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Leading Article

Primary chronic intestinal pseudo-obstruction – an update

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Intestinal pseudo-obstruction is defined as a syndrome in which symptoms and signs of intestinal obstruction occur without evidence for a mechanical obstruction.[1,2] Previous reviews[3,4] have highlighted the heterogeneous nature of the syndrome with a wide variety of clinical associations, pathological abnormalities of the smooth muscle or myenteric plexus, and presenting features. The acute syndrome (Ogilvie's syndrome) has been associated with postsurgical, post-traumatic and medical conditions and is potentially reversible.[5] Chronic intestinal pseudo-obstruction (CIPO) has been described in association with a large number of disease entities and drugs[3,6] but no underlying cause can be identified in a proportion of patients in whom the disease is thought of as primary.

The last few years have seen considerable advances in our understanding of primary CIPO. Both children and adults may be affected and recent reports have emphasized various aspects of this condition in children.[7,8] Widespread gastrointestinal dysfunction, neurological and urological abnormalities are now recognized (Table I). These may offer valuable clues in the diagnosis of this condition.

Various pathological subtypes of primary CIPO are increasingly recognized with the use of H&E stain, Smith's silver stain[4] and electron microscopy. Table II provides a classification of neuropathic and myopathic subtypes.

Both familial and sporadic forms of visceral neuropathies have been described.[4] Familial recessive forms are characterized by eosinophilic neuronal intranuclear inclusions[9] (NIN) composed of protein; by electron microscopy, the inclusions consist of beaded filaments which do not resemble any viral inclusions. The number of argyrophilic and argyrophobic neurons were reduced. Other patients have been described who lack NIN but

Table I Multisystem manifestations of primary chronic intestinal pseudo-obstruction

A. Gastrointestinal
   1. Oesophageal: dysphagia
   2. Gastric: nausea and vomiting
   3. Small bowel: distension, diverticulosis, bacterial overgrowth
   4. Colon: constipation, diverticulosis
   5. Sphincter of Oddi dysfunction

B. Neurological
   1. Peripheral neuropathy
   2. Autonomic neuropathy
   3. Ptosis
   4. Ophthalmoplegia
   5. Brainstem dysfunction
   6. Basal ganglia calcification
   7. Mental retardation
   8. Ataxia
   9. Deafness

C. Urological
   1. Urinary retention
   2. Recurrent urinary tract infections
   3. Megacystis/megaureter

Table II Pathological classification of primary chronic intestinal pseudoobstruction

1. Disorders of myenteric plexus
   A. Familial visceral neuropathies
      1. Recessive with intranuclear inclusions
      2. Recessive with mental retardation and basal ganglia calcification
      3. Dominant
   B. Sporadic visceral neuropathies
      1. Degenerative non-inflammatory
      2. Degenerative inflammatory
   C. Developmental
      1. Total colonic/small bowel aganglionosis
      2. Maturational arrest
      3. Neuronal intestinal dysplasia
2. Disorders of smooth muscle
   A. Familial visceral myopathies
      1. Autosomal dominant
      2. Autosomal recessive with ptosis and external ophthalmoplegia
      3. Autosomal recessive with total gastrointestinal tract dilatation
   B. Sporadic visceral myopathies
3. Unclassified

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show decreased and degenerated neurons in the gastrointestinal tract. Association with mental retardation and basal ganglia calcification[10] and dominant inheritance[11,12] have been reported. It is of interest that though the diagnosis generally depends on autopsy or full thickness operative biopsies, antemortem diagnosis of NIN disease has been reported in two generations of a family using deep-bite rectal biopsy through a rigid sigmoidoscope.[13] Sporadic forms may be non-inflammatory or inflammatory.[4] An interesting case report has linked CIPO to postencephalitic syndrome due to measles.[14]

In a recent report, a spectrum of abnormalities of myenteric plexus in infants and children with CIPO has been described.[7] These include: (a) absence of myenteric plexus; (b) small numbers of neurons present on H&E stain but absence of the plexus on silver stain; (c) myenteric plexus present but decreased argyrophilic neurons on silver stain.

