Chronic idiopathic slow transit constipation: pathophysiology and management

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Abstract

Objective  Patients with idiopathic slow-transit constipation comprise a small proportion of the total population complaining of constipation. The purpose of this review is to present an update of pathophysiology of this disorder and its application in clinical management.

Methods  Medline was used to search English language articles published up to the end of September 2002 on the subject of slow-transit constipation.

Results and conclusions  Patients with idiopathic slow-transit constipation can be divided into 2 subgroups: 1. patients with normal proximal gastrointestinal motility and with onset of constipation in connection with childbirth or pelvic surgery. This subgroup may benefit from consideration of surgical treatment; 2. patients who have a dysfunctional enteric nervous/neuroendocrine system and exhibit colonic dysmotility as part of a generalised gastrointestinal dysmotility. Surgical approach in this subgroup seems to be unhelpful and medical treatment appears to be a better approach.

Keywords  Autonomic nervous system, diagnosis, cholecystokinin, enteric nervous system, interstitial cells of Cajal, motilin, peptide YY, serotonin, treatment

Introduction

Constipation is a common complaint in general medical practice; it has been estimated to account for 0.9% in UK and 1.2% in USA of physician visits yearly [1,2]. The symptom incidence in the general population seems to be between 5 and 30% per annum [3]. Constipation increases with age [4] and is more common in women [5,6]. The vast majority of patients suffering from constipation are treated with laxatives, diet advice and encouragement of regular bowel habits [7]. Idiopathic slow transit constipation (ISTC) is a clinical syndrome characterized by intractable constipation that is not readily response to laxatives, diets or change of life style, it is characterised by delayed colonic transit without underlying systemic disorder or pelvic floor dysfunction [7,8]. In addition to the constipation, patients with ISTC present with other gastrointestinal symptoms such as bloating, abdominal pain, cramps nausea and vomiting [9]. It is difficult to distinguish these patients from patients with irritable bowel syndrome (IBS) according to Rome II criteria [10], however, patients with ISTC have a slow colonic transit.

Patients with ISTC are a small fraction of the total population complaining of constipation [11]. Thus, in tertiary referral centres about one-fifth of 91 patients [12] and about two-fifths of 70 had ISTC [13]. Despite the low number of these patients, the intractability of their symptoms cause psychological and social stress and greatly impair their quality of life [14]. Furthermore, they consume a disproportionate amount of medical resource. It appears that some of these patients are also suffering from a generalized gastrointestinal motility disorder [11].

Patients with ISTC are a heterogeneous group and understanding the pathophysiology of this disorder is essential for a proper treatment strategy. The present review aims to present current knowledge about the pathophysiology of this disorder and its application to patient management.

Diagnosis

A full history, especially concerning pelvic surgery and childbirth, clinical examination and several investigations
should be performed in order to reach the diagnosis. A screening battery of blood tests should be taken to exclude metabolic, endocrinologic or systemic diseases. Defecography, rectal manometry, anal sphincter electromyography are usually done to exclude rectoceles, enteroceles, intussusception, paradoxical puborectal contraction, and other pelvic floor disorders [15]. Colorectal transit time is essential for the diagnosis. Several techniques are used to estimate the colorectal transit time, being radiological, isotopic or biomagnetic [16–32]. Radio-opaque markers method (Fig. 1) with single plain abdominal X-ray is simple, safe and reproducible [24,32]. The methods reported by Mecalf [21] and Abrahamsson et al. [23] are the most popular. Radio-opaque marker methods are not considered to be sufficiently discriminatory in showing different segments of transit delay [33]. Colonoscopy or barium enema is necessary to exclude megacolon and megarectum as well as malignancy in patients with alarm indicators.

**Pathophysiology**

Dysmotility of the colon and in some patients a generalized gastrointestinal motility disorder seem to be the cause of ISTC [11,34]. The cause of this dysmotility is debatable.

