

## Slow transit constipation: A functional disorder becomes an enteric neuropathy

Gabrio Bassotti, Vincenzo Villanacci

Gabrio Bassotti, Gastroenterology and Hepatology Section, Department of Clinical and Experimental Medicine, University of Perugia, Italy

Vincenzo Villanacci, 2<sup>nd</sup> Pathology Section, Spedali Civili, Brescia, Italy

Correspondence to: Dr. Gabrio Bassotti, Clinica di Gastroenterologia ed Epatologia, Via Enrico Dal Pozzo, Padiglione W, Perugia 06100, Italy. gabassot@tin.it

Telephone: +39-75-5783268 Fax: +39-75-5847570

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### Abstract

Slow transit constipation has been traditionally considered and classified as a functional disorder. However, clinical and manometric evidence has been accumulating that suggests how most of the motility alterations in STC might be considered of neuropathic type. In addition, further investigations showed that subtle alterations of the enteric nervous system, not evident to conventional histological examination, may be present in these patients. In the present article we will discuss these evidences, and will try to put them in relation with the abnormal motor function of the large bowel documented in this pathological condition.

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### INTRODUCTION

In gastroenterology practice, the most frequently encountered disorders are represented by those related to an abnormal function of the abdominal viscera, the so-called functional diseases<sup>[1,2]</sup>. The term “functional” defines several variable combinations of chronic or recurrent gastrointestinal symptoms that do not have an identified underlying pathophysiology<sup>[3]</sup>, and that are often also labelled as “idiopathic”. Thus, the definition of functional relies on the exclusion of an organic disease, and it is

consequently thought to be related to abnormalities of its physiological properties or functions.

Among the so-called functional disorders, one of the most common is functional constipation, whose diagnostic criteria according to Rome II classification<sup>[4]</sup> are reported in Table 1. Patients with functional constipation may be further classified in three subgroups: normal transit constipation, disorders of defecatory or rectal evacuation (outlet obstruction), and slow transit constipation (STC)<sup>[5,6]</sup>. This latter condition affects mainly women, it is characterized by an often intractable constipation, a heavily delayed colonic transit up to true colonic inertia<sup>[7,8]</sup>, and it is usually attributed to disorders of colonic motor function<sup>[9,10]</sup>. Indeed, several abnormal motor aspects have been described in STC, such as alterations of rectosigmoid contractile activity<sup>[11]</sup>, decreased colonic propulsive function<sup>[12,13]</sup>, abnormal response to food ingestion<sup>[14,15]</sup>, and overall reduced electrical or motor activity of the large bowel<sup>[16,17]</sup>. It must also be taken into account that a further cause of delayed colonic transit may be due to the association with pelvic floor dyssynergia; this condition must be identified, since it is amenable of biofeedback treatment, which can normalize colonic transit<sup>[18]</sup>.

However, we still do not know how and why these abnormalities are present in STC patients. In recent years, clinical and manometric evidence has been accumulated that suggests how most of the motility alterations in STC might be considered as a neuropathic type. Moreover, other data showed that some subtle alterations of the enteric nervous system, not evident to conventional histological examination, may be present in these patients. In the present article we will discuss these evidences, and will try to put them in relation with the abnormal motor function of the large bowel documented in this pathological condition.

### STC AS A NEUROPATHY: CLINICAL EVIDENCE

In several patients with STC subclinical features of autonomic neuropathy may be present<sup>[19]</sup>, and other studies described selective sensory and autonomic neuropathy in these subjects<sup>[20]</sup>, often with a positive family history, suggesting a genetic basis for this condition<sup>[21]</sup>. Animal studies might help in elucidating these issues: for instance, transgenic mice with a targeted deletion of neurturin (a neurotrophin) display clinical and tissue phenotype similar to that found in STC, and display associated

**Table 1 Rome II criteria for functional constipation (adapted from reference 4)**

**Two or more of the following for at least 12 wk (not necessarily consecutive) in the preceding 12 mo:**

- Straining during > 25% of bowel movements;
  - Lumpy/hard stools for > 25% of bowel movements;
  - Sensation of incomplete evacuation for > 25% of bowel movements;
  - Sensation of anorectal blockage for > 25% of bowel movements;
  - Manual manoeuvres to facilitate > 25% of bowel movements (e.g., digital evacuation or support of the pelvic floor);
  - < 3 bowel movements per week
- Loose stools are not present, and there are insufficient criteria for irritable bowel syndrome

parasympathetic deficits<sup>[22]</sup>.

