

THE BEST OF UEGW 2008 AT DDW 2009

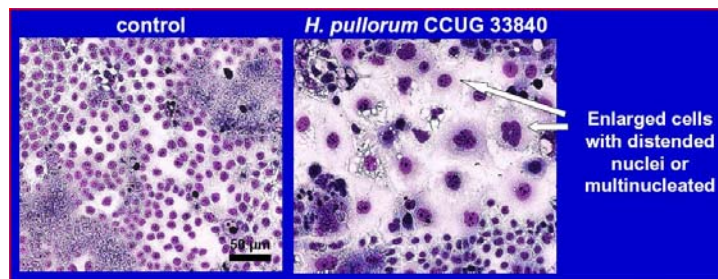
NEUROGASTROENTEROLOGY AND FUNCTIONAL DIGESTIVE DISORDERS

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At last UEGW 2008, the field of *NEUROGASTROENTEROLOGY AND FUNCTIONAL DIGESTIVE DISORDERS* was well represented in the programme, with 5 oral and 6 poster sessions. In oral sessions, 48 papers were presented, including 12 studies of basic science or translational medicine, mainly targeted to pathophysiological investigations of the brain-gut axis. Poster sessions were more clinically oriented with 115 posters showing results of clinical studies, out of 123 posters.

Amongst the oral presentations, have been selected papers that all deal with the concept of post-infectious Irritable Bowel Syndrome (IBS) and the nerve-immune relationships.

The first study presented by Varon et al. (1) investigated the mechanisms of the intestinal inflammatory reaction observed during *H. pullorum* infection. *H. pullorum* is a newly recognized pathogen, more often present in animals but also responsible for infections in humans, described as episodes of intestinal and liver/gallbladder inflammation. As others strains of Helicobacter, *H. pullorum* displays a pro-inflammatory effect in vitro on human intestinal epithelial cells involving bacterial adherence and NF- κ B signalling and expresses a Cytolethal Distending Toxin «CDT» that has cytotoxic effects mediated by the B subunit, through cell cycle arrest in G2/M phase and cellular distending phenotype.



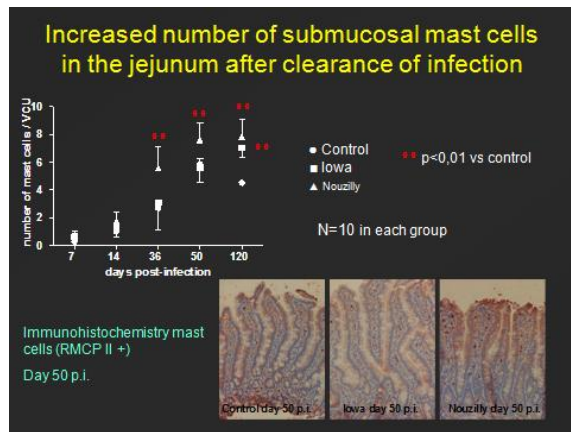
H. pullorum strains (human and avian) have CdtB-dependent cytopathogenic effects on human intestinal epithelial cell lines, characterized by cellular enlargement, nuclear distention/multinucleation, cellular proliferation arrest, actin cytoskeleton remodelling (lamellipodia formation and disturbance of the focal adhesions and the cell/cell junctions), up-regulation of genes related to actin cytoskeleton (vinculin and cortactin) and contribution to the proinflammatory cellular response (by stimulating IL-8 secretion).

Beside the insight in the pathophysiological mechanisms of *H. pullorum* infection, this study shows possible intracellular pathways of inflammatory processes that link control of cell proliferation to changes in cell-cell communications and triggering of a pro-inflammatory reaction by stimulating the IL-8 secretion.