**Dysfunction of the autonomic nervous system**

Selective small fibre neuropathies have been found in 12 patients with ISTC [35]. It has been proposed that ISTC arises as a consequence of pelvic autonomic dysfunction [36]. This dysfunction would arise after pelvic surgery such as hysterectomy, tubal ligation and even appendectomy as well as after childbirth [36]. In idiopathic cases, the cause has been suggested to be neuronal degeneration in the pelvic autonomic nervous system [36]. Although this hypothesis is based on circumstantial evidence, it appears to be applicable to a considerable number of patients with ISTC. Thus, of 31 patients with ISTC, 14 have been reported to develop severe constipation following a hysterectomy [37]. In another study, 12 of 48 patients with ISTC developed symptoms following pelvic surgery or childbirth [38].

**Disturbed enteric nervous system/neuroendocrine system**

The enteric system of the gut regulates gastrointestinal motility [39,40]. The neuroendocrine system of the gut consists of two parts: endocrine cells scattered among the epithelial cells of the mucosa facing the gut lumen, and the peptidergic and sertonergic as well as nitric oxide-containing neurones and nerves of the enteric nervous system in the gut wall. The structure of this regulatory system, its signal substances and their functions have been covered in a recent review [40]. Moreover, interstitial cells of Cajal (ICC) are required for generation of smooth muscle electrical slow wave [41,42], which determine smooth muscle contractile activity. Because of the importance of these regulatory systems, it is not surprising that a disturbance in them has been assumed to be the cause of ISTC.

In the colonic myenteric plexus of the enteric nervous system in patients with ISTC, the number of neurones has been found to be reduced using argyrophilic reaction [43], neurofilaments [44], or Protein-Gene Product (PGP) 9.5 [45] as a marker. Using S-100 as a marker, an increase of the colonic neurones of the myenteric plexus has been reported in patients with ISTC [46]. However, S-100 is not an optimal marker for nerve elements. Whereas hypertrophic nerve fibres and giant ganglia have been reported in the submucosal plexus of constipated patients [47,48], such changes could not be confirmed in another study [45]. The volume of interstitial cells of Cajal has been found to decrease in all layers of sigmoid colon in patients with ISTC [49].

The neuroendocrine system in patients with ISTC has been the subject of several studies. The results of these studies seem at first sight to be contradictory. As ISTC has been considered to a disease of the large intestine, it is not surprising that most studies have concentrated on the colonic neuroendocrine system.
The pancreatic polypeptide family namely, pancreatic polypeptide (PP), peptide YY (PYY) and neuropeptide Y (NPY) regulate intestinal motility and absorption of water and electrolytes [40]. PP and PYY are localized in intestinal endocrine cells and NPY in nerve cells and their fibres in the enteric nervous system [40]. PYY is colocalized with enteroglucagon [40]. The density of large intestinal PYY- and enteroglucagon-cells (Fig. 2) in patients with ISTC has been reported to be low [51]. Fasting and postprandial plasma levels of PP have been found to be high and postprandial PYY level to be low in patients with ISTC [52]. On the other hand, an increase in the number of large intestinal PYY cells and unchanged fasting and postprandial plasma levels of PP and PYY in patients with ISTC have been reported [53–55]. Serotonin-cell density in the large intestine (Fig. 3) has been reported to decrease [51], or increase [53] and serotonin concentration to increase in patients with ISTC [55]. Similarly, substance P (Fig. 4), and vasoactive intestinal peptide (VIP) have been reported to increase or decrease in patients with ISTC [53,57–63]. The large intestine of patients with ISTC has been reported to be more densely innervated by nitric oxide nerves [62–64]. Of the proximal gastrointestinal neuroendocrine peptides studied in patients with ISTC, fasting and postprandial plasma levels of cholecystokinin (CCK) are high [52,54,55]. The high plasma level of CCK was confined to the ISTC patients with delayed gastric emptying [55]. Whereas plasma basal and postprandial motilin levels has been found to be reduced in constipated patients with ISTC [54,65,66], it has been unaffected in another investigation [52].

