Refresher Course

Neuronal Intestinal Dysplasia: an Allied Hirschsprung's Disease

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INTRODUCTION

There are many clinical conditions that resemble Hirschsprung's disease, despite of the presence of ganglion cells on rectal biopsy. Meier Ruge proposed the term "neuronal colonic dysplasia" in 1971.[1] Various functional bowel disorders diagnosed using adequate biopsy and different histological techniques include neuronal intestinal dysplasia type A and B, hypoganglionosis, immature ganglia and unclassifiable dysganglionosis.

Hirschsprung's disease and these allied Hirschsprung's conditions may be considered as different manifestations of the same developmental abnormality.[2] Among those malformations, neuronal intestinal dysplasia is the mildest form of an inborn error of intestinal innervation. Second only to Hirschsprung's disease, neuronal intestinal dysplasia is one of the most frequent causes of chronic constipation and pseudo-obstructive intestinal dysmotility. The condition is a distinct entity that can be clearly proven by histological means which include the formation of giant ganglia, an increase of the acetylcholinesterase activity in the mucosa and muscularis mucosa and hyperplasia of the myenteric plexus. Patients with neuronal intestinal dysplasia not only have abnormalities of submucosal and myenteric plexus, but also defective innervation of the muscle and neuromuscular junction as well as the internal sphincter.

Incidence

The incidence of neuronal intestinal dysplasia in the total population is unknown. Meier Ruge W, et al, studied 3,699 colonic mucosal biopsy specimens of 773 cases. In 358 cases, a classifiable colonic defect was present. In those classified abnormalities, aganglionosis, neuronal intestinal dysplasia and hypoganglionosis were found 52.2, 42.8 and 5.0 percent of the cases respectively.[3]

Diagnosis

The gold standard for diagnosis of this condition depends on histological criteria of the bowel section. The criteria of the diagnosis of the condition remain controversial, but the most accepted criterion is that the giant ganglia that contain seven or more ganglion cells are found. (Normal ganglia con-

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tain 2.16 +/- 0.31 ganglion cells/ganglia[4]). Some experts have proposed more criteria that would enhance reliability of diagnosis, i.e., at least 30 sections, specific nerve cell.dehydrogenase reaction staining.[5]

Giant ganglia have been found to show age-independent change, while the other criteria for diagnosis, i.e., hyperplasia of the submucosal plexus, increase of acetylcholinesterase activity in muscularis mucosae, and lamina propria and low succinate dehydrogenase activity in nerve cells, have been proved to be age-dependent findings which disappear during the maturation of the enteric nervous system.[2,6]

Classification

1. Type A (congenital hypoplasia or aplasia of the sympathetic innervation) is characterised by acute symptoms such as constipation, diarrhoea, ulcerating enterocolitis and bloody stool in the newborn period.

2. Type B (dysplasia of the parasympathetic submucous plexus and normal sympathetic innervation) has late onset and chronic symptoms and is associated with megacolon, constipation, faecaloma development, soiling and deficiency of propulsive bowel activity.

The ratio of type B: type A is 18.1: 1.[3]

Pathogenesis

The causes of bowel dysmotility in allied Hirschsprung's disorders such as neuronal intestinal dysplasia, hypoganglionosis and immature ganglia, remain unexplained but the possible hypotheses include:

(a). Peptidergic neurotransmitters deficiency. Peptidergic neurotransmitters such as VIP, substance P and neurotensin apparently act to a lesser extent in colons with neuronal intestinal dysplasia and hypoganglionosis; however, and these effects are almost absent in aganglionosis.[7-9]

(b). Decreased innervation of the non-adrenergic, non-cholinergic excitatory nerve that is related to the impaired motility observed in aganglionosis, neuronal intestinal dysplasia and hypoganglionosis.[7,8]

(c). An imbalance of the peptidergic and synaptic vesicle's innervation, both in the circular and longitudinal muscle layers as well as the morphological abnormalities of synaptic vesicles.[7]

(d). Ncx/Hox11L.1 gene deficiency. The Ncx/Hox11L.1 gene is mainly expressed in neural crest-derived tissues. It is required for the maintenance of the proper function of the enteric nervous system.[10,11]

(e). A lack of intestinal pacemaker C-KIT+ cells.[12]

(f). Defective innervation of the neuromuscular junction.[13]

(g). Abnormal internal anal sphincter innervation.[14]

Clinical Manifestations

(a). Chronic constipation which usually mimics Hirschsprung's disease, is the most common manifestation of neuronal intestinal dysplasia. Second only to Hirschsprung's disease, neuronal intestinal dysplasia is one of the most frequent causes of chronic constipation and pseudo-obstructive intestinal dysmotility. Even the histological criteria of neuronal intestinal dysplasia offer uncertain value in assessing the clinical picture[15,16], the isolated neuronal intestinal dysplasia is recognised as a majority of the pseudo-obstruction cases.

