Pediatr Surg Int (2002) 18: 13–20

MAIN TOPIC

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Unusual variations of gastrointestinal smooth muscle abnormalities associated with chronic intestinal pseudo-obstruction

Abstract The clinicopathological spectrum of gastrointestinal (GI) smooth-muscle abnormalities associated with chronic intestinal pseudo-obstruction (CIPO) includes numerous heterogeneous conditions that are often ill-defined and poorly understood. Primary GI smooth-muscle abnormalities include familial and sporadic forms. Secondary involvement of GI smooth-muscle may result from associated GI and systemic conditions, but is less frequent than in adults. This study documents the clinicopathological findings observed in 12 South African patients with unusual forms of visceral smooth-muscle abnormalities not conforming to the diagnostic criteria of known primary visceral myopathies at the Tygerberg and Red Cross Childrens' Hospitals over a 14-year period (July 1985 through January 1999). Congenital muscle defects occurred in 5 patients where layers of bowel-wall muscle were absent or attenuated. Idiopathic fibrosis and ultrastructural features of perinuclear and mitochondrial vacuolisation were noted in 2 patients. A 21-year-old female with long-standing pseudo-obstruction demonstrated diminished immunohistochemical expression of enteric alpha-smooth-muscle actin without associated muscular degeneration or fibrosis. A secondary complication of dermatomyositis (bowel perforation) occurred twice in 1 patient. In 3 further patients (1 each with anorectal malformation, long-segment Hirschsprung's disease, and intestinal neuronal dysplasia), muscle fibrosis appeared during progression of the pre-existing disease. Visceral myopathies are poorly understood conditions that may present with CIPO. Unusual variations occur that do not conform to the usual recognised histological patterns. Secondary involvement may also be more common than anticipated in children. The challenge to further understanding these uncommon conditions lies in timely diagnosis and identification of early, subtle signs. Optimal and extensive application of various diagnostic modalities, including the development of new diagnostic tools, is of considerable importance in identifying hitherto unexplained CIPO due to GI smooth-muscle abnormalities.

Keywords Pseudoobstruction · Intestinal · Visceral myopathy · Non-familial

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Introduction

Congenital or acquired disorders affecting visceral smooth-muscle are uncommon causes of chronic intestinal pseudo-obstruction (CIPO). Many of the congenital conditions are genetically determined [10, 40–42] and include both familial [10, 42] and sporadic [28] types of visceral myopathies (VM). The familial forms are the most frequently described, and at least two distinct forms exist (autosomal dominant or recessive) [1, 2, 19]. Secondary causes, on the other hand, appear to be less frequent than in adults and have not been a feature of previous reports of VMs in children [1, 2, 40, 42, 43].

VMs are characterised by degeneration and progressive fibrous replacement of intestinal smooth muscle, which results in poor neuromuscular control with subsequent motility disturbances. Although segmental forms of VM do occur, the entire gastrointestinal (GI) tract is more frequently affected. In addition, the smooth-muscle of other organs such as the urinary tract, arteries, and bronchioles may be affected. Prominent involvement of the urinary tract may include hydroureter and megacystis as well as other features of the

megacystis-microcolon-intestinal hypoperistalsis syndrome [16, 31, 34]. African degenerative leiomyopathy (ADL) is a distinctive form of degenerative VM of uncertain etiology occurring in our geographical area [24, 25, 35] that is distinguished by a generally older age group as well as typical histopathological and ultrastructural features.

Recently, other variants of smooth-muscle abnormalities associated with CIPO have been identified that do not necessarily conform to the above descriptions and require further study. This miscellaneous group represents a heterogeneous spectrum of clinicopathological conditions and includes developmental abnormalities of the intestinal muscle coats [46]. CIPO may also result from secondary GI involvement in other conditions such as scleroderma, Chagas' disease [10], intestinal amyloidosis [47], cytomegalovirus infection [3], idiopathic myositis of the small intestine in children [15], and myotonic dystrophy [4]. There also appear to be a number of ill-defined forms of smooth-muscle degeneration and/or fibrosis of the muscularis propria that are poorly understood and may be due to other factors such as DNA viruses [9]. Current evidence [46] indicates that early morphological changes or cellular defects of smooth-muscle may escape routine histological examination [42, 46].

The aim of this study was to document the clinicopathological features observed in patients with GI smooth-muscle abnormalities associated with CIPO that did not conform to the diagnostic criteria of the acknowledged variants of familial and sporadic VMs or ADL.

