Brainstem Viral-like Encephalitis as a Possible Cause of a Gastroduodenal Motility Disorder: A Case Report

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The case of a 36-year-old caucasian woman who suffered for many years from gastric retention and duodenogastric reflux due to gastroduodenal motor dysfunction resistant to therapy with prokinetic drugs is described. As the patient died suddenly of an unexplained cardiocirculatory collapse a few hours after a low-risk operation, an autopsy examination was carried out to clarify the cause of death. No alterations were found in the heart, lungs, and central nervous system with the exception of a subacute viral-like brainstem encephalitis involving the dorsal motor nucleus of the nervus vagus, the nucleus XII, the nucleus tractus solitarius, and the nucleus ambiguus. A clinico-pathologic correlate between the clinical alterations and the lesions of the brainstem centers, which modulate gastrointestinal and cardiovascular functions, is surmised. (Journal of Gastrointestinal Motility 1989; 1:99–104).

Key Words: Brainstem; duodenum; encephalitis; gastrointestinal motility; stomach; virus.

Introduction

Gastrointestinal motility disorders can be caused by diseases involving the smooth muscle and/or the intrinsic or extrinsic nervous system (1–12). However, in most patients with common motor disorders such as gastric stasis or duodenogastric reflux, and underlying disease responsible for these motor alterations cannot be demonstrated, because it is too difficult to examine the muscular layer with its neural control system, unless the patient has to undergo an abdominal operation. The gut disorder is not usually considered important enough to justify a postmortem examination of the intrinsic and extrinsic nervous control system of the gut. This report illustrates a case of a patient with long-standing severe "idiopathic" gastroduodenal motility dysfunction with gastric retention and duodenogastric reflux, who at autopsy was found to have a subacute viral-like encephalitis selectively involving the brainstem centers that control gut motility.

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Case Report

A 36-year-old woman presented to the University Hospital of Bologna with a 12-year history of epigastric pain, postprandial fullness, and occasional bile-stained vomiting. Barium upper-gastrointestinal radiography and upper-gastrointestinal endoscopy did not reveal an organic lesion. Treatment with spasmolytics did not give any improvement, and the symptoms did not subside after cholecystectomy. Repeated upper-GI endoscopy only revealed esophagitis and duodenitis. Investigations carried out 5 years ago revealed an acid hypersecretion and a moderate delay in gastric emptying, and treatment with antacids and prokinetic drugs gave only temporary improvement. Consequently, the patient was considered to have a psychosomatic disease.

When first seen in the University Hospital of Bologna 1 year ago the patient had experienced a weight loss of 15 kg in 12 months, caused by severe postprandial discomfort that was relieved only by self-induced vomiting. On physical examination, the only positive findings were leanness, hypotension, a recent abdominal scar, epigastric tenderness on palpation, and postprandial succussion splash. Upper-gut x-ray showed a dilated hypotonic stomach, and en-