Moreover, since in a sizable proportion of STC patients the symptoms start after pelvic surgical procedures<sup>[23-25]</sup> or following childbirth<sup>[26]</sup> it has been hypothesized (although the anatomic proof has never been given) that pelvic nerve injury may occur following hysterectomy and childbirth, and that STC could be considered a disorder of pelvic autonomic nerves at least in a subgroup of patients<sup>[27]</sup>.

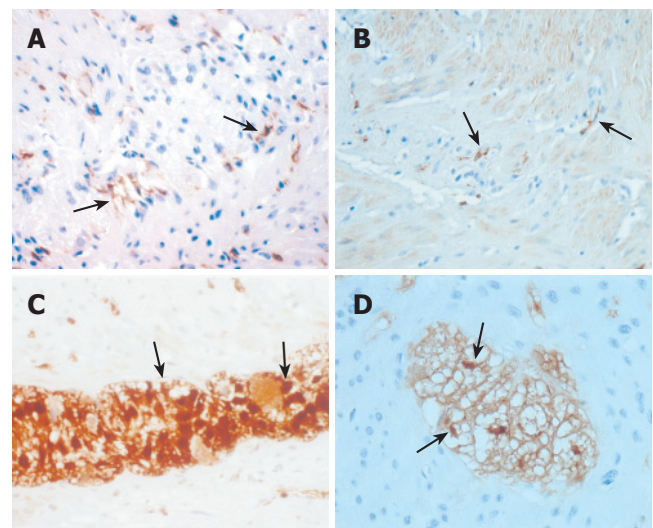
## STC AS AN ENTERIC NEUROPATHY: INSTRUMENTAL EVIDENCE

Several manometric studies carried out in patients with STC have reported findings that suggest the presence of neuropathic-type abnormalities. Such abnormalities have been described in many instances with respect to the periodic motor activity of the rectosigmoid area (including the so-called rectal motor complex), that appears either decreased or disorganized<sup>[28-30]</sup>, the contractile colonic motor response following intravenous cholinergic stimulation, that in results impaired<sup>[31]</sup>, the early motor response following ingestion of a meal, reported as decreased or absent<sup>[32]</sup>, the overall daily colonic motility, usually decreased to a lesser or greater extent<sup>[33,34]</sup>, the daily organization of regular contractile colonic patterns, that is often impaired<sup>[35]</sup>, and the lack of propulsive response to intraluminal instillation of bisacodyl (a powerful stimulant of mass movements in healthy subjects)<sup>[36]</sup>.

It is worth noting that neuropathic-type abnormalities in patients with STC are not necessarily confined to the large bowel, but may be also documented in other viscera such as the esophagus<sup>[37,38]</sup>, the stomach<sup>[39,40]</sup>, the gallbladder<sup>[41]</sup>, and especially the small bowel<sup>[42-45]</sup>, suggesting the presence of a pan-enteric motor disorder in these patients, particularly in those with more severe symptoms.

## STC AS AN ENTERIC NEUROPATHY: PATHOLOGICAL EVIDENCE

Most of the pathologic descriptions related to STC are pertinent to the large bowel, and only sporadic reports from other gastrointestinal viscera (terminal ileum) exist. Therefore, the discussion of pathological findings will



**Figure 1** Interstitial cells of Cajal (arrows) at myenteric plexus level in a control subject (A) and in a patient with slow transit constipation (B). Note the considerable decrease of these cells in the patient (CD117, original magnification x 40). Panels C and D show the enteric glial cells (arrows) in the myenteric plexus of a control and of a patient with slow transit constipation, respectively. Note the important reduction of these cells in the patient, where only a few ones may be identified (S100, original magnification x 40).

focus on the colonic studies.

### Conventional histology

Most studies employing routine light microscopy have failed to identify consistent abnormalities of the enteric nervous system (ENS) in patients with STC<sup>[46-50]</sup>, apart from the presence of melanosis coli. However, we have recently demonstrated that melanosis coli *per se* does not have any relationship with colonic ENS abnormalities (in particular with the loss of enteric neurons, as hypothesized in older studies only evaluating the submucosa) in these patients<sup>[51]</sup>.

### Silver staining technique

Morphological abnormalities of colonic innervation have been described in STC patients using the silver staining technique introduced by Smith<sup>[52]</sup>. These studies have generally reported a reduction in the total number of argyrophilic neurones and morphological neuronal and/or axonal abnormalities<sup>[53,54]</sup>. However, the silver staining technique has been subsequently replaced by more modern and reliable immunohistochemical methods (see below).

