

## CASE REPORT

## Ischaemic enterocolitis complicating idiopathic dysautonomia

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### Abstract

**A previously fit 23 year old adult male who presented with a sudden onset of profound autonomic neuropathy, for which no cause could be found, is described. The patient subsequently developed ischaemic enterocolitis that ultimately necessitated colectomy and subtotal enterectomy. Potential neural and humoral mechanisms are discussed.**

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### Case report

A previously well 23 year old male office worker was referred to the neurology service of this hospital in 1994 with recent onset of syncopal episodes. Apart from a brief episode of diarrhoea and mild abdominal pain one week earlier, there were no other prodromal symptoms. In addition to frequent severe postural syncope, he described abnormalities of taste and smell, blurred vision, and felt cold. His bowel habit became irregular and intermittently loose but not bloody. Micturition was normal. There was no history of significant illness in the family.

On examination he was ill; he was pyrexial and had a distended abdomen and quiet bowel sounds. His blood pressure dropped from 90 mm Hg systolic on lying to unrecordable levels on standing. His pupils were unequal in size and unresponsive to light or accommodation. No other cranial or peripheral neurological abnormalities were detected. Autonomic function testing revealed a significant combined deficit of sympathetic and parasympathetic components: head up tilt table testing at 60° caused a blood pressure drop from 116/60 to 40/20 mm Hg within two minutes, associated with only a small increase in heart rate from 66 to 82 beats per minute. A quinarizine/starch test showed almost complete anhydrosis apart from a small patch on the right side of his face, and instillation of pilocarpine 0.05% into both eyes produced meiosis after two hours. The cardiac response to the Valsalva manoeuvre was blunted, there was little R-R variation on 24 hour electrocardiography, and carotid sinus massage had no effect on the pulse rate.

Investigations performed included a normal full blood count and erythrocyte sedimentation

rate. Routine biochemical profile, C reactive protein, thyroid function tests, and serum immunoglobulin electrophoresis were within the laboratory's normal range. Autoantibodies including ANCA (antineutrophil cytoplasmic antibodies), antinuclear, and antiganglioside antibodies were not detected. Blood and stool cultures were negative, as was stool optical and electron microscopy, and *Clostridium difficile* toxin A was not present. The peripheral CD4:CD8 ratio was normal. Short Synacthen tests on two occasions were normal. Urine was negative for porphyrins and cerebrospinal fluid was sterile and acellular with no oligoclonal immunoglobulins. A chest radiograph, cardiac ultrasound, and computed tomography (CT) examination of the head were normal. Peripheral electrophysiology showed normal motor and sensory conduction.

An acute profound autonomic neuropathy was diagnosed and several oral therapeutic interventions were tried—including xamoterol, fludrocortisone, and midodrine—in order to ameliorate syncopal symptoms. Only intravenous gammaglobulin achieved objective improvement.<sup>1</sup>

Some two weeks later, the patient's intestinal symptoms became more prominent with abdominal distension, diffuse pain, and profuse bloody diarrhoea. Bowel sounds were present but quiet and there was no evidence of peritonism. A fluctuating high pyrexia was noted and there was a rising acute phase response with a sedimentation rate of 90 mm/h and a fall in serum albumin to 23 g/l, and haemoglobin to 6.8 g/dl. Repeated stool samples were negative for pathogens. A plain abdominal radiograph revealed gaseous distension of the small and large bowel. Computed tomography showed a greatly thickened wall in the caecum and ascending colon. Sigmoidoscopy to 40 cm showed an inflamed mucosa and biopsy specimens were consistent with a severe active non-specific colitis. He was initially treated with high dose intravenous hydrocortisone together with ciprofloxacin and metronidazole intravenously. His condition continued to deteriorate, and he was submitted to laparotomy.

