Paediatric gastrointestinal motility disorders

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Abstract

Normal gastrointestinal function requires an intact enteric musculature and enteric nervous system. There is a group of disorders in which abnormalities of either enteric nerves or muscle, or both, lead to clinical features of intestinal obstruction in the absence of physical obstruction — chronic intestinal pseudo-obstruction. These disorders may be congenital or acquired. The best known of the congenital enteric nervous system disorders is Hirschsprung disease where there is absence of nerve cells in the distal colon. Others include ganglioneuromatosis. Muscular disorders include degenerative leiomyopathy and mitochondrial disorders. The nervous or muscular system may also be affected secondarily in many systemic disorders. Surgical intervention is frequent in cases of chronic intestinal pseudo-obstruction and yields specimens for pathological examination. The pathological investigation of these specimens may yield only non-diagnostic features, but care is needed not to overlook those cases where a specific diagnosis may be made on the basis of the histopathology.

Keywords degenerative leiomyopathy; dysmotility; enteric muscle; enteric nervous system; ganglioneuromatosis; Hirschsprung disease; pseudo-obstruction

Introduction

Normal, healthy, gastrointestinal function requires an orderly movement of the contents of the stomach distally through the small and large intestines. This is achieved by coordinated contraction (and relaxation) of enteric smooth muscle, mediated via an intact enteric musculature and enteric nervous system. Disease of either the enteric smooth muscle or the enteric nervous system (or both) results in disruption of this coordinated function. The affected individual may then manifest signs of intestinal obstruction in the absence of a mechanical blockage — Chronic Intestinal Pseudo-Obstruction (CIPO).[1] Commonly, no pathological alterations to explain the pseudo-obstruction are identified or the features present are non-specific, or there is confusion about their significance.[2] This review concentrates on those cases in which biopsy of affected intestine may aid in diagnosis.

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Clinical classification (Table 1)

Gastrointestinal motility disorders can occur in either adults or children; some forms are much more common in, or exclusive to, childhood[3] and some of the childhood cases are congenital. These diseases are rare and many are poorly characterised. The symptoms are caused by abnormalities affecting muscle or nerves within the gastrointestinal tract. When the abnormality results in weakened or absent contractions, it is classified as myopathic. When the abnormality results in unsynchronized contractions, it is classified as neuropathic. Commonly, both the muscle and nerves are affected by the disease process. There is no universally agreed clinical classification system, but such clinical classifications as exist are based on age, clinical presentation and associated features (Table 1): no system is universally accepted. The primary clinical entities encompassed include:

- Hirschsprung disease
- Congenital and acquired CIPO
- Mitochondrial disorders
- Slow transit constipation
- Idiopathic megarectum/megacolon.

Slow transit constipation may occur in children and refers to a specific subset of patients who can be shown by studies employing radio-opaque markers to have delayed passage of intestinal contents through the colon.[4] Although pathological changes have been reported they are not diagnostic and their significance is unknown.

Of particular relevance to children is the condition megacystis-microcolon-intestinal-hypoperistalsis syndrome a variety of severe neonatal CIPO affecting principally girls and showing a large bladder, narrow colon and ileum and intestinal malrotation.[5] The condition may be detected in utero. Pathological findings are not diagnostic. Mortality is high.

Dysmotility may also occur as a secondary phenomenon, secondary to such systemic conditions as muscular dystrophy, multiple endocrine neoplasia type 2B (MEN 2B), neurofibromatosis, diabetes mellitus, connective tissue disease, cystic fibrosis and paraneoplastic syndromes.[2]

Pathological classification (Table 2)

Recently there has been an attempt to standardise the pathological investigation and classification of gastrointestinal dysmotility.[6]

From the point of view of pathology, primary gastrointestinal dysmotility is subdivided into myopathic and neuropathic forms (and a much rarer group of abnormalities of interstitial cells of Cajal) depending on whether the condition results primarily in abnormalities of muscle or nerves within the gastrointestinal tract.[3] A variety of poorly understood familial and acquired disorders that damage intestinal muscle or nerves can cause primary gastrointestinal dysmotility and may be separated into congenital, familial and sporadic forms. Familial cases of primary gastrointestinal dysmotility may be inherited as autosomal dominant, recessive or X-linked traits.