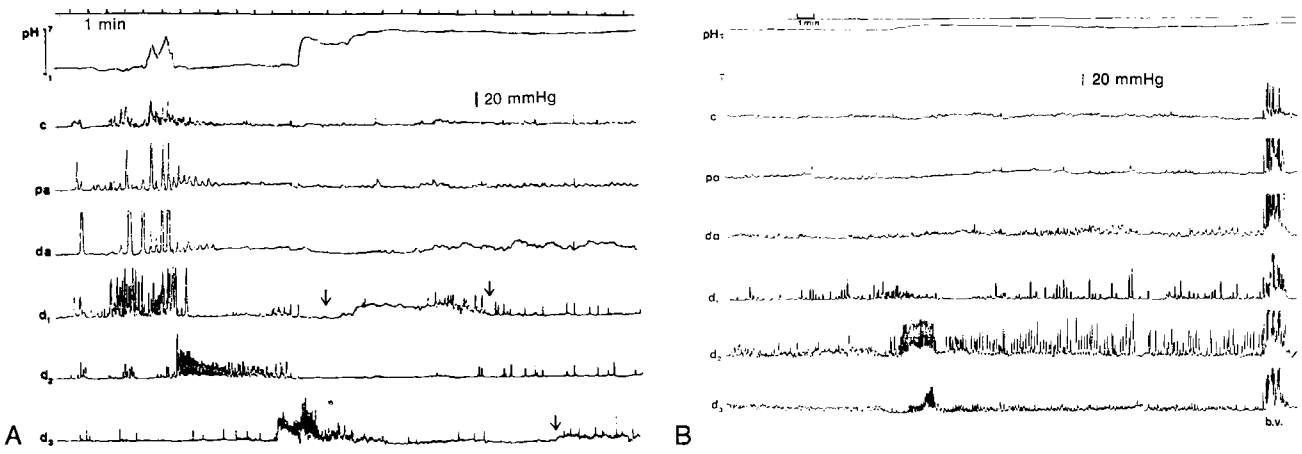

Figure 1. **(A) Gastroduodenal motor recording carried out in a patient with brainstem encephalitis localized in the centers that control gastrointestinal motility. Recording ports 5 cm apart are placed in the distal gastric corpus (c); proximal antrum (pa); distal antrum (da); first part of the duodenum (d_1); and descending duodenum (d_2 and d_3). Note the slower than normal propagation velocity of the duodenal MMC activity front, 0.9 versus 6.7 ± 1.8 ($\bar{x}$ ± SD) cm per minute, of the normal controls of our laboratory and the abnormal increases in duodenal tone in traces d_1 and d_3 (arrows). These motor alterations are associated with sudden increases of intraluminal pH of the antrum that may be related to duodenogastric refluxes.**

(B) Gastroduodenal motor recording in the same patient showing an activity front that appears simultaneously at different levels in the duodenum, whereas the gastric component is lacking. The antral pH is abnormally high, and this fact is related to a presence of bile juice in the stomach, as is proved by the subsequent biliary vomit (b.v.). Note the absence of duodenal phase I after the activity front and the continuous sequences of phasic pressure waves (trace d_2).

doscopy revealed only a mild esophagitis and hypersecretory gastroduodenitis. Basal and pentagastrin-stimulated gastric acid secretion were markedly increased. Ultrasonographic gastric emptying time (13) of a solid meal was 480 minutes, well above the normal range of 180 to 240 minutes, and the half-emptying time of a radiolabeled semiliquid meal (14) was 150 minutes, markedly increased with respect to the normal range of 45 to 65 minutes. Frequent and pathologic gastroesophageal and duodenogastric refluxes were also detected with esophageal and antral 24-hour ambulatory pH metric monitoring (15,16).

Gastroduodenal manometry using a multilumen pneumohydraulic perfusion system showed marked alterations of the migrating motor complex (MMC), such as longer than normal duration of the MMC cycle (164 minutes versus a normal range of 65–114 minutes), disordered activity front propagation, and abnormal tonic and phasic pressure waves (Fig. 1). These motor alterations were sometimes associated with duodenogastric reflux and with epigastric pain, and were not abolished by domperidone or intragastric infusion of isoosmotic bicarbonate (17). Esophageal manometry showed a hypotonic lower esophageal sphincter with slight alterations of pressure waves. A virologic study revealed the presence in the serum of a high titer of IgG against cytomegalovirus (CMV) and a slight positive IgM anti-CMV: low nonsignificant titers were found against some other viruses such as herpes simplex, rubella, measles, and adenovirus, whereas the reactions against varicella-zoster virus, poliovirus, and coxsackie were negative.

Because a further medical treatment with prokinetic drugs, H_2 antagonists, and antacids gave only a transient improvement, the patient underwent duodenal extramucosal myotomy extending from the bulb to 3 cm after the inferior duodenal knee associated with the antireflux procedure according to Dör (18). This kind of operation was conceived in order to reduce the duodenal hyperdysmotility and improve the gastric stasis and probably the duodenogastric reflux (19). The patient's immediate postoperative clinical course was satisfactory with normal routine blood tests and electrocardiogram, but 36 hours after operation the patient began to show supraventricular tachycardia on ECG, associated with a progressive decrease in arterial pressure (80/50 mm Hg) and followed by atrial flutter and arrhythmia. Despite cardiocirculatory treatment in the Intensive Care Unit the hemodynamic condition progressively worsened and the patient died a few hours later.

