NEW PATHOPHYSIOLOGICAL CONCEPTS ABOUT CHRONIC CONSTIPATION

THE POINT OF VIEW OF THE GASTROENTEROLOGIST AND OF THE PATHOLOGIST

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CONSTIPATION

from the Latin cum-stipare (to press together), constipation is one of the most ancient complaints in human history

CONSTIPATION: A FUNCTIONAL DISORDER

Furi...nec decem totos cacas in anno, sed id durius est faba et lapilli

Catullus, Carmina
FUNCTIONAL DISORDERS

• the so-called “functional” gastrointestinal disorders are usually thought to occur in the absence of anatomical or biochemical abnormalities. However, this definition now seems outdated, because structural and molecular abnormalities have begun to be recognized in subsets of patients.

HOW “FUNCTIONAL” ARE GI FUNCTIONAL DISORDERS?

• IBS: recent demonstration of lymphocytes/mastocytes infiltration in the myenteric plexus (Tornblom, Gastroenterology 2002) and the small bowel (Guilarte, Gut 2007) and colon mucosa (O’Sullivan, NGM 2000; Barbara, Gastroenterology 2004)
• new pathophysiologic concept of “low grade inflammation” for IBS (and, perhaps, for non-ulcer dyspepsia…)

“FUNCTIONAL” OR “IDIOPATHIC” CONSTIPATION

• exclusion of organic abnormalities (e.g., tumours) or associated pathologic conditions (e.g., hypothyroidism)
• no use of constipating drugs (e.g., antidepressants)
• normal colorectal anatomy

PATHOLOGICAL FINDINGS IN SEVERE CONSTIPATION

• decrease of argirophylic neurons (Krishnamurti et al, 1985)
• abnormalities of enteric neurotransmitters (Koch et al, 1988; Zhao et al, 2002)
• decrease of intraganglional neurofilaments (Schouten et al, 1993)
• hypoganglionosis of myenteric plexus (Wedel et al, 2002)
• reduction of interstitial cells of Cajal (ICC) (Lyford et al, 2002; Tong et al, 2004)

HOWEVER…

• most studies recruited small number of pts, with very different clinical and instrumental characteristics
• only one or two aspects of the ENS have been investigated in these studies
OUR CLINICOPATHOLOGICAL EXPERIENCE WITH A MULTI-COMPREHENSIVE APPROACH TO THE E.N.S. IN PATIENTS WITH SEVERE CHRONIC CONSTIPATION

ENS FINDINGS IN STC (26 pts with homogeneous features and intractable symptoms)
- decreased number of enteric neurons (SP and MP);
- decreased number of EGC (SP and MP);
- decreased number of ICC (IC-MY and IC-SM);
- decreased number of bcl-2+ neurons (SP and MP);
- increased number of apoptotic neurons in the MP;
- no giant ganglia;
- no lymphocytic infiltration of the MP


THE POINT OF VIEW OF THE PATHOLOGIST

Vincenzo Villanacci
COLON

Submucosal plexus
Intramuscular plexus

Nerve fibers
Cajal cells

Interstitial cells of Cajal
Ganglion and enteroglial cells
Muscle cells
Vessels

Muscular propria
Serosa
Submucosa
Mucosa

Ganglion Cells
Enteroglia
Cajal cells
CD3  + S 100

Cajal cells

Glial cells

Gangliar cells

Cajal cells

GANGLIAR CELLS

IMMUNOHISTOCHEMISTRY

Muscularis propria

Submucosa
Glial Cells

Gangliar Cells

Neuron Cells
THE MOST IMPORTANT PROBLEM!