Failure of development of neurons can be morphologically distinguished from degeneration[4] and aganglionosis of the colon or the entire intestine has been described.[15,16]

Amongst visceral myopathies, familial hollow visceral myopathy can be dominant[17] or recessive.[18] The dominant form may have a better prognosis. Though it has been suggested that endoscopic biopsy may be useful in making a diagnosis,[19] this generally has not been the experience of most workers. Marked dilatation of the entire gastrointestinal tract[20] and an association with dysplastic naevus and multiple basal cell carcinoma[21] have been described. The muscle cell abnormalities in all these types have been well described.[4] Sporadic cases have also been reported including a childhood case caused by a disorder closely resembling progressive systemic sclerosis.[22]

It is of interest that a French group[23] has reported mitochondrial abnormalities in a patient with CIPO associated with myopathy and ophthalmoplegia. The muscle mitochondria had a crystalline appearance with a dense core and decreased cytochrome *c* oxidase and succinate cytochrome *c* reductase activities. No mitochondrial DNA deletion could be demonstrated in the skeletal muscle but this does not exclude such abnormalities in intestinal muscle.

Conventional contrast radiology continues to be the first-line investigation to exclude mechanical obstruction. Moreover, radiological features[24] along with associated clinical features help in classifying CIPO into neuropathic and myopathic forms (Table III).

Oesophageal manometry is useful as a normal recording makes CIPO an unlikely diagnosis.[25] Antroduodenal motility may help in distinguishing neuropathic and myopathic forms. Stanghellini[26] has described abnormal small bowel manometric patterns in 42 consecutive CIPO patients. These include: (a) aberrant propagation and/or configuration of interdigestive motor complexes; (b) prolonged bursts of non-propagated pressure activity in the fasting and fed states; (c) sustained and incoordinated phasic pressure activities; and (d) inability of an ingested meal to convert a fasting into a fed pattern of motility. A large proportion of patients had previous abdominal surgery which could have affected their manometric findings.

Table III Characteristic differences between visceral neuropathy and visceral myopathy

	Visceral neuropathy	*Visceral myopathy*
Oesophagus	Hyperkinetic Non-peristaltic	Hypokinetic Non-peristaltic
Duodenum	Slight enlargement	Gross enlargement
Small bowel	Hyperactive contractions	Few contractions
Bladder	Rarely involved	Megacystis
Neurological	Autonomic and peripheral neuropathy	Ptosis, ophthalmoplegia

A recent study reported colonic manometric patterns in children with CIPO.[8] Encouragingly, manometry distinguished between myopathy, neuropathy and normal colonic function. No contractions were recorded from children with myopathy. Children with neuropathy had contractions but the gastrocolonic response was absent and there were fewer high-amplitude propagated contractions.

Little is known about biliary tract motility in CIPO. Low basal pressure in the sphincter of Oddi has been reported together with low-amplitude phasic contractions.[27] Aerobilia is an associated observation. A laparoscopic method of small bowel biopsy has been described[28] and this may be useful in obtaining full thickness intestinal biopsies.

Patients with primary CIPO can thus be categorized into distinct subgroups by histological features (silver stain in addition to routine H&E) and manometric findings. Occasionally, endoscopic biopsies will prove to be useful but in others, laparoscopic full thickness intestinal biopsies are necessary. Such categorization into subgroups is essential to have insights into possible aetiological and treatment options. Mitochondrial and other biochemical abnormalities may underlie some cases and molecular biological techniques might detect the genetic abnormalities responsible for these defects. Studies of gut neuropeptide distribution in patients with CIPO may detect imbalances between stimulatory (substance P, enkephalins) and inhibitory (neuropeptide Y, vasoactive intestinal peptide) neuropeptide fibres.[29] This approach has already yielded valuable information in other

disorders.[30] New developments in management can only follow an understanding of basic pathogenesis and prevent morale sapping and hopeless blind prescription of a variety of prokinetic and spasmolytic drugs. In future, more specific drugs to induce motility in the intestine or even pacemakers may be a feasible possibility in this presently hopeless condition.

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