Instead of looking at patients with ISTC as a group, an individualized profile of the colonic neuroendocrine peptides was made [67]. This study has shown that all patients had a disturbance in the colonic neuroendocrine peptides. The nature and the neuroendocrine peptides affected were, however, different in different individuals.

**Figure 2** Peptide YY (PYY)-immunoreactive cells in sigmoid colon of a patient with idiopathic slow transit constipation (a) and in a control (b). The control is a morphologically normal colon obtained from a patient with colon carcinoma. Note that the number of the PYY-cells in the constipated patient is lower than that of the control.

**Figure 3** Serotonin-immunoreactive cells in a normal sigmoid colon of (a) a patient that had undergone colectomy because of colon carcinoma and (b) in a patient with idiopathic slow transit constipation. The density of serotonin cells is reduced.
It is reasonable therefore to suggest that patients with ISTC in common have a disturbed neuroendocrine system, the nature and the colonic segment affected being variable in different individuals. This may explain the contradictory results obtained in separate investigations on the neuroendocrine system in different groups of ISTC patients. In other words, the ISTC patients are a homogenous group in the sense that they have a disturbed neuroendocrine system, but heterogeneous considering the nature of this disturbance.

Colonic myopathy

The inhibition of cisapride on carbachol-induced responses in colonic smooth muscles has been investigated in patients with ISTC [68,69]. The results of this study indicate that colonic smooth muscle from patients with ISTC is hypersensitive to cholinergic stimulation. Inclusion body myopathy has been identified in the ileal and colonic smooth muscles of patients with ISTC [70]. It has been suggested that these inclusion bodies may be secondary to denervation [70]. The evidence for ISTC as a colonic myopathy disease is not convincing at present.

Psycho-social factors

Defaecation is voluntary and can be suppressed or delayed. Social convenience or other psychological factors may affect the frequency of defaecation. It has been reported that personality type might influence stool weight and frequency [71–73]. Coexisting psychiatric problems such as depression are less common in patients with ISTC than in constipated patients with normal colonic transit [74,75]. Although constipated patients have more psychological stress than healthy subjects, ISTC patients have less dimensions of hypochondriasis and disease affirmation [76]. Psychosocial factors may contribute to the aggravation of the disease, but can not be considered as a major factor for the development of ISTC.

Management

As these patients are a heterogeneous group, treatment should be individualized. The treatment of patients with ISTC has been the subject of recent comprehensive reviews [5–7,34,76]. The following presentation emphasizes some of the points mentioned in these reviews and present our clinical experience of different treatment strategies.

Medical treatment

Clinical experience [76] shows that the benefits of continuous intake of laxatives (which are effective in the short term) tends to decline with time. In our clinical practice we try to alternate between two drugs in order to reduce side-effects and avoid dependence. We have the same clinical experience as Wald [8] that dietary fibre supplements and osmotic laxatives that consists of unab- sorbed sugars are generally ineffective. Instead, they aggravate nausea, abdominal pain and bloating in these patients. The drugs available and used in patients with ISTC are stimulant laxatives as bisacodyl, nongas-producing...
osmotic laxatives including polyethylene glycol, saline laxatives as milk of magnesia and enemas. Colchicine and misoprostol can also be used, but we do not have any experience with these 2 drugs. Dosage, contra-indications, interactions, side-effects and effectiveness are covered in the reviews by Bhaurcha and Philips [7] and Wald [8].

Erythromycin is a motilin receptor agonist [77]. As mentioned previously, at least some of the patients with ISTC exhibit reduced basal and postprandial plasma levels of motilin. Erythromycin in low doses has been found to stimulate distal colonic motility in these patients [78]. In our experience, oral administration of 40 mg erythromycin ethylsuccinate (metabolized to about 17 mg erythromycin) 20 min before meals three times daily improved bowel habits, nausea, abdominal pain and bloating in some patients with ISTC.