Materials and methods

The clinical and pathologic records of 11 children and 1 young adult who presented to the Red Cross Childrens' and Tygerberg Hospitals over a 14-year period (July 1985 through January 1999) with GI pseudo-obstruction due to unusual variants of GI smooth-muscle abnormalities were reviewed. Patient characteristics evaluated included age, sex, nutritional status, concomitant diseases, and age of onset, frequency, and nature of symptoms in addition to the physical findings.

In 5 cases with muscular defects the specimens consisted of surgical resections of bowel following perforation. In the remaining 7, fresh full-thickness biopsies of bowel wall were rapidly transported to the laboratory, divided, and orientated for histological examination. One half of each specimen was snap-frozen and stored at −80 °C for acetylcholinesterase (AChE) stains. Small pieces of the muscularis propria were then fixed in 2,5% glutaraldehyde for electron microscopy (EM). The remaining tissue was fixed in 10% buffered formalin, processed, and paraffin-embedded according to routine histopathological techniques.

Serial 5-μm paraffin sections were stained with haematoxylin and eosin (H&E) and Masson trichrome for light microscopy. In certain cases additional histochemical techniques were used such as prolonged exposure to H&E with added safranin, which stains degenerating muscle fibres pink, and Smith's silver stain for assessment of the myenteric plexus. The AChE was studied using cryostat sections and well-established routine techniques with appropriate positive controls. EM was performed where indicated with documentation of the contractile filaments, cytoplasmic vacuolisation, integrity of cell membranes, swelling and degeneration of organelles, lysosomal abnormalities, and intercellular stroma.

A routine streptavidin-biotin-complex technique was used to immunostain representative paraffin sections with antibodies directed against neurofilament, vasoactive intestinal polypeptide (VIP), neuron-specific enolase, and alpha- and gamma-smooth-muscle actins (SMA) (Cga7; 35BETA E11; Universal Biologicals, London). Large- and small-bowel sections from patient 8 were immunostained with monoclonal antibodies to α-SMA (1A4) and desmin (Dako, High Wycombe, UK).

Results

Clinical features

Twelve patients presented over a 14-year period (July 1985 through January 1999) with CIPO and unusual GI smooth-muscle abnormalities that did not conform to the acknowledged variants of familial, sporadic, or ADL; 39 patients presenting with ADL during the same time period are reported elsewhere. The ages ranged from 1 day to 21 years and the sex distribution was more or less equal. Because of the low-amplitude peristalsis, the major clinical presentation was chronic constipation, pseudo-obstruction with abdominal distention, and associated pain. Radiographic motility studies showed a marked delay in GI transit in 3 cases. None of the patients had clinicopathologic features of progressive systemic sclerosis.

Case Reports

Congenital muscle defects (Cases 1–5)

Five neonates presented with an acute abdomen and peritonitis. Abdominal X-ray films showed free intra-abdominal air. At surgery, intestinal perforation of the terminal small bowel and colon was identified. In each case the edges of the perforated area were biopsied and submitted for histology. Sections included the perforated bowel as well as areas around the perforation. On histological examination, the bowel was oedematous with haemorrhage into the submucosa in affected areas. There was marked attenuation or absence of the muscularis propria in isolated segments with intervening segments of normal bowel. A few circular-muscle fibres were present in the defective areas in 4 of the 5 patients (Fig. 1).

Idiopathic fibrosis of intestinal wall (Case 6)

One 9-year-old female presented with chronic constipation and pseudo-obstruction. Radiographic studies showed a normal upper GI tract, but colonic inertia was present on follow-through. A transit study demonstrated normal small-bowel motility with slow colonic transit. Colonoscopy revealed no abnormalities and a

Fig. 1 Section of bowel wall showing developmental disturbance of muscularis propria, congested blood vessels, and only rudimentary portions of muscularis propria but relatively good development of muscularis mucosae (× 25)

full-thickness rectal biopsy was performed 4 °cm above the dentate line. Clinical findings suggestive of associated systemic disease were not observed. Full-thickness rectal biopsies showed extensive fibrosis of the bowel wall without other diagnostic features, associated with atrophy and replacement of smooth-muscle. Degeneration and vacuolisation characteristic of a VM or ADL were absent. Normal ganglion cells were present in the superficial and deep plexuses and AChE staining did not show abnormal neurite proliferation.