(b). Chronic intestinal pseudo-obstruction post-adequate pull-through operation for Hirschsprung's disease. Neuronal intestinal dysplasia associated with Hirschsprung's disease is usually type B and often occurs proximally to aganglionic segment. The fact that neuronal intestinal dysplasia also accompanies Hirschsprung's disease, creates difficulty in concluding the real clinical effect of the neuronal intestinal dysplasia component. Moreover, the significant clinical impact of the associated neuronal intestinal dysplasia with aganglionosis is still being debated. Some experts are convinced that the additive effect of neuronal intestinal dysplasia to Hirschsprung's disease and children with aganglionosis associated neuronal intestinal dysplasia more often need a second resection compared with those with isolated aganglionosis[17] and have more enterocolitis, soiling and constipation.[18] On the other hand, some literature has revealed that the patients with Hirschsprung-associated neuronal intestinal dysplasia have no difference in complications from isolated Hirschsprung's disease.[19]

(c). An abdominal mass.[20]

(d). Neonatal enterocolitis with intestinal stricture.[21]

Neuronal intestinal dysplasia was reported in clinical associations with neurofibromatosis, ganglioneuromatosis[22], cystic fibrosis[23], multiple endocrine neoplasia (MEN) II syndrome, intraluminal mucosal web[24] and lipoblastomatosis.[25]

Investigations

(a). Intestinal biopsy is the investigation of choice. A correctly practised rectal suction biopsy which includes parts of the submucosa layer, remains the procedure of choice for diagnosis[26]. The first step is to exclude Hirschsprung's disease which reveals no ganglia. After the bowel sections are obtained, various techniques are applied to the section to specify the definite diagnosis. The details of various sophisticated histological techniques have been discussed elsewhere.[7-9,13-14,27-29]

(b). Electromanometry, which reveals that the rectoanal inhibitory reflex is absent or abnormal in children with neuronal intestinal dysplasia as in Hirschsprung's disease.[15,30,31] Anorectal hyperexcitability and increase of amplitude of anorectal fluctuation are also observed.[30,31] Electromanometry is only suitable as a suggestive investigative method and it cannot provide a conclusive diagnosis.

Barium enema has no role in the specific diagnosis of this condition.

Treatments

Among the enteric nervous system malformations, the single malformation that requires surgical intervention is aganglionosis. The histological criteria of neuronal intestinal dysplasia are unhelpful in predicting the clinical outcome and therefore should not influence clinical judgement.[15,16] Whether the patients need surgical intervention or not depends on the clinical outcome, which is not relevant to the histological findings. The treatment of neuronal intestinal dysplasia has centred on the clinical picture, with most cases managed medically with prokinetic agents, colonic irrigations and bowel cathartics until clinical improvement occurs. The effect of Cisapride is usually transitory.[18] Surgery is indicated for patients with severe clinical deterioration after failed medical management.[32]

Surgical Management

There is no definite conclusion for the surgical procedure of choice for this condition. A double-blind study has never been accomplished and at most centres judge the decision on the types of operation is made on a case-by-case basis.

In cases of presenting with chronic constipation, and where Hirschsprung's disease is ruled out, the surgical options are posterior sphincteromyotomy,[27] proximal stoma, Malone antegrade catheterizable enema operation (ACE), subtotal colectomy with preservation of the rectum with ileostomy[9] and the Duhamel or Soave pull-through procedure.[32]

On the other hand, where the chronic intestinal pseudo-obstruction post-adequate pull-through operation for Hirschsprung's disease is the clinical manifestation, some experts propose posterior anorectal myectomy as an initial procedure[17,33] followed by a re pull-through operation when posterior anorectal myectomy shows no improvement.[17,33]

Prognosis

The symptoms of neuronal intestinal dysplasia often improve with age[32,34] and that improvement may be accompanied by a reversion of the histochemical change to normality.[4] Although the majority of neuronal intestinal dysplasia patients do not require surgical intervention, the outcome of surgical treatment for this condition is poorer than in patients who have resections for Hirschsprung's disease.[17]

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