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CASE REPORT

Familial Visceral Myopathy

A Family with Involvement of Four Generations

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Chronic intestinal pseudoobstruction is characterized by recurrent or persistent symptoms and signs of intestinal obstruction in the absence of an anatomical obstructive lesion. It can be classified as either primary (idiopathic) or secondary when it is due to an underlying disorder such as scleroderma, autonomic neuropathy (as in diabetes mellitus), myxoedema, myotonic dystrophy, or Chagas disease (1, 2).

Primary pseudo-obstruction may be due to a disorder either of the myenteric plexus (visceral neuropathy) or of the smooth muscle (visceral myopathy) of the bowel, either of which may be familial or sporadic. The commonest type is familial visceral myopathy.

Familial visceral myopathy can be transmitted either by a dominant or recessive gene and was first documented in 1938 by Weiss et al, who described six members of a German family with megaduodenum or megacolon (3). Two other families were reported (4, 5), but the disease was first described histologically and named "hereditary hollow visceral myopathy" by Schuffler and Pope in 1977 (6), who found abnormal esophageal manometry in four relatives and a flaccid bladder and bilateral ureteric reflux in two relatives of a 15-year-old girl with chronic intestinal pseudoobstruction. Since 1977, another 11 families with familial visceral myopathy have been described (7–17). The disorder was transmitted as an autosomal dominant in eight (3–9), although sex-linked dominant could not be ruled out in four (3, 6, 7, 10), and in seven families transmission was presumed to be autosomal recessive.

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CASE REPORT

Case 1. A 29-year-old physiotherapist was referred with a history of generalized abdominal pain, bloating, watery diarrhea, and weight loss of 14 lb. These symptoms had been present for at least 10 years but had recently become worse, although she had noticed some improvement following a trial of a gluten-free diet.

At 17 years of age she was seen in a urology outpatient clinic with a history of frequent urinary tract infections, and an IVP revealed a large residual volume of urine in the bladder. At age 19 she was admitted to hospital with symptoms of bowel obstruction, and at laparotomy a volvulus of the ascending colon was reduced. A few months later she was readmitted with similar symptoms and underwent a repeat laparotomy, which was normal. At the age of 27 she became pregnant for the first time and progressed satisfactorily until the 32nd week when she began to lose weight. Contractions commenced in the 39th week but then ceased, and she was admitted for induction of labor due to continuing weight loss, diarrhea, and vomiting. Despite two prostaglandin pessaries, artificial rupture of membranes and syntocinon infusion at maximum dosage, labor failed to progress and she underwent cesarian section 60 hr later.

Examination was normal except that she was underweight. Although she also gave a history of Raynaud's phenomena, there was no evidence of scleroderma.

Initial investigations, including full blood count, urea and electrolytes, liver function tests, thyroid function tests, B_{12}, and folate, were normal but at gastroscopy the stomach was full of food and the duodenum was described as a "dilated atrophic food filled tube." Endoscopic biopsies of the second part of the duodenum showed some shortening of the villi and an increased number of inflammatory cells in the lamina propria but did not support a diagnosis of celiac disease. Flexible sigmoidoscopy and rectal biopsy were normal. Barium studies revealed mild dilatation and impaired peristalsis of the esophagus, gross flaccid dilatation of the duodenum (up to 10 cm) and small bowel, and a long, featureless but not dilated, colon (Figures 1 and 2). An autoantibody screen, including anti scl-70 and anti-centromere antibody, was normal, and it was felt that in view of the family history, familial visceral myopathy was the likely diagnosis. This has now been retrospectively confirmed histologically in her father who had undergone bowel

