Research Paper

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Autonomic dysfunction in patients with chronic intestinal pseudo-obstruction

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WE prospectively evaluated autonomic function in 50 patients with clinical and manometric features of a neuropathic form of chronic intestinal pseudo-obstruction (CIP). In 26 patients, there were underlying disease processes that may have affected extrinsic neural control to viscera: diabetes mellitus ($n = 16$), previous gastric surgery ($n = 5$), and other neurologic disorders ($n = 5$). Our aim was to characterize autonomic function in these patients, and those 24 with CIP unassociated with a known underlying neurologic disorder (idiopathic group). We assessed vagal function and sympathetic cholinergic and adrenergic function by means of standardized autonomic tests and quantitated postprandial antral pressure activity. We also measured postprandial levels of pancreatic polypeptide and neurotensin as indicators of vagal function and of the delivery of nutrients to the distal small bowel. Among the idiopathic group ($n = 24$), two had evidence of a generalized sympathetic neuropathy and five abdominal vagal dysfunction (one had both). Among diabetic patients, three had sympathetic adrenergic failure, six had orthostasis with normal plasma noradrenaline, ten had signs of generalized sympathetic neuropathy and eight had abdominal vagal dysfunction. Vagal dysfunction was identified in all three patients who underwent vagotomy as part of their previous gastric survery. In the other neurologic syndromes, vagal function was abnormal in three of the five patients. Thus, autonomic and, particularly, vagal dysfunction are confirmed in a majority of patients with CIP associated with known diabetes or neurologic disorders; however, a previously unrecognized autonomic (chiefly vagal) neuropathy of undetermined cause has been identified in five of the 24 'idiopathic' CIP patients. Autonomic function should be evaluated in patients presenting with the syndrome of chronic intestinal pseudo-obstruction.

Key words: Dysautonomia, Vagus, Sympathetic, Pancreatic polypeptide, Neurotensin, Pseudo-obstruction, Gastroparesis, Dysmotility

Introduction

Chronic intestinal pseudo-obstruction is a clinical syndrome characterized by evidence of stasis of food in the upper gastrointestinal tract and episodes of apparent subacute intestinal obstruction without any demonstrable obstruction or mucosal disease on small bowel barium radiography.[1–3] The autonomic nervous system constitutes one of three levels of control of gastrointestinal motor function and serves at least a modulatory role, interacting with the enteric nervous system and the excitable smooth muscle cells.[4] There is an abundance of clinical literature[5] that documents disturbances of gastrointestinal motility in patients with disorders affecting the extrinisic nervous system to the gut. Thus, several general neurologic and endocrine disorders are accepted as aetiologic factors of the syndrome of chronic intestinal pseudo-obstruction.[1] There is also compelling histologic evidence for the role of myenteric plexus degeneration among patients with idiopathic chronic intestinal pseudo-obstruction (CIP).[6] However, such degenerative processes are not demonstrable in almost half the patients with idiopathic CIP;[6] similarly, there are usually no pathologic processes identifiable in the enteric smooth muscle. Thus, we postulated that disorders of motility in idiopathic CIP may result from previously unrecognized dysfunction of extrinsic neural control to the digestive tract.

Our aim was to characterize sympathetic and vagal function in 50 patients with primary (idiopathic) or secondary CIP; these patients demonstrated manometric findings indicative of a

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neuropathic dysmotility,[5] and no clinical, laboratory or intestinal manometric features to suggest a myopathic process. Fourteen of the patients included in this study have been reported in far less detail in previous reports: three 'idiopathic' CIP patients in Ref. 7; two neurologic syndrome patients in Refs 8 and 9; and three diabetic, two neurologic syndrome, and eight 'idiopathic' CIP patients in Ref. 10. The latter report included the three patients in Ref. 7.

