe persistent vomiting necessitating continuous 24 h tube feeding for 3 weeks. Patient 4 developed persistent vomiting after a prolonged sore throat with documented EBV infection, several weeks after onset of the disease. The other patients were referred long after the acute illness had resolved and no causative agent could be identified at that time. Time to referral ranged from 3 weeks to 6 months after the initial episode, rendering viral diagnosis difficult.

Routine previously defined biochemistries including transaminases, creatinine, BUN, amylase, endoscopies and radiological imaging were non-diagnostic in all patients.

Gastric emptying and electrogastrography

Gastric scintigraphy or C^{13} octanoic acid breath tests were attempted in all patients. Gastric emptying was assessed by the C^{13} octanoic acid breath test over 4 h with a standard meal in three adolescents, and was used for follow-up in these patients without symptom resolution. The results of these studies appear in Table 1.

EGG data are presented in Table 2. The EGG was pathological in six cases. The most prominent feature was bradygastria, both pre- and postprandial. There was no correlation between the type of EGG dysrhythmia and the delay in gastric emptying as measured by scintigraphy. An example of a pathological EGG is presented in Figure 2.

Outcome

Treatment with metoclopramide, domperidone, H_2 blockers and proton pump inhibitors was not effective in most of the patients. Patient 7 obtained symptomatic relief of nausea with ondansetron and patient 5 had partial relief from domeperidone. Patient 1 required continuous 24 h nasogastric feeding for over 2 weeks after failing treatment with cisapride and later erythromycin. The other patients were maintained on oral feeding with a low fat diet.

Table 2 Electrogastrography results

Patient no.	Pre-prandial			Postprandial			Final conclusion
	Brady-gastria (%)	Normo-gastria (%3 cpm)	Tachy-gastria (%)	Brady-gastria (%)	Normo-gastria (%3 cpm)	Tachy-gastria (%)	
1	56	39	5	7.4	92.6	0	Pathological
2	50	50	0	32	68	0	Pathological
3	13	83	4	0	88	12	Normal
4	18	61	21	35	61	3.5	Pathological
5	74	16	10	37	55	8	Pathological
6	93	7	0	47	52	0	Pathological
7	28	56	7	14	84	2	Pathological

Duration of symptoms ranged from 4 weeks to 18 months (Table 1), however, patients, 6 and 7 remained symptomatic. Patient 4 had daily vomiting 12 months after disease onset, her symptoms gradually improved and a gastric emptying test 12 months later showed an improved T1/2 from 166 to 100 min, but she still suffers from nausea and early satiety. Patient 2 was symptomatic for 13 months, his symptoms gradually improved and a gastric emptying test after 13 months was normal with a T1/2 of 65 min. He is currently asymptomatic. Patient 4 was the oldest of our patients and her disease was characterized by very severe symptoms, despite a relatively benign EGG, and by prolonged duration of more than 18 months of symptoms that had not resolved at the time of the writing of this paper.

Discussion

Gastroparesis after an acute viral illness has been described both in an acute form[16,17] lasting only a few days, and in a chronic form, lasting several months.[2–4] It is not always possible to detect the causative agent due to the time lapse between onset of the preceding viral/infectious disease and presentation or referral for evaluation of the patient.

Viruses previously incriminated as causing post-viral gastroparesis include CMV, varicella virus, rotavirus and the Norwolk agent.[2,4,5,16–18] In our study, we managed to identify the causative virus in only three of our patients and these were all of the herpes family.

The diagnosis of gastroparesis was not made in any of our patients, despite severe symptoms, until they were referred to adult or pediatric gastroenterologists. The cases we describe here are probably the 'tip of the iceberg' and represent the most severe cases of PIGP.

During the earlier phases of the disease, none of our patients had significant clinical improvement with prokinetic agents, although low fat diets significantly improved subjective patient well-being in several cases (less nausea and vomiting). Three of our patients were misdiagnosed as eating disorders or functional/psychogenic vomiting after an evaluation by pediatricians or adult gastroenterologists, based on a 'negative' workup,even though their symptoms appeared suddenly after an obvious infectious disease.

EGG has been used as a measure of gastric motility. This method is particularly attractive in children due to its non-invasive nature. Normal ranges of EGG in children have been defined by Riezzo *et al*.[19] who have measured EGG in 114 healthy children, in the age range of 6–18 years. All healthy children had a dominant frequency between 2.9 and 3.1 more than 70% of the time both pre-prandially and postprandially. These results were supported by other studies in similar age groups,[20–22] so we therefore selected the values of between 2.4 and 3.6 cpm more then 70% of the time as the normal range.