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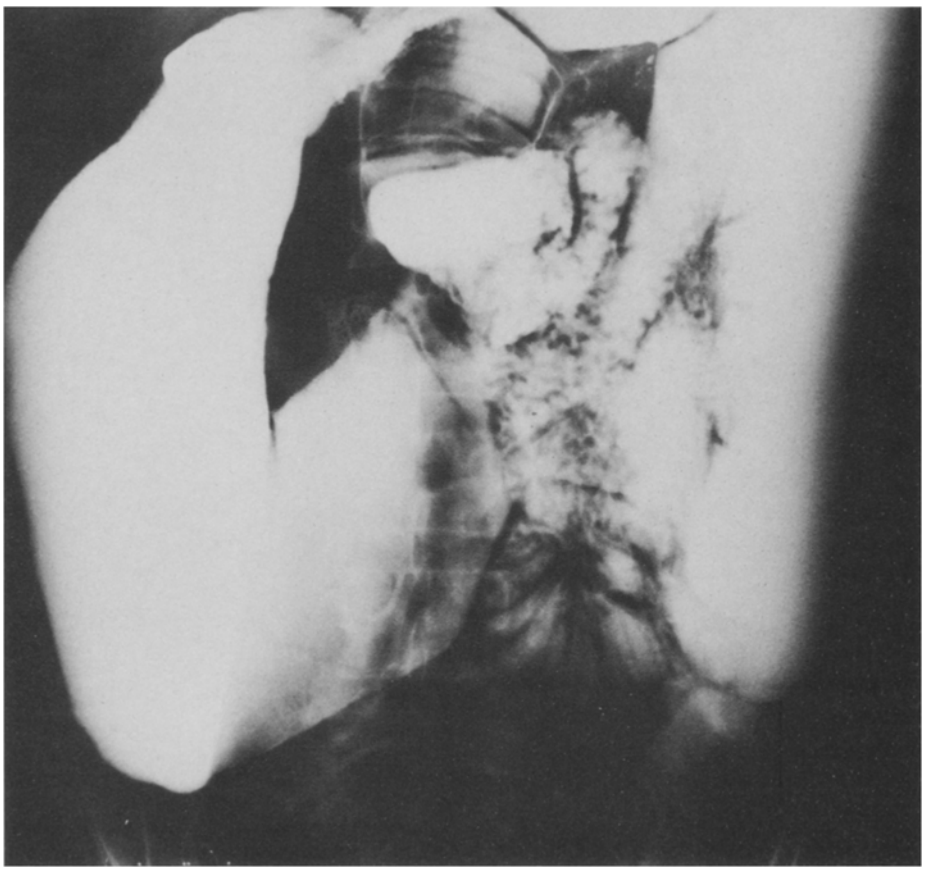

Fig 1. Small bowel examination—early film showing megaduodenum.

resection a few years earlier, although at the time of resection the diagnosis had been overlooked.

A glucose hydrogen breath test was grossly abnormal, and she was treated with a two week course of tetracycline and metronidazole with excellent results. Six months later she has no pain, has put on 5 kg in weight, and is eating a normal diet. Her bowel habit is much improved to three times a day with formed motions, and bloating has diminished.

Case 2. The 28-year-old brother of the patient described in case 1 was noted as an infant to be slow in gaining control of his bowels and bladder and at the age of 8 was referred to the urology outpatient clinic with recurrent urinary tract infections and leakage of urine when laughing. IVP demonstrated megacystis and megaureters. Bladder neck outlet obstruction was excluded by cystourethroscopy. At the age of 12 years he developed acute appendicitis, and the resected appendix measured 15 cm. He is now asymptomatic apart from requiring suprapubic pressure to start the urinary stream.

He agreed to undergo a modified barium swallow and small bowel examination to help in the diagnosis of his sister. This showed markedly reduced peristalsis in both esophagus and small bowel, although there was no bowel dilatation.

Case 3. The 60-year-old father of the patient described in case 1 had a history of alternating constipation and diarrhea, bloating, and abdominal discomfort for at least 20 years. He was investigated for the above symptoms at the age of 53. Barium enema revealed a redundant sigmoid loop and very long colon. Two years later he was admitted as an emergency with abdominal pain and underwent a sigmoid colectomy for volvulus. Postoperatively he went into urinary retention, and an IVP revealed a grossly distended bladder. A small amount of prostate and bladder neck was resected transurethrally, although there did not appear to be any significant obstruction.

Currently he is fit for his years but does have to sit down to generate sufficient pressure to start the urinary stream and he does not have the desire to urinate. His gastrointestinal symptoms remain, but have improved since the sigmoid colectomy. He also agreed to undergo a modified barium swallow and small bowel examination. This showed megaduodenum (6 cm) and markedly reduced peristalsis throughout the esophagus and small bowel.

The histological material obtained at sigmoid colectomy was initially reported as unremarkable but was recently reviewed. This revealed variable thinning of the outer longitudinal coat of the muscularis propria, which was completely atrophied, in places. The muscle fibers, some of which contained large, atypical nuclei were surrounded by fibrous tissue. Some muscle fibers ap-