Materials and Methods

Patients. We studied 50 patients referred to one of us (M.C.) for evaluation and treatment of CIP. The diagnosis was based on clinical findings and standard, previously published, manometric criteria.[11,12] Identification of the patients' underlying diseases were based on standard clinical criteria. Thus, the inclusion criteria were: (i) symptoms suggestive of upper gastrointestinal stasis of >12 weeks' duration (nausea, vomiting, early satiety, anorexia, bloating, distention, postprandial pain); (ii) absence of mucosal disease or mechanical obstruction in stomach or small bowel on upper gastrointestinal endoscopy and barium follow-through; (iii) intestinal manometry showing at least two of the four criteria previously reported in patients with neuropathic forms of CIP.[12]

Autonomic function tests. The following tests [described in detail elsewhere[5]] were performed:

A. Cardiovascular tests, as indicators of sympathetic adrenergic function
   (i) Orthostatic change in blood pressure in response to 5 min of an 80° head-up tilt.
   (ii) Pulse and blood pressure responses to the Valsalva manoeuvre, with particular attention to the blood pressure in phases II and IV, and the Valsalva ratio (that is, the ratio between the longest and shortest R–R intervals).
B. Plasma noradrenaline [measured by HPLC with electrochemical detection[13]] in the supine and upright positions, indicators of muscle sympathetic adrenergic function.[14,15]
C. Quantitative sudomotor axon reflex test [QSART[14]], in which sweat output (latency and volume) in response to iontophoresed acetylcholine was measured in the forearm and three sites in the lower extremities, reflects postganglionic sympathetic cholinergic function.
D. Plasma pancreatic polypeptide in response to modified sham feeding (by chew-and-spit technique), a test of abdominal vagal function[16] which we have previously used in our laboratory to identify vagal dysfunction among patients with functional dyspepsia.[17]

Postprandial antral motility and selective gut hormone responses. Distal antral phasic pressure activity in response to a standardized 535 kcal solid–liquid meal was evaluated by pneumohydraulic perfusion manometry,[12] and quantitated as a motility index. This information was obtained from the original recordings which provided the manometric criteria for diagnosis of the intestinal dysmotility. Antral motility was assessed by three to six sideholes, each separated by 1 cm, and placed fluoroscopically in the distal antrum. This method has been used extensively in our clinical laboratory (>1300 patients studied in the past 10 years), and is described fully elsewhere.[18,19] The 5th percentile of 25 healthy subjects for the 2-h distal antral motility index is 13.67 and the 95th percentile 15.65.[18] We declared antral motor function abnormal if the antral motility index was <13, since the range of values in healthy controls was 13.05 to 16.2. Antral motor function could not be quantitated in eight of the 50 patients because of previous partial gastrectomy ($n = 3$) or malposition of the manometric assembly ($n = 3$) for more than 10 min out of the 2-h postprandial period, or the patient did not ingest the test meal ($n = 2$).

Plasma levels of pancreatic polypeptide and neurotensin were measured by established radioimmunoassays[20,21] during fasting, and 1 and 2 h after ingestion of the same standardized 535 kcal meal used in the motility study. Previous studies in healthy controls[17] show that there should be a postprandial change from fasting levels of at least 100 pg/ml for pancreatic polypeptide, and 25 pg/ml for neurotensin.

Data analysis. The results for each autonomic testing in patients were contrasted with those of age- and sex-matched healthy controls; laboratory control values have been reported previously.[5,9,17,18] We determined the proportion of patients in each major subgroup with abnormal vagal function (based on the pancreatic polypeptide response to modified sham feeding), sympathetic adrenergic function (based on blood pressure and plasma noradrenaline responses to the upright posture), and generalized sympathetic function (based on the blood pressure responses to the Valsalva manoeuvre and results of the QSART distribution).

Results

Patient groups. All patients (Table 1) had symptoms suggestive of CIP and manometry of the small bowel showing normal amplitude but incoordinated pressure profiles. Based on clinical and

Table 1. Causes of 'neuropathic' chronic intestinal pseudo-obstruction

Group	*n*	Comments
Idiopathic	24	
Diabetes mellitus	16	14 type I (insulin-dependent, ketosis-prone) 2 previously type I, currently euglycaemic post-pancreatic transplant
Previous gastric surgery	5	1 vagotomy and pyloroplasty 2 Billroth II gastric resection (1 with vagotomy) 1 Billroth I + vagotomy 1 Nissen fundoplication + Hill's repair
Neurologic syndromes	5	1 amyotrophic lateral sclerosis 1 selective cholinergic dysautonomia 1 paraneoplastic neuropathy 1 primary amyloidosis with neuropathy 1 corrected spina bifida

laboratory criteria, our group of 50 patients comprised 16 diabetics (of whom two had undergone pancreatic transplantation), five post-gastric surgery, and five with neurologic syndromes. The remaining 24 patients had no identifiable underlying disorder and were considered 'idiopathic'.

