Painful Bladder Syndrome / Interstitial Cystitis and histamine intolerance – a link?
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Hypothesis / aims of study
The cause of Painful Bladder Syndrome / Interstitial Cystitis is currently unknown. However, several explanations have been proposed and include: autoimmune, nerve fiber, mast cell, leaky GAG layer and infection hypotheses as well as a possible production of a toxic substance in the urine. Especially histamine seems to play a major role in IC. Antihistamines are part of the guideline recommendations, foods high in histamine aggravate IC symptoms, pentosan polysulfate not only repairs the GAG layer but also binds histamine. Elevated histamine levels in urine have been found in some IC patients. Within this retrospective case collection the role of histamine overproduction is highlighted.

Study design, materials and methods
Between September 2012 and January 2014 a total of 33 women (age 19 to 70, mean age 51) were surveyed. Histamine in fecal samples was measured with a commercially available ELISA kit (LDN Labor Diagnostika Nord GmbH & Co. KG, Nordhorn, Germany). Additionally, vaginal swabs were analysed for histamine producing bacteria of the Enterococcus and Enterobacteriaceae family. In addition serum diamine oxidase levels (Sciotec Diagnostic Technologies, Tulln, Austria) were measured in 25 patients and methylhistamine in 24-hour urine (LC-MS/MS assay, Waters Corp., USA) in 19 patients.

Results

Stool and Serum results
In 25 of the 33 analysed women elevated histamine levels were found in fecal samples. Diamine oxidase levels were not decreased and histamine-forming microorganisms were not significantly increased (Figure 1).

Vaginal swab results
In 16 out of the 25 women the presence of Enterococcus spp. in vaginal swabs was also detected. In further 4 women only the presence of Enterococcus spp. was found. Only 3 women did neither show elevated histamine levels nor the presence of Enterococcus spp. in vaginal swabs (Figure 2).

Methylhistamine in the urine was not elevated.

Interpretation of results
Elevated histamine levels in fecal samples and the presence of histamine producing bacteria in the vagina could be found in the majority of women with diagnosed Interstitial Cystitis. Histamine overproduction in the gut or vagina may mimic a mast cell burst thus explaining the symptoms of IC. There are parallels between IC and histamine intolerance, a poorly described disease which may be responsible for a variety of symptoms (e.g. digestive complaints, non-allergic food hypersensitivity, migraine, runny nose): prevalence 1%, >80% female and middle aged, symptom improvement in pregnancy because of a 300 fold higher level of the histamine eliminating enzyme diamine oxidase (DAO) in pregnancy. DAO in the gut eliminates exogenous histamine taken in by food but also naturally produced histamine by gut bacteria. Histamine can increase intestinal permeability; the leaky gut (still not accepted by the scientific community) prompts the body to initiate immune reactions causing autoimmune diseases. IC is often associated with autoimmune diseases. The compromised intestinal barrier function is also found in irritable bowel syndrome, another comorbidity of IC: abdominal pain correlates here with activated mast cells in proximity to colonic nerves which leads to the hypothesis of a neural-mediated crosstalk between colon and bladder afferents.

Conclusions
Histamine plays a major role in neurogenic inflammation; substance P release from neurons induce the release of histamine from adjacent mast cells. This has been demonstrated recently in rodent neurogenic cystitis. Moreover histamine as shown in mice can also cause pelvic pain. A neural-mediated crosstalk between pelvic organs could be the answer to the histamine overload in the gut and vagina.

References
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