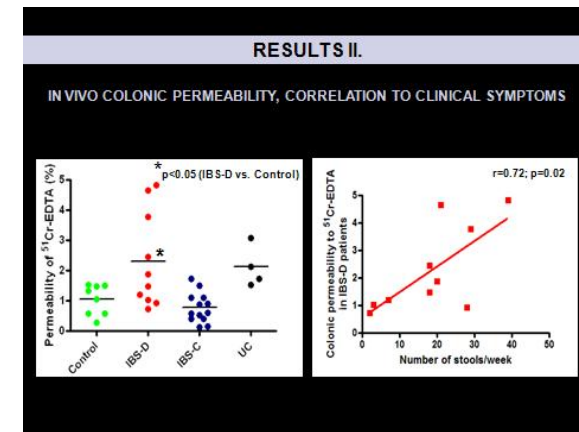
Many studies published over the last decade have established the concept of post-infectious IBS, that can be defined as typical IBS defined by clinical criteria, with an acute episode of intestinal infection, often a common gastro-enteritis. IBS patients in this subgroup complain more frequently of diarrhoea and several studies have shown that inflammatory markers are elevated in the blood and the colonic mucosa in these patients. AT UEGW 2008, several papers presented results of studies on the mechanisms of this inflammatory reaction in IBS patients.

The study by Khaldi et al. (2) investigated a model of post-infectious IBS in rats, after infection by *Cryptosporidium parvum*, a protozoal agent causing diarrhoea in humans and shown to trigger visceral hypersensitivity in a rat model. By studying infected rats two months after infection, these authors could show that the chronic inflammation induced by the protozoal infection resulted in a visceral hypersensitivity to luminal distension, related to a persistent inflammatory process, as shown by the increased number of lymphocytes and mast cells in the jejunal mucosa.

The main clinical outcome of this study is that the results show that the influence of an inflammatory process on the triggering of visceral hypersensitivity may occur in inflammatory or post-inflammatory conditions in the absence of an active inflammatory reaction. Subsequently, this model could be used to investigate the pathophysiological mechanisms on inflammation-related visceral hypersensitivity.

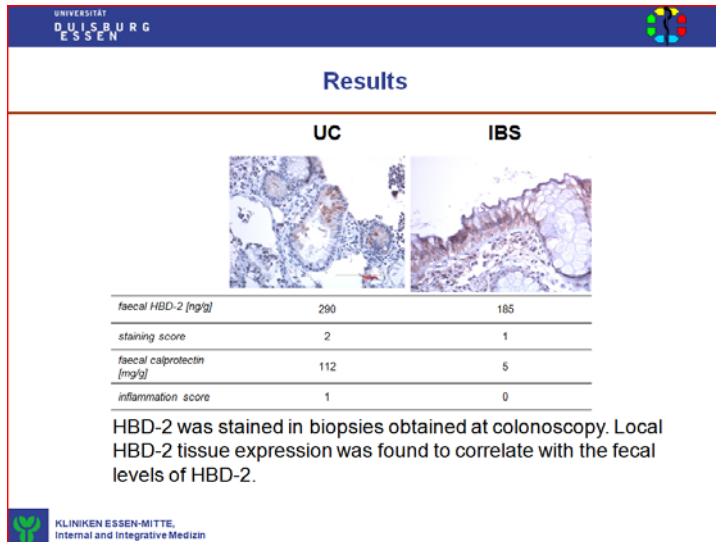


The next very interesting study has been published by the group of L. Buéno, in cooperation with the University of Szeged in Hungary. Gece et al. evaluated markers of colonic mucosa permeability in diarrhoea-predominant IBS patients (3). Intestinal permeability was assessed by measuring the absorption of ^{51}Cr -EDTA in various groups of IBS patients, defined by their bowel pattern. Diarrhoea-predominant patients were characterized by an increased intestinal permeability as compared to other IBS patients and had similar changes as those observed in patients with ulcerative colitis.