Absence of approved and confirmed normal range values of the different types of Enteric Nervous Cells!
In conclusion, quantitative data on the ENS are generally insufficient to recommend normal ranges at the present time. The data reported in this manuscript represent an interim set of values that can be used to set contemporary boundaries around what is normal.
THE HISTOPATHOLOGICAL APPROACH

To identify the presence and importance of changes that occur in nerves and muscles in the slow transit constipation

Original Article

The Enteric Nervous System in Chagasic and Idiopathic Megacolon

Guido Santonja, MD*; Gabrio Beccatii, MD, PhD†; Zubia Koyan, MD;‡
Carlos Miguel Lomelí, MD*; Ana Maria Calzada, MD; Simon Florent, MD;§
Liliana Menahan Fuentes, MD*; Claudia R. Bilello, MD*; Juan Pablo Mancini, MD;§
Barbara Kanura, MD; Antonio Moccetti, MD; and Vincenzo Ulloaazzi, MD;*
Severely constipated patients displayed a significant decrease in enteric gangliar cells, glial cells, and interstitial cells of Cajal. Fibroblast-like cells associated with the latter did not differ significantly between patients and controls. Patients had significantly more apoptotic enteric neurones than controls.

Conclusion: Severely constipated patients have important neuroenteric abnormalities, not confined to gangliar cells and interstitial cells of Cajal. The reduction of enteric neurones may in part be due to increased apoptotic phenomena.
APOPTOSIS

BCL2
MONOCLONAL ANTIBODY TO SINGLE STRANDED DNA

BCL2
was significantly lower in the enteric neural elements of STC patients compared with controls in both the myenteric and submucosal plexus

MONOCLONAL ANTIBODY TO SINGLE STRANDED DNA

Apoptotic enteric neurones were significantly increased in the myenteric but not in the submucosal plexus
Data analysis showed that 45.5% of patients displayed significant (>10%) aneusomy of chromosome 1 in enteric neurons. Aneusomy <10% for the same chromosome, but less than the cutoff suggested (10%), was found in enteric glial cells in 45.4% of the same patients. One patient had <10% aneusomy in enteric neurons for chromosome 8. No other abnormalities were found for the remaining probes, and no abnormalities were found in controls. We concluded that in a subgroup of patients with slow transit constipation a genetic basis may be present.
Obstructive IBD

Diverticular Disease

Neurologic Disease

Drug Damage

THE POINT OF VIEW OF THE GASTROENTEROLOGIST

EGC ARE CONSTANTLY DECREASED IN SEVERAL CONDITIONS CHARACTERIZED BY CONSTIPATION

- diverticular disease (normal no. of enteric neurons, ICC decrease) (Bassotti et al, 2005);
- Chagasic and idiopathic megacolon (decreased no. of enteric neurons/disappearance (Chagas) – not due to increased apoptosis; IC-MY decrease) (Iantorno et al, 2007);
- obstructed defecation (decrease of SP neurons, normal no. of ICC) (Bassotti et al, 2007)
Enteric glial cells and their role in gastrointestinal motor abnormalities: Introducing the neuro-giopathies

Enteric glial cells: new players in gastrointestinal motility?

not only “gluing” functions, but also...
• homeostatic functions (loss of EGC causes neurodegeneration and/or alterations of the neurochemical coding of enteric neurons) (Bush et al, 1998; Aube et al, 2006)
• neurotransmitter function (Ruhl, 2005)
• immunological functions (interactions with lymphocytes, activation as antigen-presenting cells) (Hirata et al, 1986; Geboes et al, 1992)

WHY EGC ARE DEPLETED IN CONSTIPATED PATIENTS?

• Aging? (Phillips, 2007)
• Genetic background? (Rossi, 2007)
• Infectious agents? (Marruchella, 2007; Albanese, 2008; Selgrad, 2009)
• Luminal microenvironment abnormalities? (Di Giancamillo, 2010)

CONCLUSIONS

• constipation should not be considered as a “functional” or “idiopathic” disorders
• evidence is accumulating that suggest this complaint might be reconducted to a true neuro-giopathy
• maybe it is time to reconsider classifications…
“...he that increaseth knowledge increaseth sorrow”

Ecclesiastes, 1:18