At operation, a large inflammatory mass was found in the right iliac fossa with a thick walled and dilated caecum and ascending colon. An extended right hemicolectomy was performed and an ileostomy and colonic mucous fistula

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Figure 1 Plain supine abdominal x ray showing notably distended small bowel with gas in the tissues of the intestinal wall.

were fashioned to avoid primary anastomosis. Examination of the resected specimen revealed diffuse ulceration of 25 cm of terminal ileum and 15 cm of caecum and ascending colon. Histology revealed full thickness mucosal ulceration with superficial fissuring and striking myocytolysis. There was no transmural inflammation or granulomata, and no evidence of arterial or venous thrombosis. Despite a prolonged postoperative ileus, the patient made an uneventful recovery and was readmitted for restoration of bowel continuity two months later. At this time he had no abdominal symptoms, but there was no improvement in autonomic function. At routine side to side anastomosis of the terminal ileum and distal transverse colon, the bowel appeared normal. He subsequently developed a prolonged postoperative ileus and abdominal radiography showed gaseous distension of small intestinal loops. There was clinical evidence of sepsis despite negative blood cultures, and ultrasonography revealed a fluid collection in the left upper quadrant that was drained percutaneously. Two weeks later, a further laparotomy was performed when massive dilatation of the small intestine from the anastomosis to the duodenojejunal flexure was found. The left colon looked dusky and non-viable and there was a perforation of the splenic flexure with localised faecal peritonitis. A left hemicolectomy was performed and the ileostomy and mucous fistula were refashioned. The resected intestine once again revealed changes of ischaemic necrosis on histological examination.

Recovery was slow with little return of intestinal function. Oral and enteral feeding were poorly tolerated and parenteral nutrition was instituted and continued after discharge. Two months later he presented as an emergency with a short history of nausea and vomiting. The abdomen was tensely distended and quiet.

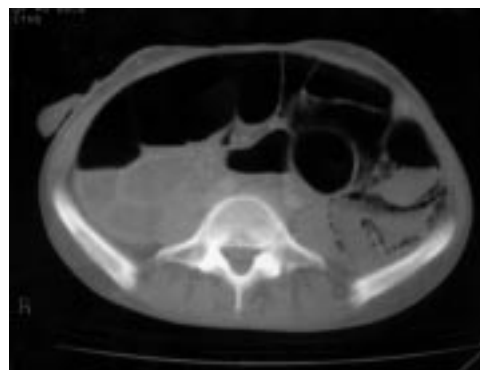


Figure 2 Abdominal CT scan.

Abdominal radiography revealed massively dilated loops of small bowel with gas in the intestinal wall (fig 1). This was confirmed on computed tomography of the abdomen (fig 2) and an urgent laparotomy was performed. The intestine was thin walled and distended with visible pneumatoses in the serosa and patchy areas of ischaemia. A subtotal enterectomy was performed with closure of the mucous fistula, leaving only enough jejunum to form a stoma; the patient subsequently recovered well. He remains dependent on parenteral nutrition, and to date there has been no significant improvement in objective tests of autonomic function.

### Discussion

Ischaemic enterocolitis in the absence of vascular occlusion has been reported as a result of diverse aetiologies that share the common features of hypovolaemia or vasoconstriction. Although this is often due to severe illness and accompanying trauma, haemorrhage, or systemic sepsis,<sup>2</sup> non-occlusive ischaemia has been described sporadically in otherwise well patients that have taken cocaine,<sup>3</sup> have had infectious diarrhoea,<sup>4</sup> or ingested anti-diarrhoeal drugs<sup>5</sup>; it has even been reported after long distance running.<sup>6</sup> We report the occurrence of ischaemic enterocolitis in a patient with severe postural hypotension secondary to idiopathic autonomic neuropathy.