Peri-*nuclear mitochondrial* vacuolisation (case 7)

A 5-year-old male presented with chronic constipation and pseudo-obstruction. Radiographic studies showed a normal upper GI tract, but colonic inertia was present on follow-through. A transit study demonstrated normal small-bowel motility with slow colonic transit. Colonoscopy revealed no abnormalities, and a full-thickness rectal biopsy performed 4 cm above the dentate line showed severe myofibrosis associated with muscle-cell atrophy and degeneration. The smooth muscle varied in density on EM, and large vacuoles were noted in perinuclear mitochondria (Fig. 2). However, mitochondrial inclusions were absent.

Complex GI muscular defects with diminished expression of α-SMA (case 8)

A 21-year-old woman presented with long-standing CIPO since early childhood. Surgical resection of the colon failed to prevent progression of the disease to the small bowel and she continued to present with obstructive episodes in the absence of a mechanical obstruction, requiring a number of small-bowel resections. She has had numerous obstructive episodes but managed to continue enteral feeding. There was no family history of similar problems. Evidence of systemic or syndromic manifestations was absent. X-ray films of the thoracic and lumbar vertebrae revealed no abnormalities. There were no other features of possible split notocord syndrome.

Several full-thickness biopsies of the large and small intestine including surgical resection of the colon and ileum revealed separate foci of fusion between the muscularis mucosae and muscularis propria, occasionally with associated fibrosis (Fig. 3a). Thick but incomplete layers of smooth-muscle occasionally occurred in the submucosa, immediately internal to the circular-muscle layer (Fig. 3b). An additional thin, incomplete layer of smooth-muscle was present on the outside of the external longitudinal muscle layer. None of these changes were in association with scarring, inflammation, foreign-body reactions, or hemosiderin, which might have pointed to previous surgery. There was no evidence of an enteric duplication. Ganglion cells appeared morphologically normal and there was no increase in AChE-positive nerve fibres. Immunohistochemistry showed absent or markedly reduced expression of α-SMA within segments of the circular layer of the muscularis propria (Fig. 3), except for strong α-SMA expression at the border immediately adjacent to the submucosa. Although this change was seen in several sections, there were other areas with normal α-SMA positivity. α-SMA was present within the muscularis mucosae, longitudinal layer of the muscularis propria, and vessel walls in all sections. Interpretation was made difficult by the fact that control α-SMA stains revealed some degree of variation of expression in the circular-muscle layer of the colon. Desmin was positive in all layers. EM of the circular-muscle layer in an affected small-bowel biopsy showed normal myofilaments and dense bodies without degenerative features, changes in organelles, or cytoplasmic vacuolisation.

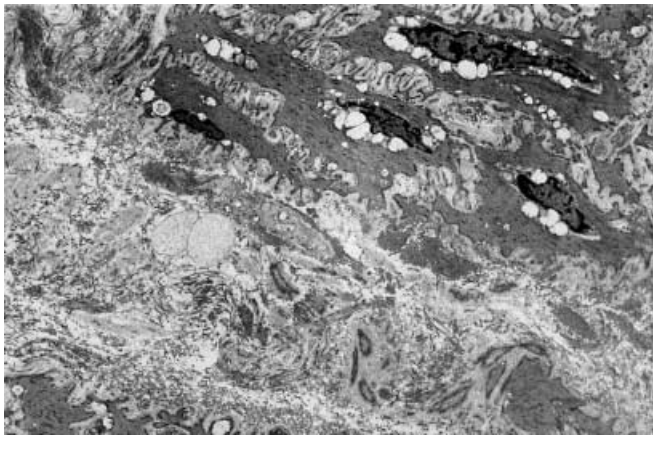

Fig. 2 Electron microscopy shows occasional atrophied smooth-muscle cells separated by granular extracellular material and type 1 collagen, no characteristic peripheral subplasmalemmal or perinuclear vacuolation, but striking mitochondrial vacuolation. No marked disarray of contractile filaments

Secondary involvement of visceral smooth-muscle: intestinal smooth-muscle abnormalities secondary to dermatomyositis (case 9)

A 6-year-old girl with active dermatomyositis on muscle biopsy presented with an acute abdomen and underwent surgery at another institution for possible appendicitis; the diagnosis of perforation of the third part of the duodenum was made on an upper contrast study following referral to our unit. Pyloric exclusion and direct repair eventually resulted in healing. A second duodenal perforation occurred some 2 years later at a different site, but was sealed off and successfully treated conservatively. Full-thickness muscle necrosis was present at the area of perforation and a further biopsy of the bowel wall adjacent to the perforation showed oedematous, haemorrhagic mucosa and submucosa with plasma cells, lymphocytes, and eosinophils but no evidence of vasculitis.