Autonomic function. Table 2 summarizes the results of autonomic function, antral motility and postprandial levels of pancreatic polypeptide and neurotensin. Orthostatic changes in blood pressure and noradrenaline suggesting adrenergic sympathetic neuropathy were observed in a minority ($n = 3$) of patients, all of whom were diabetic. On the other hand, orthostatic changes in blood pressure without abnormality in supine or standing plasma noradrenaline were recorded in six diabetic, two idiopathic, and one post-gastric surgery patients. Since this pattern of observations is sometimes seen in patients who are intravascularly depleted, we chose to cautiously categorize these patients separately rather than including them in the category of 'selective adrenergic dysfunction'.

A more generalized sympathetic neuropathy characterized by abnormal QSART in arm or legs and Valsalva responses was identified in two idiopathic, ten diabetic, one post-gastric surgery and four patients with neurologic syndromes. Among diabetic patients, peripheral cholinergic sympathetic dysfunction was almost invariably associated with peripheral sensory or sensorimotor neuropathy. In the group with neurologic syndromes, one patient with selective cholinergic dysautonomia had markedly abnormal QSART but normal Valsalva responses.

Abdominal vagal dysfunction, based on a low plasma pancreatic polypeptide response (peak <25 pg/ml) to modified sham feeding, was identified in five idiopathic, eight diabetic, three vagotomy and three neurologic syndrome patients.

Postprandial antral motility and selective gut hormone responses. Postprandial antral hypomotility was a frequent motor dysfunction in all groups. In three out of the nine idiopathic CIP patients who had antral hypomotility, there was associated evidence of vagal dysfunction. Among idiopathic CIP patients, postprandial pancreatic polypeptide and neurotensin responses were respectively abnormal in five and three patients; all these patients also had antral hypomotility. Seven of the 13 evaluable diabetic patients had antral motor dysfunction; vagal dysfunction was proven in four of the five patients with diabetes in whom antral motility and hormonal response to modified sham feeding could be evaluated. Postprandial pancreatic polypeptide and neurotensin reponses were rarely abnormal among diabetics; all three abnormal neurotensin responses were associated with antral hypomotility in this subgroup.

Among patients with previous gastric surgery, antral motor function was impaired in both patients that had not undergone partial gastrectomy; both

Table 2. Abnormal tests of autonomic, antral motor and gut hormone function

Group	*n*	Sympathetic		Abdominal vagal[c]	Postprandial		
		Selective adrenergic[a]	Generalized[b]		Antral MI	PP	NT
Idiopathic	24	0/24	2/21	5/24	10/21	10/24	5/24
Diabetic	16	3/16	10/13	8/13	8/14	2/13	3/13
Previous gastric surgery	5	0/5	1/4	3/5	2/2	4/5	2/5
Neurologic syndromes	5	0/5	4/5	3/5	4/5	3/4	2/4

[a] Based on orthostatic BP change and supine or standing plasma norepinephrine.
[b]Based on abnormality on QSART test and Valsalva response.
[c]Based on plasma pancreatic polypeptide response to modified sham feeding.
MI = motility index. PP = plasma pancreatic polypeptide, maximal change postprandrially.NT = plasma neurotensin, maximal change postprandially.
Denominator indicates number of patients with evaluable data.