The patient experienced brief profound symptomatic drops in blood pressure on postural change, but at other times maintained an average systolic blood pressure of 90–100 mm Hg. Extrinsic denervation is thought to have relatively little effect on the regulation of intestinal blood flow but may be associated with vasodilatation rather than vasoconstriction.<sup>7</sup> Indeed, denervation necessarily occurs with intestinal transplantation but vascular compromise of the graft is rare. Intrinsic neuronal pathways in the gut may play an important role in the autoregulation of intestinal blood flow, and it is possible that the neuropathy in this patient extended to this system despite the normal appearance of enteric plexi on histopathological examination. Immunohistochemical studies of substance P, vasoactive intestinal polypeptide, and neuropeptide Y were not performed. However, vasoconstriction mediated by the autonomic system is normally subject to “autoregulatory escape” by

local factors that are currently poorly understood. An imbalance in extrinsic autonomic innervation is therefore unlikely to explain the critical mesenteric ischaemia that occurred in this patient.

A plausible explanation of the cause of ischaemia might be activation of the renin-angiotensin system. The mesenteric vasculature may vasoconstrict disproportionately when compared with the systemic response in the setting of hypovolaemia, presumably as a means of maintaining blood flow to the "vital" organs of kidney and brain. In an elegant series of experiments using pericardial tamponade in pigs, this disproportionate increase in mesenteric vascular resistance was attenuated effectively by specific angiotensin II blockade.<sup>8</sup> The mechanism of this increased sensitivity to angiotensin in the mesenteric vasculature is unclear. High affinity angiotensin receptors have been characterised in the enteric circulation,<sup>9</sup> although this has been disputed<sup>10</sup> and there is no convincing evidence of such receptor heterogeneity in the human. Measurement of plasma renin activity was undertaken in our patient, but only some months after enterectomy and while he was dependent on parenteral nutrition. The elevated supine level (2.08 nm/l/h) is therefore of uncertain physiological significance. However, increased angiotensin secretion might contribute to the maintenance of blood pressure in view of the almost complete ablation of measured systemic autonomic responses and could have lead to a "steal" phenomenon from the mesenteric vasculature.

In certain disease states, an infective cause of enterocolitis has been clearly established although the pathological appearances may be remarkably similar to those of ischaemia. Neonatal necrotising enterocolitis occurs in an epidemic fashion and outbreaks on neonatal units can be controlled by attention to sterile precautions, although no single microorganism has been implicated in the aetiology of this condition.<sup>11</sup> A specific clostridial toxin has however been implicated in the pathogenesis of Pigbel, a necrotising jejunoileitis syndrome that occurs in the highlands of Papua New Guinea, and vaccination against this agent appears to prevent the disease.<sup>12</sup> Histopathological changes of ischaemia might occur as a result of infection if increased metabolic demands in the mucosa outstrip vascular reserve, or if inflammatory mediators lead to vasoconstriction, as has been postulated in the neonatal form of necrotising enterocolitis.<sup>13</sup> In our patient, infection with a toxin producing organism could have occurred as a result of the profound ileus secondary to autonomic (cholinergic) denervation leading to stasis and bacterial overgrowth.<sup>14</sup> Indeed, a Gram stain of

colonic tissue from this patient did reveal the presence of Gram positive bacilli, but this is a common secondary feature of necrotic bowel mucosa and insufficient evidence for a bacterial aetiology.

The evidence suggests a primary vascular aetiology in this patient. The presenting location of the condition at the terminal ileum and caecum is consistent with non-occlusive mesenteric ischaemia which has a predilection for this site. The vascular supply to the right colon is variable and the vessels may lack collateral flow by the inconstant development of the marginal artery of Drummond, and therefore behave physiologically as end arteries.<sup>15</sup> At the time of reversal of the ileostomy, the bowel was normal, but only a few days later required further resection for ischaemic necrosis, possibly as a result of perioperative hypotension confounding the underlying autoregulatory deficit. Similarly, the time course of the condition, requiring "piecemeal" resection over a period of six months, would support episodic ischaemia.

Non-occlusive mesenteric ischaemia is an important, if rare, diagnosis and with this case report we add autonomic dysfunction as part of the growing list of potential causes.

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