Many systemic, metabolic and organic diseases have been associated with secondary GI dysmotility. Such diseases include scleroderma, lupus erythematosus, dermatomyositis, mixed connective tissue disorder and rheumatoid arthritis, diabetes mellitus, hypothyroidism or hypoparathyroidism, paraneoplastic

Causes of chronic intestinal pseudo-obstruction in children (Ref 2)

Post-operative	Small bowel ileus
	Colonic pseudo-obstruction
Autoimmune	
Generalised	Scleroderma
	Systemic Lupus Erythematosus
	Coeliac disease
Gastrointestinal	Autoimmune leiomyosists
	Autoimmune ganglionitis
	Eosinophilic ganglionitis
Developmental	Delayed maturation cells of Cajal
Neuropathies	Intestinal Neuronal Dysplasia
	Hirschsprung disease
Infectious/post-infectious	Chagas disease
	Cytomegalovirus
	Herpes Zoster
	Ebstein Barr Virus
Endocrine	Diabetes mellitus
	Hypothyroidism
	Hypoparathyroidism
Metabolic \ toxins \ drugs	Mitochondrial cytopathy
	Fetal alcohol syndrome
	Narcotics
	Anti-cholinergics
	Muscle relaxants
	Cyclopentolate/phenylephrine
Oncology \ haematology	Chemotherapy
	Bone marrow/stem-cell transplant
	Phaeochromocytoma
	Ganglioneuroblastoma
	Multiple myeloma
Miscellaneous	Ehlers Danlos
	Radiation injury

Table 1

The London classification of gastrointestinal neuromuscular pathology 2010 (Ref 6)

Neuropathies
1 Absent neurones
2 Decreased number of neurones
3 Increased numbers of neurones
  Ganglioneuromatosis
4 Degenerative neuropathy
5 Inflammatory neuropathy
  Lymphocytic
  Eosinophilic
6 Abnormal content in neurones
  Nuclear inclusions
  Megamitochondria
7 Abnormal neurochemical coding
8 Relative immaturity of neurones
9 Abnormal enteric glia
  Myopathies
1 Muscularis propria malformations
2 Muscle cell degeneration
  Degenerative leiomyopathy
  Inflammatory myopathy
3 Muscle hyperplasia \ hypertrophy
4 Abnormal content in Myocytes
5 Abnormal Supportive Tissue
  Interstitial Cell of Cajal Abnormalities

Table 2

syndromes, muscle disorders (myopathies), including desmin myopathy, Duchenne muscular dystrophy or myotonic dystrophy; or additional disorders such as amyloidosis, coeliac disease, Ehlers–Danlos syndrome or mitochondrial neurogastrointestinal encephalopathy (MNGIE).[2]

Infections including Chagas disease, Epstein Bar virus, or cytomegalovirus can also result in secondary GI dysmotility. Dysmotility can also occur secondary to the use of certain drugs or medications such as tricyclic antidepressants, anticholinergic agents or narcotics.

Dysmotility can also develop in utero in select cases due to toxins or insults affecting the developing fetus. One such cause of dysmotility developing in utero is fetal alcohol syndrome.

In some cases, CIPO is caused by damage to the interstitial cells of Cajal (ICC), which are the pacemaker cells of the GI tract. These cells are now known to be critical for proper GI motility.[7] Interstitial cells of Cajal help to generate and maintain electrical rhythmic activity within the GI tract. Interstitial cells of Cajal also play a role in amplifying signals from neurones to smooth muscle cells. Individuals with dysmotility due to abnormalities of these cells have signs of both muscle and nerve disease in the GI tract.[8]

Specimen handling in bowel resection for dysmotility

The aim of pathological examination is to identify any intrinsic neuromuscular abnormality. The specimen may be a length of either large or small intestine with attached mesentery, or may be a stoma site or a short length of bowel taken from the site of intended stoma. Care should be exercised if the specimen is from the vicinity of an existing stoma, since secondary changes may be caused by the presence of the stoma. Ideally, the bowel should be received fresh and a small full-thickness piece removed for snap freezing and frozen storage; a sample of the muscle coat can be fixed in glutaraldehyde for electron microscopy (if needed). The bowel should then be opened along the antimesenteric border, washed out and fixed in an adequate volume of buffered formalin. Once fixed it should be measured (length and diameter) and a longitudinal strip cut through the full length of the bowel (Figure 1). This strip should be embedded entirely, maintaining the orientation, by inking if necessary. Transverse section may also be embedded.

Once the H&E sections have been viewed suitable blocks can be chosen for special staining. If there is no apparent abnormality, any block with optimum orientation of the muscle coats should be chosen. The panel of stains that we employ currently is:

- Sirius red
- PAS
- Masson trichrome
- Smooth muscle actin
- Desmin
- CD117