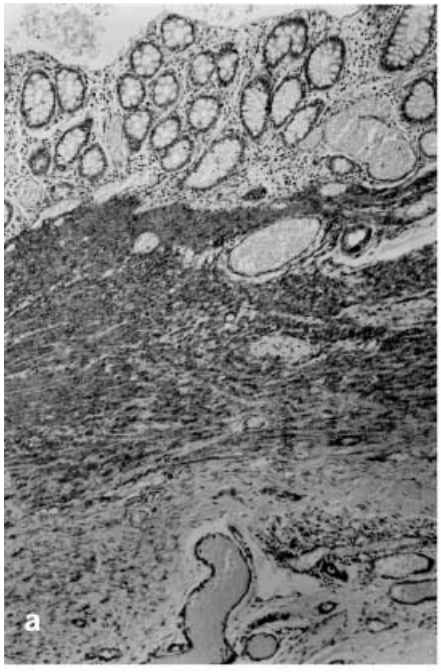

Fig. 3a Immunohistochemical staining reveals absence or reduced expression of alpha-smooth-muscle actin in circular layer of muscularis propria. Note positive staining throughout longditudinal layer and in innermost muscle cells (*arrows*) adjacent to submucosa. Note fusion of layers of muscularis propria with associated fibrosis on right side

Fig. 3b Immunohistochemical staining for alpha-smooth-muscle-actin shows thin and incomplete muscular layer outside longitudinal muscle layer (*arrows*)

Secondary association with other GI malformations (cases 10–12)

In 3 patients, muscular degeneration was identified secondary to other long-standing conditions affecting the colon. The histological specimens were obtained from surgical procedures performed at a late stage because of persisting dysfunction. These included 1 patient with chronic dysfunction for a number of years following a low anorectal malformation (ARM), 1 in whom Hirschsprung's disease (HD) had previously been identified and treated surgically, and 1 with a previous histological diagnosis of intestinal neuronal dysplasia (IND). This patient had symptoms relating to early childhood and presented with a functional intestinal obstruction similar to that of HD. A biopsy was taken some years later because of the recurrence of obstructive symptoms.

A resected massive megacolon in patient 10 with a low ARM showed chronic inflammatory cells in the lamina propria, oedematous submucosal tissue, and oedema of the muscularis propria. The biopsy was not related to any previous surgical site. There were areas of perimuscular fibrosis in the muscularis mucosae and muscularis propria on Masson trichrome stains. Although present in this case, inflammatory foci were strikingly absent in the remaining patients. A late biopsy of the transverse colon in patient 11 with ichthyosis and long-segment HD (splenic flexure), showed the presence of ganglion cells, but the muscularis propria was oedematous and interstitial extracellular fibrosis similar to that seen in ADL was present. The bowel of the patient with IND (case 12) showed hyperganglionosis as well as excessive AChE secreting nerve fibrils in the lamina propria of the colonic wall, in keeping with the diagnosis of IND. Although early specimens showed normal musculature in the limited tissue available, biopsies taken because of recurrent obstruction some years later demonstrated vacuolar degeneration of smooth-muscle fibres and early fibrous replacement similar to that seen in ADL.

Discussion

The causes of CIPO have been divided into neuropathic, myopathic, and those with no recognisable neuropathy or myopathy [28, 39]. Current emphasis remains on neural pathology [28], but in many cases of megacolon and megarectum no adequate explanation may be

identified. Although disorders of smooth muscle are a well-documented cause of intestinal pseudo-obstruction, they are poorly understood and probably underreported. Reasons for possible underreporting include a lack of awareness as well as the fact that suction rectal biopsies (unless full-thickness) used in the diagnosis of HD are not generally representative of the muscularis propria, preventing its evaluation.

Krishnamurthy and Schuffler [28] previously classified these conditions, with different subtypes being separated by the anatomical nature or extent of the muscular changes. Further variants have since been reported with emphasis on associated clinical findings such as multiple basal-cell carcinomas and atypical naevus syndrome [13], or mitochondrial abnormalities [30, 34] observed on EM. It is possible that some of these conditions do not represent well-defined entities, but rather variants of either known or currently ill-defined disorders. A lack of detailed information on clinical, pathological, EM, immunohistochemical, genetic, and molecular features in many studies complicates the accurate and relevant clinical classification of these conditions. As a result, there is currently no generally accepted up-to-date classification of GI muscle disorders resulting in CIPO. An attempt by us to update the classification is presented in Table 1, but cannot be viewed as final or comprehensive and will be added to as further information becomes available. Future efforts to classify these conditions should emphasise clinicopathological entities rather than histopathological features only.