### Immunohistochemistry

Concerning the hypothesized imbalance of enteric neurotransmitters or the enzyme markers (mostly neuropeptides) in STC, the various studies (using immunostaining, immunoassays, or both methods) have frequently yielded inconsistent results. In fact, looking at the findings related to the most commonly investigated neuropeptides (VIP, substance P, neuropeptide Y and 5-HT), decreased, increased or unchanged levels or immunoreactivity has been described in these patients<sup>[55-59]</sup>. Overall, on the basis of the above reports it might be stated that it is unlikely that alterations of the enteric neurotransmitters may play

a major role in the pathophysiology of STC. However, more recent observations suggest that an excessive production of nitric oxide in the colonic myenteric plexus of patients with STC could play a pathophysiological role, concurring in the persistent inhibition of contractions<sup>[60,61]</sup>.

More consistent results have been reported with respect to enteric neurons, interstitial cells of Cajal (ICC), and enteric glial cells (EGC). In fact, a decrease of enteric neural elements (neurons and/or neurofilaments) seems to be a constant feature in studies evaluating patients with STC severe enough to require surgery for symptoms' relief<sup>[62-66]</sup>, and these abnormalities are often associated with a reduced number of ICC<sup>[67-71]</sup>, although this latter finding is not constantly present<sup>[72]</sup>. We have recently shown in a relatively large and homogeneous group of patients with severe and intractable STC, compared to age-matched controls, that the ICC are significantly decreased in patients (Figures 1 A and B), that the enteric neuronal loss may be partially due to apoptotic phenomena, and that these patients display a significantly decreased number of EGC with respect to controls (Figures 1 C and D), in both the submucosal and myenteric plexuses<sup>[73]</sup>.

## STC AS AN ENTERIC NEUROPATHY: CLINICAL, INSTRUMENTAL, AND PATHOLOGICAL RELATIONSHIPS

On the basis of the above evidences, it seems now possible to track a link between the clinical picture, represented by severe constipation with heavily delayed colonic transit, often refractory to medical treatment, the instrumental manometric findings, that mostly show impaired motility and propulsive activity of the large bowel (sometimes with the participation of the upper gastrointestinal segments too), and the abnormalities of the colonic ENS.

The neuronal loss is likely to affect the motor activity of the large bowel, reducing the likelihood of enteric neurotransmission. This defect is then strengthened by the concomitant reduction of the number of ICC, a cell population of paramount importance for the correct homeostasis of gastrointestinal motility. In fact, the primary role of ICC as intestinal pacemakers has been established in experimental animal models, where it has been shown that a lack of ICC networks leads to the absence of slow waves and is accompanied by delayed or absent intestinal motility<sup>[74,75]</sup>. A decreased ICC function might therefore impair the colonic electrical slow wave activity, thereby affecting the contractile response and causing delayed transit in STC patients. In addition, it has been recently demonstrated that in patients with STC the expression of c-kit mRNA and c-kit protein is significantly decreased compared to controls, suggesting that alterations in the c-kit signal pathway may play an important role in ICC reduction in such patients<sup>[76]</sup>.

An interesting findings, never described before, was the significant decrease of EGC in both the myenteric and submucous plexuses in STC patients compared to controls. This cell population originates from the neural crest and provides both mechanical and physiological support for neuronal elements<sup>[77]</sup>. The chief known function of the

glia in the adult is the formation of myelin sheaths around axons, allowing the fast connections essential for the nervous system function. Moreover, EGC maintain the appropriate concentrations of ions and neurotransmitters in the neuronal environment and are essential regulators of the formation, maintenance and function of synapses, the key functional units of the nervous system<sup>[78,79]</sup>. Since EGC are thought to act as intermediaries in enteric neurotransmission<sup>[80]</sup>, it is likely that their decrease could synergistically act in further weakening the already precarious neuroenteric balance due to the decrease of neuronal elements and ICC found in patients with STC.

## STC AS AN ENTERIC NEUROPATHY: CONCLUSIONS

The case for reclassifying STC other than an "idiopathic" or "functional" disorder is built. In fact, as seen above, clinical, instrumental, and pathological evidences exist that all point toward to a (perhaps) more precise definition of this condition as a true enteric neuropathy. It is probably too early to target STC with a different label, but at least we are now aware of some basic pathophysiological mechanisms potentially responsible for the symptoms and the manometric abnormalities found in this condition. Moreover, apart from mere semantic considerations, the demonstration of such background abnormalities might reveal useful for more targeted therapeutic approaches. For instance, in a mouse model the blockage of Kit receptors caused transdifferentiation of intestinal ICC to a smooth muscle phenotype<sup>[81]</sup>; if the same would occur in the human colon and if ICC do not die in STC but rather redifferentiate, it might be possible to create conditions that would shift the phenotype back toward ICC.

In conclusion, the advancement of our knowledge of the possible pathophysiological mechanisms of "functional" disorders is important for a more correct clinical and therapeutic approach. Further studies are obviously needed before we can drop the "idiopathic" label from these disorders.

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