AUTOPSY

At autopsy only pulmonary edema and congestion of the liver were found. The heart weight was normal and no significant macroscopic lesions were observed in the valve system and coronary arteries. Samples of the conduction system taken following the technique described by Rossi and Thiene (20)

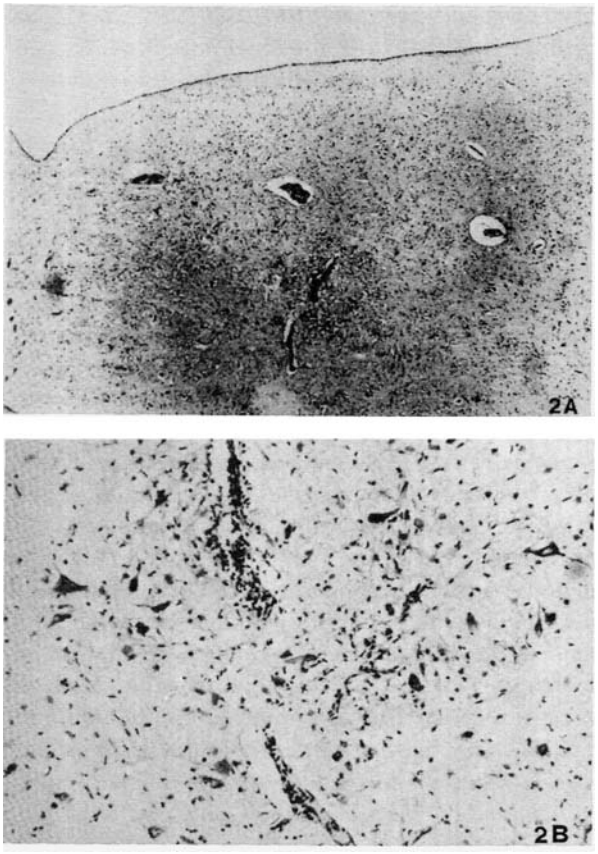

Figure 2. **(A) Section from the medulla of the patient with gastroduodenal dysfunction showing lymphocytic perivascular cuffing and increased cellularity. (Cresil fast violet; magnification 30×)**

(B) At higher power this area shows gliosis with plum astrocytes, microglial proliferation, and neural loss.

did not reveal any hystologic lesion except a slight fibrosis of the sinoatrial node. In the upper gut the gastric outlet showed a muscular hypertrophy without clear pyloric stenosis. No significant microscopic alterations of the intrinsic intestinal plexus and of the vagus nerves were observed except a slight lymphocytic infiltration in the submucosa of the gastroduodenum, but no electron microscopy was performed.

As regards the central nervous system, the brain with its arteries and meningeal layers was macroscopically normal without signs of herniation, trauma, or brainstem compression. Microscopic sections of the cerebral cortex, cerebellum, hippocampus, basal ganglia, midbrain, pons, and medulla were stained with hematoxylin and eosin/luxol fast blue (HE/LFB), fast cresyl violet (FCV), and Bodian's stain. In selected sections an immunohistochemical staining was performed by the avidin-biotin complex technique using antisera raised against the

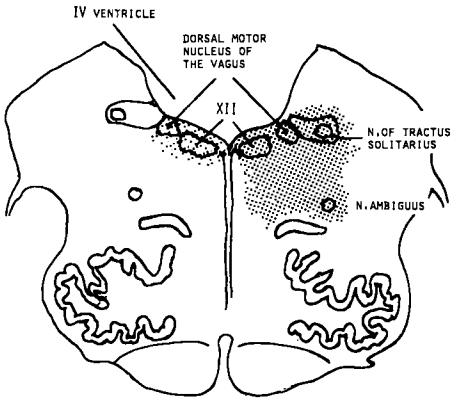

Figure 3. **Topographic distribution of the lesions in the medulla of the patient.**

following antigens: polyclonal antiglial fibrillar acid protein (GFAP) 1/400, anti-herpes simplex 2 (Dakopatts, Glostrup, Denmark) 1 : 100, and anti-CMV (Biogenex Lab, Dublin, CA) 1 : 100. Histologic alterations were observed only in mesencephalon and medulla. In particular, the mesencephalon showed diffuse chronic alterations consisting of diffuse glial proliferation, microglial nodules, and decreased number of neurons, whereas the tegmental region showed loss of neurons, intense gliosis, reactive astrocytes, neuronophagia, and lymphocytic perivascular cuffing (Fig. 2). These alterations were more evident on the right side and involved the dorsal motor nucleus of the vagus, n. hypoglossus, adjacent n. ambiguus, and n. tractus solitarius (Fig. 3); the latter two showed mainly acute lesions. Sections from cerebral hemispheres, basal ganglia, hippocampus, and cerebellum did not show any alteration. Anti-HSV-2 and anti-CMV immunohistochemical reactions were negative.