Both types of familial VM (autosomal dominant or recessive forms [1, 2, 10, 42]), have similar histological features in that the external longitudinal layer of the muscularis propria is more severely affected than the inner circular-muscle layers. Thus, classification is difficult when based on histological criteria alone. There are differences in the clinical presentation, however, with the autosomal-dominant type (hereditary megaduodenum) often presenting with oesophageal motility disorders, megaduodenum, megacolon and megacystis. In contrast, the autosomal-recessive form is associated with ptosis and ophthalmoplegia and involves the stomach and entire small bowel with numerous diverticula [1]. A third familial type in which patients have dilatation of the entire GI tract from oesophagus to rectum has been reported [2].

Sporadic forms of hollow VM syndrome are also characterised by degeneration and fibrous replacement of the smooth-muscle of the GI tract with possible additional involvement of the urinary tract [14, 18, 47]. In light of more recent reports [24, 25, 29, 34, 45], this classification may be expanded to include at least 2 or 3 additional primary VMs.

A form of sporadic VM identified mainly in African patients [24, 25] was specifically excluded from this study and is reported elsewhere (see accompanying article). In addition, some cases of megacystis-microcolon-intestinal hypoperistalsis syndrome are probably a distinct type of VM [35], but in many there are a mixture of neural and myopathic features. Two patients encountered in our series were excluded as only neurological abnormalities (ganglioneuromatosis) were identified.

Mitochondrial defects have been reported to result in intestinal pseudo-obstruction and may occur in association with ophthalmoplegia and ptosis [29], but also in mitochondrial neurogastrointestinal encepaholopathy [30, 34]. The patient described here with ultrastructural vacuolisation of mitochondria did not have any other neurological findings.

In light of our experience, it would appear that further ill-defined forms of primary VM probably exist, but most likely require special expertise to separate them from other VMs. One example is alpha-2-SMA deficiency,

Table 1 Classification of visceral myopathies

A. Primary	
1. Familial visceral myopathies	
Type 1: autosomal dominant	Oesophageal motility disturbances, megaduodenum, megarectum, and megacystis
Type 2: autosomal recessive	Ptosis, external ophthalmoplegia, stomach/small-bowel involvement
Type 3: autosomal recessive	Dilatation of entire GI tract
2. Sporadic	
a. Mitochondrial defects	Ptosis/ophthalmoplegia [29]
b. African degenerative leiomyopathy	Colon primary target/progressive/older age/geographic
c. Megacystis-microcolon-intestinal hypoperistalsis syndrome	Neurological and myenteric defects [35]
d. Alpha-2-actin deficiency	[44, 46]
B. Secondary involvement of visceral smooth-muscle	
Progressive systemic sclerosis/polymyositis	
Ehlers-Danlos syndrome	
Dermatomyositis	
Dystrophica myotonia	
Progressive muscular dystrophy	
Amyloidosis (uncommon in children)	
? Ceroidosis	

described initially by Smith et al. [45, 46]. A patient in this study had diminished α-SMA expression in association with complex and difficult-to-explain anatomical abnormalities of the muscular layers. However, the segmental distribution of this observation, the normal ultrastructural appearance of the contractile filaments, and the variable staining in control tissues raise the possibility that the diminished immunohistochemical expression of α-SMA may not represent the same condition previously reported [45, 46].

Clinical symptoms in VMs may range from none to intestinal or uropathic obstruction. Although the emphasis is mainly on the GI and possibly the genitourinary system [14, 18, 47], it may be present to a lesser extent in the smooth muscle of the blood vessels [11, 42], bile ducts, and bronchioles and give rise to other clinical symptoms. Eye-muscle involvement (ptosis and external ophthalmoplegia) has also been reported [1]. Histologically, the diagnosis is based on degeneration and vacuolar degeneration of smooth-muscle cells and their subsequent replacement with fibrous tissue with an essentially normal intermyenteric nerve plexus and the absence of an inflammatory infiltrate or vasculitis [10, 42]. These changes result in poor intestinal function [32, 38, 41, 42]. The smooth-muscle changes may, however, represent a late stage in the disease, and routine histological investigations may only identify the end-point of myofibrosis. The more subtle features that may occur at an earlier stage are difficult to evaluate without the use of special staining methods. Stains for fibrous tissue (Masson trichrome) are generally required to identify the fibrous tissue in the muscle. In addition, techniques such as longer exposure to H & E where the diseased muscle stains degenerating muscle a pinker color, Smith's silver stain, and EM are generally required to classify the abnormal histological features.