At least some of the patients with ISTC have a low density of colonic serotonin cells. Two specific 5HT4 receptor agonists have been developed, namely prucalopride and tegaserod [79]. Both agonists accelerate colonic transit [79]. Prucalopride is more selective for HT4 receptor and has no effect on gastric or small bowel transit [80,81]. In a placebo-controlled double-blind study of 74 constipated patients, prucalopride improved symptoms, upper gut transit and gut sensitivity in both slow and normal transit patients [82]. On the other hand, tegaserod accelerate both gastric emptying and small bowel transit [83]. Our clinical experience showed that tegaserod works well in long-term (12 months) treatment in a large proportion of patients with ISTC.

**Surgical treatment**

Surgical treatment has been based on the belief that ISTC is caused by colonic stasis [84,85]. Thus, total colectomy, subtotal colectomy with ileorectal, cecorectal or ileosigmoid anastomosis as well as segmental resection (hemicolecction) have been used [86–95]. The most common operation used for ISTC is total colectomy with ileorectal anastomosis [86]. Subtotal colectomy with cecorectal anastomosis has been proposed to be superior to the other operations, as it spares distal ileum, iloeeacal junction and cecum. This reconstruction preserves important functions such as absorption of water, bile, vitamin B12 and electrolytes [96]. Subtotal colectomy with antiperistaltic cecorectal anastomosis without wide mobilization of the right colon or torsion to the vascular pedicle has been applied with good short-term post-operative results [90,91].

The incidence of postoperative complication in ISTC are variable [86]; However, long-term (5–12 years) follow-up of patients with ISTC, who had undergone colectomy with ileorectal anastomosis has reported a high complication rate [97]. Thus, 71% of the patients had at least one episode of small intestinal obstruction and 42% of these episodes resulted in laparotomy [97]. Furthermore, gastrointestinal complaints such as abdominal pain, bloating, urgency of defaecation and straining to defecate did not improve after surgery [97]. Comparison of the outcome in ISTC and that in patients with ulcerative colitis and colonic carcinoma, who had undergone colectomy, has shown that postoperative complications are significantly higher in patients with ISTC [97]. Patients with ISTC after hysterectomy or childbirth with normal proximal gastrointestinal function seem to be suitable for surgical management [98]. Supporting this proposal is the finding that in two patients with severe invalidating ISTC after radical hysterectomy, a left-sided hemicolecctomy resulted in a dramatic improvement in their symptoms [99].

### Biofeedback

Biofeedback is advocated as a method for treating patients with intractable constipation [100–103]. The mechanism of this therapy effect is unclear and contingent upon who performs it, how often and how it is performed [104]. It appears that this treatment serves a more global psychological counselling function [104]. Whereas the success of biofeedback treatment has been reported to be between 75 and 90% [105,106], others report success rates to be between 30 and 40% [107–109]. Randomised controlled trials of slow transit patients with this mode of therapy are few [110]. Until a larger group of patients with ISTC are examined in randomised controlled studies with a long follow-up, the efficacy of this treatment remains uncertain.

### Conclusion

Patients with ISTC represent a sizable number of the patients referred to tertiary referral centre. Their symptoms cause psychological and social stress and greatly impair the quality of life. They also consume disproportionate amount of medical resources. Patients with ISTC can be divided into 2 subgroups. the first subgroup has onset of constipation in connection with pelvic surgery or childbirth. This subgroup has normal proximal gastrointestinal motility and could benefit from surgical treatment. The other subgroup has a dysfunctioning enteric nervous/neuroendocrine system and exhibits colonic dysmotility as part of a generalized gastrointestinal dysmotility. A surgical approach in this subgroup seems to be inappropriate and individualized medical treatment appears to be the proper approach.
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