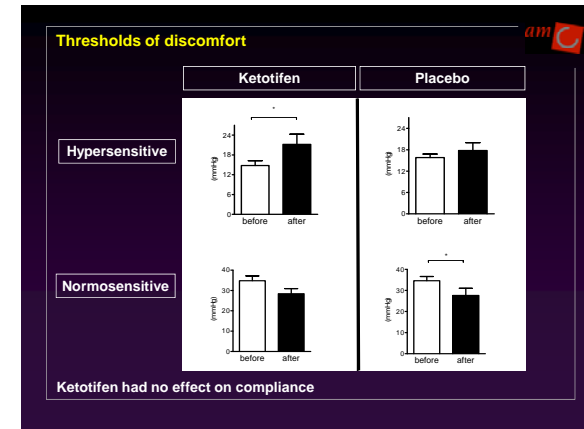


Investigating IBS in the same direction, Langhorst et al. investigated the pathophysiological role of defensins in patients with diarrhoea-predominant IBS (4). Defensins are anti-microbial peptides that contribute to mucosal innate defence to limit access to enteric bacteria and other microorganisms. Defensins exhibit antibiotic activity towards gram-positive and gram-negative bacteria as well as towards enveloped viruses and fungi. These authors could show that defensins are overexpressed in digestive mucosae, especially colonic mucosa, both in patients with ulcerative colitis and diarrhoea-predominant IBS.

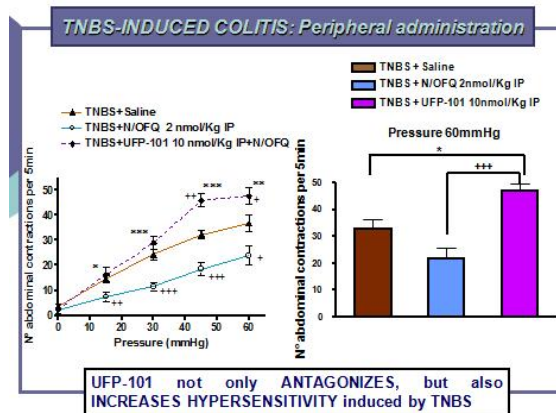
These results suggest an activation of the mucosal innate defence system towards a proinflammatory response in IBS patients in the absence of macroscopic signs of inflammation in ileo-colonoscopy. The functional significance of these findings remains to be elucidated but this observation brings a new insight into the pathophysiology of diarrhoea-predominant or post-infectious IBS. On the other hand, faecal defensins could be tested as a possible non-invasive biomarker of IBS in these particular subgroups of patients.



Beyond the pathophysiological concepts, the increasing knowledge on post-infectious IBS and the relationship between the brain-gut axis and the immune system results in practical proposals for the treatment of these patients. In a preliminary study, Klooker et al. evaluated the clinical benefit of a mast cell stabilizer, ketotifen in patients with IBS (5). They could show that 8 weeks of treatment with ketotifen increases the threshold of discomfort in hypersensitive IBS patients, reduces IBS symptoms and improves quality of life in both hypersensitive and normosensitive patients. However the mechanism of action of ketotifen in this indication remains to be elucidated since it had no effect on spontaneous release of tryptase and in vitro incubation of rectal biopsies with mast cell stabilizers did not affect spontaneous release of tryptase.



Beside the use of pharmaceutical compounds with established pharmacodynamic properties, the concept of post-infectious IBS and the research into the brain-gut-immune relationships may in the future bring novel approaches in the treatment of these disorders. In an animal study, Agostini et al. evaluated the effect of Orphanin/FQ peptides on visceral sensitivity (6). Nociceptin/Orphanin peptides display inhibitory effects on intestinal motility and analgesic effects in allodynia and supra-spinal hyperalgesia. These authors could show that whatever the route of administration (i.p or i.c.v.) nociceptin/orphanin does not affect basal visceral sensitivity and colonic muscular tone while it has an antinociceptive effect on visceral hyperalgesia triggered by inflammation. This antinociceptive effect is not linked to anti-inflammatory properties and is independent of its effect on colonic muscular tone.



Conclusion

Research in the field of post-infectious IBS dominated the field of Neurogastroenterology at last UEGW. This research provides new insights in the concept of a disturbed nerve-immune relationship, which appears to be a main determinant of IBS pathophysiology in this particular subgroup of patients. Beyond the pathophysiological concept, this research also results into interesting therapeutic approaches.

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