The question arises as to whether in younger age groups the normal values change. Chen *et al*., when comparing the EGG patterns of different age groups, found that preterm infants did have an abnormal EGG, with normal 2–4 cpm present only 26% of the time. However, this changed to a normal rhythm present more then 70% of the time by the age of 2–6 months. As the youngest patient in our study was 3-months-old, we used the same reference values for her too.[23]

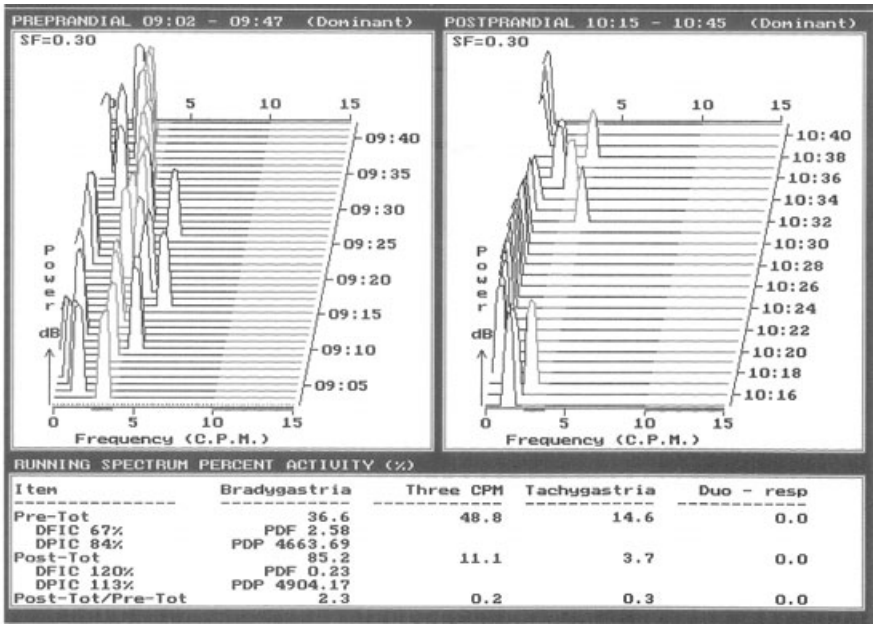

Figure 2 Pathological electrogastrography.

Normal values for gastric scintigraphy in children are hard to evaluate, as this test uses radioactive isotope and cannot be justified in healthy pediatric controls. Spiroglou *et al*. examined 28 children with sever asthma that was not responding to medical treatment. These children underwent gastric scintigraphy to rule out reflux and those who did not have evidence of reflux served as a control group. Twenty-eight children in the age range of 2–14 years were studied, T1/2 of gastric emptying was 87 min and this was the value we used as the normal value for children.[11]

The mechanism by which viruses cause gastroparesis in not known. Most studies proved impaired gastric emptying by scintigraphy or antroduodenal motility studies, but they did not examine the pathophysiological mechanism that caused this impairment. One study found that patients with gastroparesis had some degree of neuropathy, but this could have been another aspect of their disease, not necessarily connected to their gastroparesis.[4] Viruses of the herpes family are neurotrophic and are known to involve the stomach. The pathological EGG we found in most cases of our study may shed some light on the pathophysiology of PIGP, as it might suggest viral mediated damage to the interstitial cells of Cajal as the causative mechanism of PIGP.[24–26]

The course of the disease was benign in all patients and led to very extensive workups in most as gastroparesis was not entertained as a diagnosis at an early stage. The duration was quite prolonged, especially in adolescents, with two patients aged 14 and 15 having symptomatic disease that had not yet completely resolved or lasted >1 year during follow up. These patients had evidence of delayed gastric emptying present at 12 months.

In conclusion, PIGP can occur in children and adults. The disease in childhood appears to be self-limiting in younger children, although the duration of clinical symptoms may be very prolonged in adolescents and, in our cohort, was most commonly related to viruses of the herpes family and to flu-like or gastrointestinal infections characterized by diarrhea. Treatment with prokinetics and anti-emetics was disappointingly unsuccessful in most patients. EGG is pathological in the majority of patients with PIGP, suggesting impairment at the level of the gastric pacemaker. A high index of suspicion is needed to identify the disease and its etiology, and reassurance that the disease is self-limiting in most cases and especially in young children is of paramount importance in lieu of the prolonged course in many patients.

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