Using these and newer techniques, Smith and Milla [45] have described four histological types (type 1: myopathy with autophagic activity; type 2: pink-blush myopathy with nuclear crowding; type 3: familial diffuse abnormal muscle layering; type 4: segmental additional muscle coat). In addition, a miscellaneous group with varying degrees of fibrosis, atrophy of myocytes, vacuolisation, and immunohistochemical changes were observed in their series. It is probable that some of our study cohort may fall into this category and require further evaluation. We have found the technique of longer exposure to H&E staining to be of value, but it is clear that more specific staining techniques will be required to identify subtle changes in the muscle fibres, particularly in the early stages of the disease process.

The association with long-standing conditions of the GI tract particularly raises the issue of whether certain myopathies could be a final common pathway for other conditions affecting the GI neuromuscular system. Although the identification of secondary muscle changes in patients with long-standing conditions (as in 3 patients in this study) favours this hypothesis; the absence of neuronal changes mitigates it as a generalised explanation.

Although rare, secondary causes such as progressive systemic sclerosis (PSS), Ehlers-Danlos syndrome, dermatomyositis, systemic lupus erythematosis (SLE), or dystrophica myotonia, although more common in adults, are not unknown in children and should be looked for. PSS is defined by typical cutaneous and serologic criteria, and the differentiation of VMs from PSS is generally made on the basis of atrophy and smooth-muscle replacement and, more specifically, the lack of vacuolar degeneration and preference for the circular-muscle layer characteristic of this multisystem disorder [22, 41, 43]. In our series, the characteristic features of PSS, e.g., atrophy and smooth-muscle replacement, were absent. In addition, the presence of vacuolar degeneration and preference for the circular-muscle layer as well as absence of the typical cutaneous and serologic features of PSS mitigates against this condition being present. The absence of features of SLE as well as a lack of anti-ribonucleoprotein and speckled anti-nuclear antibodies differentiates these from other connective-tissue diseases of childhood [26, 43]. Dermatomyositis is a recognised cause of secondary smooth-muscle involvement, and intestinal perforation has been known to occur, typically in the upper part of the GI tract [39] as in the patient reported in this study.

Currently, VMs mostly carry a poor prognosis. Symptomatology may be severe and disabling, and the condition may be life-threatening in the long term. Manometric studies have proved helpful in distinguishing between neuropathic, myopathic, and normal peristaltic bowel movements [8]. Medical treatment of CIPO aims to overcome the underlying motility disorder and includes the use of low-residue diets, prokinetic agents, and colonic irrigation [36]. Prokinetic drugs may be of value [5, 7] in attempting to restore normal GI motility [5, 7], but have limited value in the long term as the intestinal smooth-muscle is progressively replaced by fibrosis in the majority of cases.

Surgery is generally regarded to be of value in rare segmental forms of the disease, but is usually avoided unless essential for the management of an intra-abdominal emergency in patients with diffuse intestinal involvement. Gross abdominal distention may, however, be relieved by a percutaneous gastrostomy if gastric distention is prominent [12]. Jejunal plication with a feeding jejunostomy has also been described in an adult patient [31]. Similarly, a decompressing caecostomy or caecostomy button may be of value in decompressing patients with troublesome megacolon [17]. Long-term parenteral nutrition may be required to maintain nutrition in some patients. An understanding of the basic pathogenesis of VM should be used to direct the clinical management in these cases. Future development of more specific drugs is required to maximise intestinal function. In addition, evaluation of the role of electrical intestinal pacemakers and/or intestinal transplantation will give some hope in the management of these conditions.

In conclusion, VMs are poorly understood clinicopathological conditions that may present with CIPO due to heterogeneous and unrelated types of GI smooth-muscle abnormalities. Unusual variations occur that do not conform to the usual recognised histological patterns. Secondary involvement may also be more common than anticipated in children. The challenge to further understanding of these uncommon conditions lies in the timely diagnosis and identification of early, subtle signs. The development and evaluation of new diagnostic tools is of considerable importance in identifying hitherto unexplained motility disturbances.

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