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Non-familial visceral myopathy: clinical and pathologic features of degenerative leiomyopathy

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Abstract Degenerative leiomyopathy (DL) is a distinctive form of acquired degenerative visceral myopathy of uncertain etiology that occurs largely in Africa and results in intestinal pseudo-obstruction (IP). In this review of 39 patients from the Western Cape region of South Africa, the mean age at presentation was 9.5 years (range 6 months to 16 years). Characteristic clinical features included a chronic, insidious history of repeated attacks of abdominal distension, abdominal pain, and vomiting. Marked gaseous distension with atony and IP, especially of the colon, was noted on X-ray films. Megacolon was the most common radiologic feature, but pseudo-obstruction extended proximally into the small intestine in some patients with advanced disease. In the majority of cases the condition was progressive and eventually affected the entire gastrointestinal (GI) tract.

Histologic features included smooth-muscle degeneration with vacuolated cytoplasm, extracellular edema, and increased fibrosis of both muscular layers of the muscularis propria, particularly the longitudinal layer. Similar changes occasionally occurred in the muscularis mucosae and vascular walls of the involved bowel. Neuronal loss was absent, but hyperplasia of the myenteric plexus was observed in 7 cases. Electron microscopy showed atrophic, degenerative smooth-muscle cells with intervening collagen fibers. Intracellular fluid accumulation immediately adjacent to the cytoplasmic membrane was a constant finding in the less severely affected areas. Other characteristic ultrastructural findings included nuclear chromatin margination, diminished pinocytosis, and fragmentation of cytoplasmic membranes. Although specific morphologic changes of DL always primarily affected the most distal part of the GI tract, megacystis and megareuter were also noted in some patients. In addition, at postmortem examination in a few terminal cases, arterial smooth muscle was also affected in other organs and was associated with considerable fibrosis and proliferation of the intima. Immunohistochemistry revealed excessive expression of vasoreactive intestinal peptide (VIP) in bowel sections from 29 of 35 cases, while unequivocal hyperplasia of the myenteric plexus occurred in 7 of the 29 cases with increased VIP expression. Patients with increased VIP expression had enlargement of the neurons of all threeplexuses,associated with frequent vacuolization of the cytoplasm. There was increased expression of VIP in bowel specimens from a number of different sites in the GI tract in these patients. The lamina propria also contained positive VIP-staining neurofibrils. Within the neurons, the VIP staining was homogeneously distributed in the cytoplasm and large droplets or granules were located along individual nerve fibrils and axons. The increased expression of VIP is the opposite effect of neuronal causes of IP such as Hirschsprung’s disease, and combined with study of myosin and actin is a fairly consistent marker for DL. Management was preferably conservative with a low-residue diet supported by prokinetic agents. Surgical decompression was reserved for patients not responding to conservative management in the acute phase. Surgical resection was generally not advocated, as it failed to correct the underlying intestinal problem.

Keywords Pseudoobstruction · Intestinal · Visceral myopathy · Non-familial · Degenerative leiomyopathy

Introduction

Intestinal pseudoobstruction (IP) includes a large group of dissimilar conditions that result from neurogenic or
myogenic-mediated disturbances of gastrointestinal tract (GI) motility [3, 5, 9, 13, 15, 21, 24, 32, 34, 35, 37, 39]. A distinct clinical group of IP, chronic idiopathic IP (CIIP), occurs in adolescent family members or young adults [1, 9, 10, 14, 25, 34]. The causes may be congenital or acquired and related to nerves or muscles. The pathology may be focal, affecting a localized segment of bowel, or diffuse, affecting the entire GI tract [1]. It may also be primary (familial and non-familial) or secondary to an underlying systemic condition.

Neurologic causes of functional intestinal obstruction such as Hirschsprung’s disease (HD) are relatively well-described and have attracted considerable attention in recent years because of genetic associations with the RET (10q22) gene and endothelin [28]. Muscle disorders of the intestine are rarer, but may similarly result in IP [23, 26]. Clinically, visceral myopathies are complex problems generally presenting with recurrent attacks of abdominal pain, distension, and vomiting, and remain difficult to identify and treat. Malnutrition and starvation frequently result from the deranged motility, and the majority of patients are subject to a protracted, debilitating illness that often eventually results in death.

