Friday, June 17, 2005

8.30 Welcome

Session I
Pathogenesis of Diverticular Disease

Chairmen: B. Göke, Munich; A. Revhaug, Tromsø

8.45 Patterns of Inflammation
N. Y. Haboubi, Manchester

9.15 Enteric neuropathy
T. Wedel, Lübeck

9.45 Altered Motility
M. Kreis, Munich

10.15 Genetic disposition, environment
A. Forbes, London

10.45 Coffee break and poster viewing
Enteric Neuropathy and Diverticular Disease

**Classic pathogenetic concepts**

- **Ageing**: predominant in the elderly
- **Diet**: low fiber intake
- **Connective tissue disorder**: elastosis
- **Smooth muscle disorder**: myochosis
- **Enteric neuropathy**

?
Why should enteric nerves be involved?

**Increased intraluminal pressure**
- final common pathway for mucosal herniation
- segmental hypercontractility ("bladder colon" / "concertina colon")

**Increased motor activity**
- high amplitude propagated contractions
- increased motility indices (manometric + myoelectric studies)
- most evident after postprandial + pharmacological stimulation

**Increased painful sensations**
- abdominal bloating
- intestinal spasms
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Why should enteric nerves be involved?

- intraluminal pressure
- motor activity
- painful sensations

... mediated by the enteric nervous system (ENS)
Structural alterations of the ENS

First evidence in the literature

- increase of nerve tissue
- glial cell proliferation
- ectopic ganglia

MacBeth, J Clin Pathol, 1965
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**Structural alterations of the ENS**

- submucous giant ganglia
- submucous nerve fiber hypertrophy

Intestinal neuronal dysplasia

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**Structural alterations of the ENS**

- decreased ganglionic size
- decreased nerve cell content
- increased glial cell content

*myenteric hypoganglionosis (25% of cases)*

Wedel et al., *Viszeralchir*, 1999
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Structural alterations of the ENS

- submucous giant ganglia
- submucous nerve fiber hypertrophy

Intestinal neuronal dysplasia (20% of cases)

Wedel et al., Viszeralchir, 1999
Structural alterations of the ENS

- increased intramuscular nerve fibers
- increased mucosal nerve fibers

proliferative nerve remodelling
regenerative hyperinnervation

control

chronic diverticular disease

Simpson et al., Gastroenterol, 2002
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Functional alterations of the ENS

Neurotransmitters

Milner et al., Gastroenterology, 1990
- increased VIP-positive neurons

- upregulation of tachykinins (substance P, neuropeptide K)
- upregulation of galanin
- in patients with painful diverticular disease

"...visceral hypersensitivity originates locally, possibly as a result of nerve damage following acute diverticulitis."
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Functional alterations of the ENS

Neuroreceptors

- decreased cholinergic innervation
- increased muscarinergic receptors

Golder et al., Lancet, 2003

"... cholinergic hypersensitivity due to upregulation of muscarinergic receptors."
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Functional alterations of the ENS

in-vitro contractility

Golder et al., Lancet, 2003

• increased contractions after exogenous acetylcholine

Huizinga et al., Scand J Gastroenterol, 1999

• uncoordinated contractions after exogenous acetylcholine

Figure 5: Circular muscle log-concentration response curves for exogenous acetylcholine in diverticular and healthy sigmoid colon

Data are means, bars are 95% CI.
Functional alterations of the ENS

in-vitro contractility

- decreased ability to relax after electrical field stimulation
- decreased ability to relax in response to VIP / NO

Tomita et al., Regul Pept, 1993
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Summary of ENS alterations

Structural alterations
- myenteric hypoganglionosis
- submucosal hyperganglionosis
- mucosal nerve fiber hypertrophy

Functional alterations
- upregulation of neurotransmitters
- upregulation of muscarinergic receptors
- hypercontractility
- insufficient relaxation

Enteric neuropathy
Enteric Neuropathy and Diverticular Disease

Summary of ENS alterations

**Structural alterations**
- myenteric hypoganglionosis
- submucosal hyperganglionosis
- mucosal nerve fiber hypertrophy

**Functional alterations**
- upregulation of neurotransmitters
- upregulation of muscarinergic receptors
- hypercontractility
- insufficient relaxation

Enteric neuropathy
Summary of ENS alterations

- Intraluminal pressure
- Motor activity
  - Development of diverticula
- Painful sensations
  - Generation of symptoms
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The open question:

**Primary lesion?**
- enteric neuropathy causes colonic motor disturbances
- enteric neuropathy predisposes to diverticular disease
- enteric neuropathy = *causative event*

**Secondary lesion?**
- enteric neuropathy results from inflammatory injury
- enteric neuropathy generates symptoms
- enteric neuropathy = *concomittant event*
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Conclusions

Enteric neuropathy...

- is associated with diverticular disease
- is characterized by both structural and functional alterations
- could account for the disturbed motility and symptom generation in diverticular disease
- should be considered in a targeted therapeutic approach (e.g. spasmolytics, muscarinergic antagonists, antinociceptiva)
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Thanks for your attention!