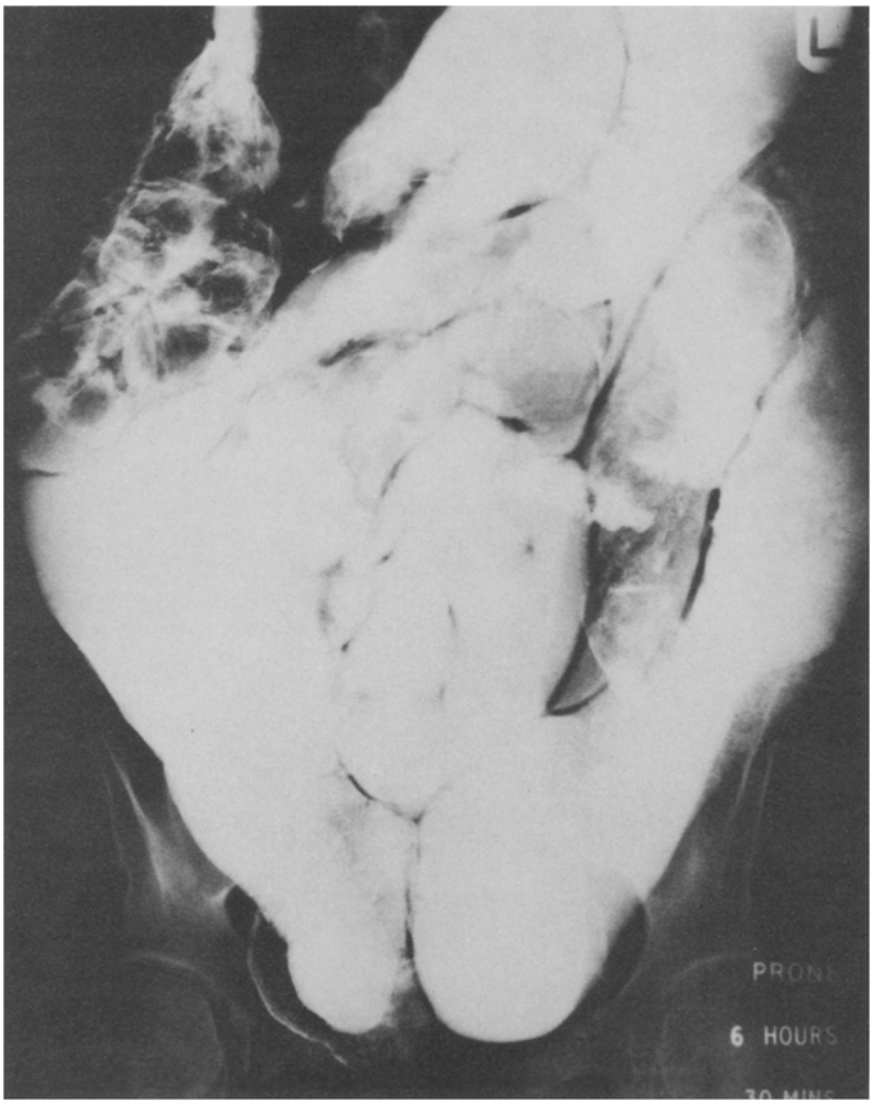

Fig 2. Small bowel examination—late film demonstrating markedly delayed transit time and dilated ileal loops.

peared vacuolated and there was variable eosinophilia. This is illustrated in Figure 3.

Cases 4 and 5. The grandfather and great-grandfather of the patient described in case 1 are both deceased but both suffered from intractable constipation as described by the grandfather in 1973. He entitled this description: "Colonic sluggishness in 2 generations."

> I am 77 years old. As a young man and increasingly as I grew older, I have found it necessary to give myself water enemas. I now do so every day. If I don't I suffer progressive discomfort due to accumulation in my lower and ultimately my upper intestine.
>
> In addition, I have to take laxatives—(currently for the last 5 years I have used 4 tablets daily of Senokot; exceptionally when needed I also take 2 Dulcolax pills).
>
> My father who was a doctor (G.P.) and who died at 91, also found it necessary to use enemas daily. We often discussed what appeared to be a family weakness or idiosyncrasy—a sluggish lower bowel.

The main features of each case are summarized in Table 1, and the pedigree of the family is illustrated in Figure 4. The family originates from Denmark—the grandfather moved to England as a young man. The proband has a 2-year-old son who has shown no evidence of familial visceral myopathy so far.