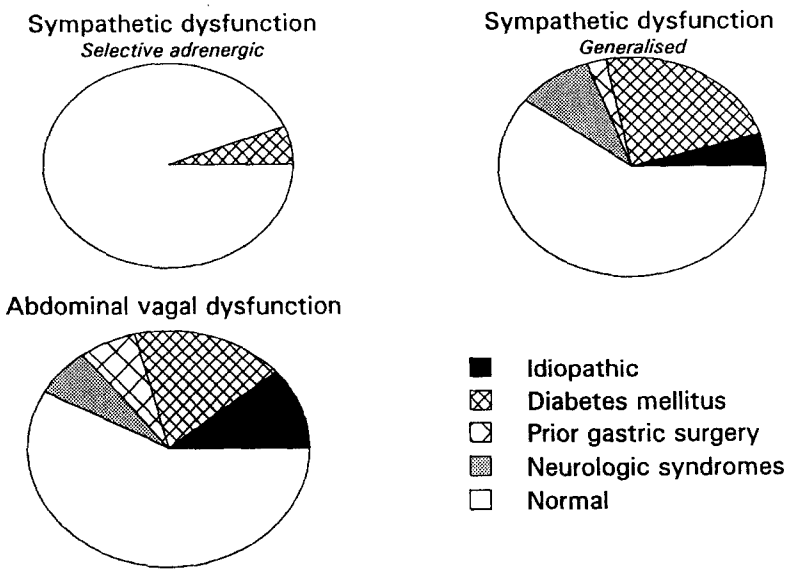

FIG. 1. Pie chart showing percentage of abnormal autonomic functions in each subgroup among 50 patients with chronic intestinal pseudo-obstruction. The portion showing normal autonomic function belongs to several disease subgroups (for details see Table 2).

patients also had impaired plasma neurotensin responses to the meal. By way of contrast, four patients with previous vagotomy had reduced pancreatic polypeptide responses to sham feeding or to the meal. The normal pancreatic polypeptide response to sham feeding correctly identified the one patient who did not undergo previous vagotomy.

All neurologic syndrome patients had postprandial disturbances of gut function: four out of five had antral hypomotility, three out of four had reduced pancreatic polypeptide and two of four had reduced neurotensin responses. The patient with treated spina bifida had abnormal postprandial hormonal responses, but normal antral motility and pancreatic polypeptide response to sham feeding.

Discussion

This study demonstrates the importance of autonomic dysfunction among patients with neuropathic variants of CIP. Our cohort consisted of almost equal numbers of patients with and without a known underlying disease that may impair autonomic function. Clearly, extrinsic denervation of the intestine is likely among patients with

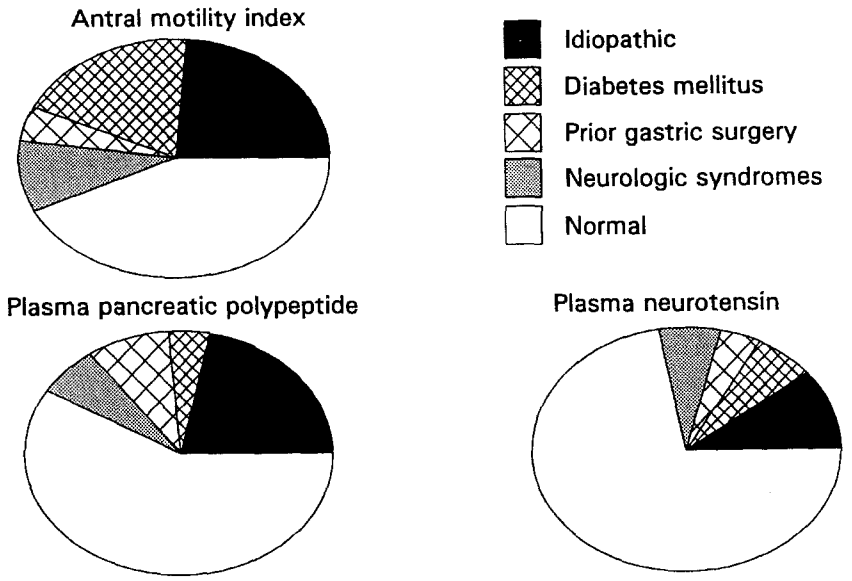

FIG. 2. Pie chart showing percentage of abnormal postprandial antral motility and postprandial neurotensin and pancreatic polypeptide responses in each subgroup among the 50 patients with chronic intestinal pseudo-obstruction. Note that the normal results were recorded in several disease subgroups (for details see Table 2).

underlying neurologic disorders and visceral autonomic dysfunction affecting either sympathetic or parasympathetic systems. However, our experience suggests that visceral denervation is also present among a subgroup of patients with otherwise idiopathic CIP.