Although familial visceral myopathies are fairly well-described [1, 9, 10, 13, 35], a paucity of information exists as regards non-familial, sporadic forms of the disease. One such entity is degenerative leiomyopathy (DL) [18, 19, 29], which was initially identified in Africa and was first described as Bantu pseudo-HD [20]. It is now recognized as a distinctive, non-familial form of degenerative visceral myopathy of uncertain etiology that has characteristic clinical and histologic features [18, 19]. It appears to be confined to Africa (particularly southern, eastern, and central Africa), [18, 19, 29], although sporadic isolated cases have been identified elsewhere. A suggestion that it be named African DL is currently being evaluated.

The aim of this study was to evaluate the clinicopathological features of DL, with emphasis on the morphologic criteria required for its differentiation from other forms of visceral myopathy.

Materials and methods

A retrospective study of resection specimens from 39 patients with DL presenting to institutions within the Western Cape region of South Africa was performed. The histopathologic features were compared with colon tissue of 15 control patients of similar age, the specimens being taken from similar levels of the bowel (i.e., lower rectum, mid-sigmoid, and transverse colon).

Sections of formalin-fixed, paraffin-embedded full-thickness specimens were stained with hematoxylin and eosin (H & E), Verhoeff van Gieson, and Masson trichrome stains for histologic assessment. Fresh full-thickness intestinal sections were snap-frozen at −70 °C and stained for acetylcholinesterase (AChE) using a routine histochemical technique (Meier-Ruge). Immunocytochemical staining was performed on paraffin sections of full-thickness bowel wall using a routine avidin-biotin–alkaline phosphatase technique and antibodies to S-100 protein, neurofilament, and vasoactive intestinal polypeptide (VIP) by a streptavidin-biotin-complex technique. Transmission electron microscopy (EM) was performed on either glutaraldehyde- or formalin-fixed tissue.

Results

Thirty-nine patients with DL presented to the Red Cross and Tygerberg pediatric surgical units from 1984 to 1997. The mean age at initial presentation was 9.5 years (range: 6 months – 16 years) and the average duration of symptoms prior to presentation was 4.3 years (5 months – 14 years). One patient presented at 35 years of age with esophageal motility disturbances, having had surgery elsewhere as a teenager (Fig. 1). There was an equal sex distribution, and 36 of the 39 patients came from a specific geographic location. Herbal enema administration was confirmed in only 5 patients.

Seventy-two percent of patients were below the 3rd percentile weight for age. There was obvious longstanding gaseous distension of the abdomen with infrequent bowel evacuation and intermittent episodes of diarrhea in all patients, often since early childhood. In 50% of cases abdominal discomfort was associated with intermittent, colicky abdominal pain. Transit times were prolonged in all 8 patients tested, being more than 60 h in 2. In 7 children evaluated, anorectal relaxation was present in response to balloon stimulation. Almost one-half of the children had a positive tuberculin skin test (Mantoux).

Radiologic findings showed gross gaseous colonic distension with atony, associated with pseudo-obstruction. Air-fluid levels were present and were often associated with marked fecal loading. The primary target organ appeared to be the large bowel, but small-bowel involvement occurred in 9 children, indicating proximal disease progression. Although upper contrast studies did not reveal duodenal distension in the majority of patients, proximal involvement of the stomach and esophagus was observed in 4. Contrast enemas confirmed generalized atony of the large intestine, with uneven dilatation and elongation of bowel and loss of haustral markings. Barium retention for periods longer than 24 h was demonstrated in 6 patients. Coexisting megacystis and megaureters were noted in a further 4 children, of whom 3 had recurrent bouts of urinary tract infection. Stool examination did not reveal any significant pathogenic organisms except a Salmonella species in 1 patient.

Histologic changes of DL occurred in all cases. Full-thickness sections of bowel wall showed smooth-muscular degeneration with pyknotic nuclei and homogeneous eosinophilic nuleoplasm, vacuolated cytoplasm, extracellular edema, and increased fibrosis of both muscular layers of the muscularis propria, particularly the longitudinal layer (Fig. 2). Similar changes occasionally occurred in the muscularis mucosae and vascular walls of the involved bowel. Degenerative changes in the muscularis propria often displayed very characteristic alternating waves of aligned muscle