Discussion

The patient presented in this report had a marked dysfunction of gastroduodenal motor activity, and no cause other than inflammatory changes involving the brainstem nuclei that modulate gut motility could be established by clinical, laboratory, and pathologic means. This case raises some important questions.

The neuroanatomy of the brainstem (21) justifies the hypothesis that a lesion of this region may cause gastrointestinal motor disturbances. Gastric motility may be increased by stimulating the cephalic half of the dorsal motor nucleus of the vagus (22), the ventrolateral part of the reticular substance (23), and the nucleus ambiguus (24). Stimulation of nucleus of tractus solitarius increases both gastric acid output and force of antral contractions (25). Central modulation of the migrating motor complex has been suggested by some studies (26–28).

However, very few cases of patients with brainstem lesions and gut dysfunctions are described in literature. A granular ependymitis protruding into the medulla and involving both dorsal motor vagal nuclei (29) was found in a patient with diffuse esophageal spasm, and a brainstem ischemic lesion was observed in another patient with colonic pseudo-obstruction (30). However, the most convincing example is represented by a patient with a brainstem tumor presenting as an upper-gut motility disorder (31). This case shares strong clinical and laboratory similarities with ours: in fact, it shows chronic nonulcer dyspepsia with sporadic vomiting, a delay in gastric emptying for liquids and solids, and alterations in cyclic interdigestive motility. The impairment of brainstem centers which led to gut dysmotility in the above mentioned patients may be due to ischemia or compression of the nervous tissue. In our case, however, the lesion of brainstem centers is a subacute inflammation of the nervous tissue, with a histologic appearance considered highly specific for viral infection of the central nervous system (32).

Although no viral particles could be detected, the presence of active neuronophagia and perivascular lymphoid infiltrate suggests the persistence of the virus in the nervous tissue, which is a well-known event in viral infections of CNS (33). By analogy with mouse infections with HSV (34) the brainstem of this patient could be considered an area of latent virus infection with sporadic reactivations resulting in a "hit and run" type of infection (35) that may explain the long-standing nature of the symptoms and the presence of intense reactive gliosis of the brainstem.

A subacute viral-like inflammatory process that selectively damages the brainstem nuclei has been rarely documented. A subacute brainstem viral-like encephalitis selectively involving the respiratory centers was demonstrated in a patient with failure of the automatic control of ventilation (Ondine's curse), which led to his death (36). Another case (37) that shares clinical and neuropathologic features with ours is that of a patient with idiopathic intestinal pseudo-obstruction and a subacute brainstem encephalitis, highly suggestive of a viral infection, and a ganglionitis of the myenteric plexus.

On the basis of these data it is reasonable to hypothesize that a slowly progressing viral infection may have damaged the bulbar centers regulating gut motility, causing the gastroduodenal motor dysfunction. Acute inflammation was also observed in the n. tractus solitarius and n. ambiguus fringes which carry the cardiac and vascular inhibitory responses (25), and this was considered the probable cause of death.

Our efforts to identify the virus responsible for the brainstem encephalitis have been unsuccessful, though we did observe high IgG titer against cytomegalovirus, which has been previously demonstrated in patients with intestinal pseudo-obstruction (38,39) and in patients with a gastroduodenal motor dysfunction (40).

In conclusion, we believe that in the present case the gut motility disturbances are related to a "hit and run" brainstem viral-like encephalitis affecting primarily the centers that modulate gut motility. Subsequently, the inflammatory process, reactivated by the surgical stress, may have involved the centers that regulate cardiovascular functions, leading to a refractory cardiovascular collapse. We believe that these "smoldering" viral-like localized encephalitis infections could be more frequent than expected from their autoptic demonstration, because some viral neurotropic infections (herpes, CMV, etc.), once acquired, persist indefinitely in the host tissues (41) and are not investigated with more invasive diagnostic tests, such cerebrospinal fluid examination and brain biopsy, unless they give life-threatening symptoms or the patient is immunodepressed (42,43), though they may also occur sometimes in patients not immunodepressed (44) or in otherwise healthy subjects (41).

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