DISCUSSION

The types of lesions seen in the dominant and recessive forms of familial visceral myopathy have some distinguishing features, although histologi-

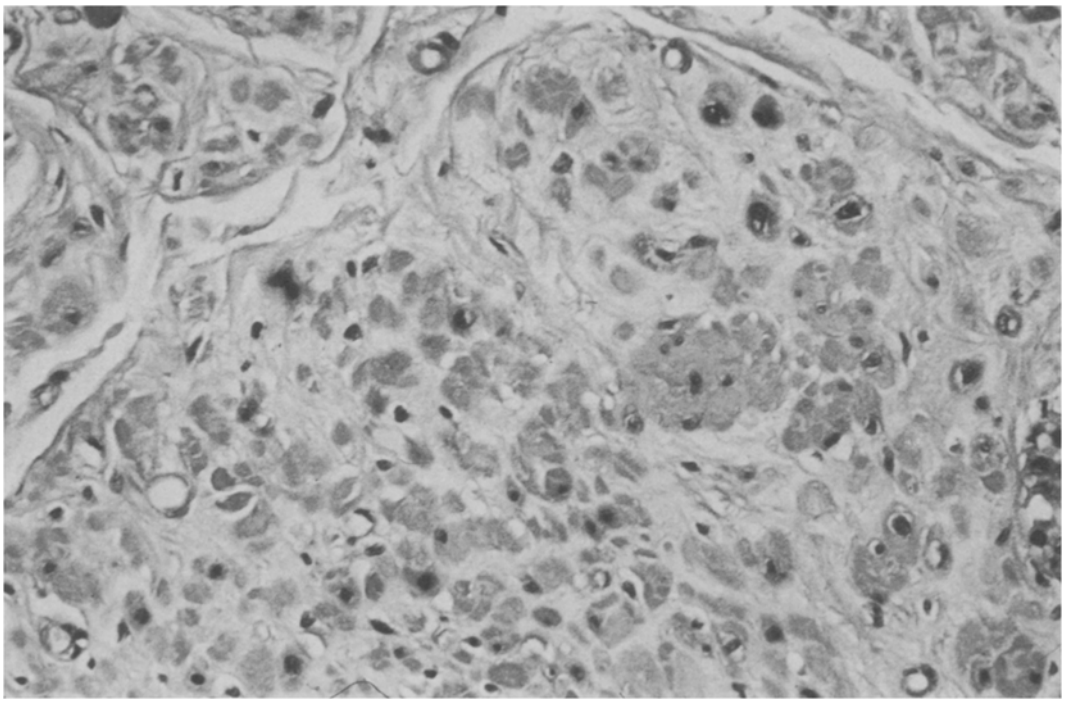

Fig 3. Part of inner circular muscle layer showing fiber loss with interstitial fibrosis and occasional vacuolated ("hollow") fibers with marked nuclear pleomorphism.

cally they are identical. Anuras et al (13) summarized the features of the two types based on the 10 families that were reported at that time and described another family with probable autosomal recessive transmission that did not seem to fit into either category in that they had marked dilatation of the entire digestive tract from the esophagus to the rectum.

TABLE 1. SUMMARY OF MAIN CLINICAL FEATURES AND LESIONS PRESENT IN THIS FAMILY

Case	*Predominant symptom*	*Gastrointestinal lesions*	*Urologic lesions*
1	Diarrhea	Megaduodenum and dilated small bowel; esophageal aperistalsis and redundant colon	Large residual volume of urine in bladder
2	Urinary retention	Aperistalsis of esophagus and small bowel	Megacystis and megaureter
3	Alternating diarrhea and constipation	Megaduodenum; aperistalsis of esophagus and small bowel; redundant colon	Large residual volume of urine in bladder
4	Constipation	Not studied	Not studied
5	Constipation	Not studied	Not studied

Lesions in the dominant type include esophageal dilatation, megaduodenum, redundant colon, and megacystis, in contrast to the recessive type in which there may be dilatation of the entire small

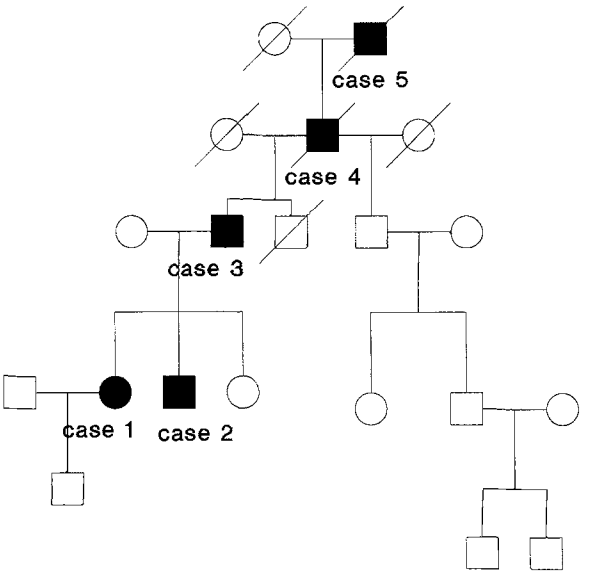

Fig 4. Pedigree of the family. Males are denoted by squares and females by circles. The dark circle or square indicates symptomatic case.

intestine but bladder involvement has never been described. Involvement of the iris has also been described in one family with autosomal dominant transmission (1). Symptoms in the dominant type are variable, whereas patients with the recessive form usually present with severe abdominal pain, intestinal pseudoobstruction, and malnutrition, and the prognosis is poorer.