Vagal dysfunction was the most frequently identified abnormality. This is not surprising among diabetic patients in whom autovagotomy is considered a major factor in the development of abnormal gastrointestinal motility.[2] Six of the eight diabetic patients with abnormal pancreatic polypeptide response to modified sham feeding also had antral hypomotility, confirming the importance of autovagotomy in this syndrome. Among diabetic patients, the modified sham feeding test appeared more sensitive to detect vagal dysfunction than the postprandial response of plasma pancreatic polypeptide, which is also considered a good test of the parasympathetic supply to the pancreatic islet F cells[22] which release pancreatic polypeptide. However, it is the release of pancreatic polypeptide during the first 30 min after a meal that is generally considered to be dependent on vagal denervation.[22] Our study included plasma samples 1 and 2 h after the meal, and the pancreatic polypeptide levels at these times are typically normal in diabetic patients,[23] unlike the impaired response which occurs earlier in patients with[16,23,24] or without[23] overt diabetic autonomic neuropathy. Our observation of impaired late pancreatic polypeptide responses in two diabetic patients suggests that there was inadequate gastric emptying of the meal into the upper small intestine to establish the local reflex involved in enteric stimulation of pancreatic F cells to release the pancreatic polypeptide.

The 30-min modified sham feeding test during fasting identified only three of the five patients with a previous history of gastric surgery. All had previously undergone vagotomy. In the other two patients, maximum changes in pancreatic polypeptide were 74 and 79 pg/ml, far in excess of the lower limit of normal. These subjects had not previously undergone vagotomy (Billroth II, hiatal hernia repair). Our data suggest that one of these two patients had abnormal gastric motor function associated with fundoplication[25] because the postprandial pancreatic peptide response and antral motility index were markedly abnormal. The cause of antral motor dysfunction after fundoplication is unclear; inadvertent vagal injury is suspected but rarely proven. The correct identification of patients with previous vagotomy by the sham feeding test is consistent with previous studies which suggest that, with meticulous care in conducting this procedure, this test of vagal function is equal to alternative methods, such as insulin-induced hypoglycaemia.[22,26]

In the idiopathic group, five patients had abnormal vagal function on the modified sham feeding test: four of these patients also had impaired postprandial pancreatic polypeptide responses and antral hypomotility was identified in three patients and could not be evaluated for technical reasons in the fourth patient. The fifth patient had normal postprandial antral motility and hormonal responses. However, it is clear that vagal dysfunction in a few patients in the idiopathic group results in changes in physiologic functions, such as the 2-h antral motility indices and two postpradial gut hormonal levels.

Among patients with neurologic syndromes, two had selective or paraneoplastic autonomic dysfunction and are discussed in detail elsewhere.[8,9] One patient with amyotrophic lateral sclerosis also had abnormal plasma pancreatic polypeptide responses to modified sham feeding and to the meal and antral hypomotility. This patient also suffered from pseudobulbar palsy and had a permanent tracheostomy. Vagal dysfunction is rarely identified in amyotrophic lateral sclerosis;[27] in contrast, sympathetic adrenergic function in this patient was normal, as in previous reports.[28,29] The patient with primary amyloidosis and autonomic neuropathy had no features to suggest abdominal vagal dysfunction; in contrast, peripheral sympathetic cholinergic dysfunction was associated with a sensory peripheral neuropathy. We have previously observed amyloid neuropathy with predominant sympathetic autonomic dysfunction and evidence of gastrointestinal dysmotility.[30] The patient with spina bifida corrected in childhood had no convincing evidence of any autonomic dysfunction, as would be expected from the level of the defect. His pseudo-obstruction affected predominantly small bowel motility and colonic function, and was associated with minor disturbances of urinary bladder function.

We acknowledge that the classification of sympathetic disturbances into 'selective adrenergic' and 'generalized sympathetic' dysfunction is artificial, but we have chosen this for two reasons. First, the tests used to categorize 'selective adrenergic' dysfunction are widely available, whereas those in 'generalized sympathetic' dysfunction are available in only a few centres. Second, blood pressure and plasma noradrenaline indices are much less sensitive than responses to the Valsalva manoeuvre[31] as indices of adrenergic function. They are also less sensitive than QSART in the evaluation of peripheral sympathetic function.[32,33] Thus, by means of this classification, it is also possible to compare the results from conventional, as well as newer tests of autonomic function.

In summary, in idiopathic or secondary CIP, we have identified a number of patients with extrinsic

autonomic dysfunctions which likely contribute to the aetiology of the gut dysmotility. Idiopathic autonomic neuropathy is demonstrable in approximately 20% of patients who present with an otherwise unexplained syndrome of CIP. These data also suggest that relatively simple tests that assess abdominal vagal function by measuring the 30-min pancreatic polypeptide response to modified sham feeding or insulin-induced hypoglycaemia should be considered in the evaluation of patients with idiopathic CIP.

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