COLONIC DIVERTICULAR DISEASE: ABNORMALITIES OF NEUROMUSCULAR FUNCTION

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CDD: ETIOLOGY

• Interaction of several factors:
  - genetic predisposition
  - intrinsic anatomic features of the colon
  - colonic wall modifications (aging)
  - dietary fibers
  - intraluminal pressures
  - neuromuscular dysfunction (abnormal motility and perception)

CDD: RECTOSIGMOID MOTILITY

- Early motility studies performed on this topic
- Blind or rigid rectoscopy positioning of catheters/electrodes
- *Actual positioning: rectum, rectosigmoid junction (the diverticular area might have been missed)*


Similiar findings also described in right-sided colonic diverticular disease (Sugihara et al, 1983; Sasaki et al, 1986)

Other studies, however, did not find significant differences in rectosigmoid motility between controls and CDD patients (Leandro et al, 1984; Kratzsch, 1985; Katschinski et al, 1990; Viebig et al, 1994)

Discrepancies were also found concerning surgical correction of motor abnormalities (Parks, 1970; Smith et al, 1974; Landi et al, 1979; Correnti et al, 1983; Cortesini et al, 1989)
CDD: RECTOSIGMOID MOTILITY

• How can the discrepancies between studies be justified?
  - use of suboptimal techniques (e.g., cutaneous EMG recording)
  - use of different methods
  - poor positioning (missing diverticular areas)
  - few recording points
  - short recording periods (30 mins-a few hours)
CDD: COLONIC MOTILITY

- The possibility of recording colonic motility for 24 or more hours added new information concerning the motor behavior of the large bowel

_Narducci, Bassotti et al, 1987_
Twenty-Four Hour Recordings of Colonic Motility in Patients with Diverticular Disease

Evidence for Abnormal Motility and Propulsive Activity

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- 10 CDD asymptomatic pts, 16 controls
- 24-hr colonic motility recording
- compared to controls, CDD patients displayed increased motor activity in the affected segments, and an increase of mass movements (HAPC): about 20% of the latter were also abnormally propagated

Table 1.
Diurnal (9 a.m. to 9 p.m.) Overall Motility Index in the Three Colonic Segments Under Observation

<table>
<thead>
<tr>
<th>Segment</th>
<th>Patients</th>
<th>Control Subjects</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transverse</td>
<td>2,481 ± 1,069</td>
<td>3,389 ± 1,256</td>
<td>0.704</td>
</tr>
<tr>
<td>Descending</td>
<td>11,129 ± 4,104</td>
<td>3,570 ± 1,122</td>
<td>0.04</td>
</tr>
<tr>
<td>Sigmoid</td>
<td>11,485 ± 3,155</td>
<td>5,362 ± 1,259</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Figure 1. Representative manometric tracing of two high-amplitude propagated contractions (the manometric equivalent of mass movements) in a patient with diverticular disease of the colon. Note that these contractions are easy to distinguish from low-amplitude background segmenting contractions. The first sequence is normally propagated in an orocaval direction from the transverse (T) to the distal sigmoid (S) colon, whereas the second one is retropropagated in the segments (sigmoid and descending, D) affected by diverticula.
in both groups, the 2- or 3-cycles/min represented more than 80% of regular contractile patterns, especially in the sigmoid colon compared to controls, CDD pts had significant increase of the duration of regular contractile patterns (31% vs 6% of the overall contractile activity) more than 30% of pts, but none of controls, had abdominal pain similar to that occurring at home while occurring a regular contractile pattern.
In the rectum, the SUDD group had increased perception scores compared with the control group (p=0.010) and the ADD group (p=0.030). In the sigmoid colon, in the pre- and postprandial periods, the SUDD group had increased perception scores compared with the control group (p=0.018).
VISCERAL SENSITIVITY IN CDD

Table 1

<table>
<thead>
<tr>
<th>Compliance (ml/mm Hg) in the rectum and sigmoid colon</th>
<th>Controls</th>
<th>ADD</th>
<th>SUDD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rectum</td>
<td>7.5 (0.1)</td>
<td>7.1 (0.7)</td>
<td>9.2 (0.9)</td>
</tr>
<tr>
<td>Sigmoid preprandial</td>
<td>4.1 (0.5)</td>
<td>3.7 (0.5)</td>
<td>4.1 (1.2)</td>
</tr>
<tr>
<td>Sigmoid postprandial</td>
<td>4.7 (0.7)</td>
<td>4.6 (0.0)</td>
<td>3.9 (0.9)</td>
</tr>
</tbody>
</table>

Data are mean (SEM).

Ingestion of the meal had no significant effect on compliance.

Preserved response to eating in all CDD pts
No differences between groups concerning this variable.
VISCERAL SENSITIVITY IN CDD

(Humes et al, 2012)

13 asymptomatic and 12 symptomatic patients, rectal barostat + investigation of inflammatory mediators

lower threshold of pain in symptomatic patients

Table 2 CD3 and 5-HT counts in sigmoid biopsies

<table>
<thead>
<tr>
<th></th>
<th>Asymptomatic patients</th>
<th>Symptomatic patients</th>
<th>Significance Mann-Whitney</th>
</tr>
</thead>
<tbody>
<tr>
<td>SHT [median [i.q.r]]</td>
<td>2 [1.0–2.4]</td>
<td>3.4 [1.4–3.8]</td>
<td>P = 0.15</td>
</tr>
<tr>
<td>CD3 [median [i.q.r]]</td>
<td>0.2 [0–0.4]</td>
<td>0.6 [0.4–1.0]</td>
<td>P = 0.50</td>
</tr>
</tbody>
</table>

Figure 1 Barostat pain detection threshold.
Figure 2 Relative expression of tumor necrosis factor alpha.
Figure 3 Relative expression of neurokinin 1.
HOW TO EXPLAIN NEUROMUSCULAR DYSFUNCTION IN CDD?

• muscular thickening of diverticular tracts (Whiteway and Morson, 1985)
• increased intraluminal pressures due to low-fiber diet (Smith, 1986)
• colonic wall elastosis (Golder et al, 2007)
• abnormal myogenic activity, basally and after cholinergic stimulation (Huizinga et al, 1999)
• marked reduction of muscular contractile responses to tachykinins (Liu et al, 2002; Burcher et al, 2008)
- CDD: neurotransmitters abnormalities
  (Jeyarajah and Papagrigoriadis, 2011)

- decreased NA-NC and NO inhibitory activity (Tomita et al, 2000)
- increased VIP-ergic activity (Grider et al, 1985; Milner et al, 1990)
- increased number of HT-containing cells (Banerjee et al, 2007)
- increased colonic mucosal neuropeptides in symptomatic CDD
  (Simpson et al, 2009)
- 5-HT4 receptor mRNA expression downregulated in *tunica muscularis*
  and upregulated in the mucosa of DD patients
  (Böttner et al, 2013)
CDD: ENS ABNORMALITIES

- A few recent studies carried out with IHC techniques have consistently shown ENS abnormalities, characterized by decrease of ICC and of EGC (Bassotti et al, 2005; Becheanu et al, 2008; Wedel et al, 2010)

CD117

S100
CDD: SM ABNORMALITIES

First demonstration that an altered pattern of factors involved in SMC contractility is present at level of the tunica muscularis of DD patients (Mattii et al, 2013)
CONCLUSIONS

• CDD frequently displays neuromuscular dysfunctions
• these dysfunctions alter both colonic motility and visceral sensation
• anatomical, neurochemical, and enteric abnormalities all play a role in this setting