Since the paper by Anuras et al, a further four families have been described (10, 15, 16, 17). In three families, transmission was thought to be autosomal recessive and consanguinous marriages were involved in two (15, 17). Rodrigues et al recently described a family with dominant transmission in whom at least two members had extensive involvement of small and large bowel and required home parenteral nutrition and surgical treatment (10).

Our propositus had marked dilatation of the duodenum, jejunum and ileum; a redundant colon; and markedly abnormal esophageal peristalsis. Two other members of our family also had abnormal peristalsis from esophagus to at least the terminal ileum. Thus, in the light of this and other recently reported families, the pattern of bowel involvement in the two types does not appear to be as clear-cut as was previously thought.

Our family's history supports the impression that the dominant form of the disease usually has a good prognosis, although in fact it can be very variable, even in members of the same family. In the family described by Faulk et al (7), two of the 18 affected members were asymptomatic and four others died between the ages of 20 and 45. Similarly, Schuffler and Pope (6) describe a family where one member was severely affected with weight loss and pseudoobstruction and four affected relatives complained only of mild dysphagia. There is a much greater similarity of severity of disease in the families who have autosomal recessive-type transmission: Anuras et al described three patients who all died in their twenties of malnutrition; Alstead et al (15) described 11 family members, eight of whom died before the age of 30.

We have no proof that the uterus was involved in this case; the failure of labor to progress may have been due to other causes. Cephalopelvic disproportion seems an unlikely explanation for this in that the head was well descended into the pelvis and the baby was small. The possibility of uterine involvement causing failure to progress during labor should be borne in mind when a patient with familial visceral myopathy becomes pregnant.

Our propositus could have been misdiagnosed as having scleroderma, particularly in view of the misleading history of Raynaud's phenomenon. Systemic sclerosis may rarely present with bowel involvement in the absence of any skin changes (18), but familial visceral myopathy may be distinguished histologically by the characteristic appearance of the degenerating muscle cells and vacuolation, the normal vasculature, and predominant involvement of the external layer (19).

As in our case some symptomatic improvement may be achieved by dietary manipulation. This feature together with the nonspecific changes reported on jejunal biopsy (probably due to damage resulting from secondary bacterial overgrowth) may cause diagnostic confusion with celiac disease. Indeed the histological changes may be so severe that one case was misdiagnosed and treated with a gluten-free diet for several years (19).

It has been suggested that familial visceral myopathy may be diagnosed by endoscopic biopsy (16). In our case neither duodenal or rectal biopsies were helpful, although several contained muscularis mucosae and the duodenum was certainly involved. There was some vacuolation of fibers in the muscularis mucosae, but this is frequently seen to some degree in any endoscopic biopsy (probably as a fixation artifact). The fact that the myopathy starts and is maximal in the external coat of the muscularis propria and involvement of the muscularis mucosae is much less marked and patchy means that diagnosis by mucosal biopsy is unlikely. The diagnosis was missed when the routine sections from the sigmoid volvulus were initially examined, and special stains are helpful in making the diagnosis.

In summary, familial visceral myopathy is a disease affecting smooth muscle mainly in the alimentary tract but to a variable extent. It is difficult both to diagnose and to treat, and it may not be as rare as previously thought as mildly affected patients may not present or be diagnosed.

SUMMARY

A family with the autosomal dominant form of familial visceral myopathy is described involving four generations. The members illustrate several different clinical presentations including severe constipation, diarrhea, alternating constipation and

diarrhea, volvulus, urinary tract infection, and retention of urine. One patient's history suggested that the uterus may have been involved. Diagnosis of this rare disease requires an awareness of the variable presentation and a careful histological examination of full-thickness sections of bowel. The potential pitfalls in both histological and clinical diagnosis of this condition are demonstrated in this family's history. The extensive involvement of small and large bowel in at least two family members is unusual in the autosomal dominant form of the disease, but their course has so far been favorable, lending further evidence to the impression that prognosis is good. This is of importance for genetic counseling of families who have this very rare disease.

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