

## CYTOKINES IN FEMAL URINE AFTER TRANSVAGINAL URETHRAL MASSAGE ; POTENTIAL INITIATORS OF URGENCY”?

### Hypothesis / aims of study

The term cytokines encompasses a large group of proteins, peptides and glycoproteins, functioning as signal substances for intracellular communication and immune modulation. The concentration of some interleukins increases in trauma inflammation and infection and are depending i.a. on the concentration of macrophages while other stimulate cytotoxicity and angiogenesis in tumors.

There are indications that a low grade inflammation in the urethra may result in a sensitization of the voiding reflex and contribute to urgency in the Over Active Bladder syndrome (OAB)(1). Increased concentrations of interleukins may be indicators of such an inflammation. Cytokines in urine are excreted from the kidneys and urinary tract. A standardized transvaginal urethra massage adds cytokines from the urethral endothelium to the first urine portion voided after the massage.

The study was performed to evaluate the presence of possible interleukins as indicators of urethra inflammation in patients applying for urgency.

### Study design, materials and methods

In 10 consecutive patients applied for OAB-symptoms, interleukin -2( IL-2), IL-4, IL-6, IL-8 and Interferon gamma (IFN gamma) was measured in two consecutive urine samples obtained after a standardized transvaginal urethra massage with a semi-filled bladder. Bacterial urine cultures were obtained in all patients.

### Results

All bacterial cultures were negative. In two patients IL-6, well-known to be found in cystitis, was slightly elevated (20 (8) and 27 (27) ng/L in the two samples with normal values < 15 ng/L). Except for IL-8, see below, these were the only samples with values outside accepted normal limits and, also except for IL-8, the only result (20 and 8 resp.), that showed an obvious different concentration between the two consecutive samples obtained.

IL-8 concentration in the first urine sample was increased, or very increased, in 8/10 patients.

Normal value in urine for the method used was < 60ng/L while the mean value for IL-8 in the first urine portion in the total material was 645 ng/L ( range 10 – 2435). The two patients with normal levels presented concentrations of 48 and 10 ng/L in their first samples.

IL-8 in the second sample was lower than in the first in all but one patient (10 and 10 ng/L respectively) – i.e., in one of the two patients with normal IL-8 values.

In five of eight patients with elevated IL-8 in the first sample, the concentrations were increased also in the second sample.

### Interpretation of results

Normal values and absence of reaction of IL-2, IL-4 and IFN gamma indicates that these cytokines are not produced in the urethra in urgency. IL-2 is usually supposed to be produced by naive T-cells, IL-4 is involved in T-cell differentiation, while IFN gamma take part in the activation of natural killer cells and macrophages.

IL-6 in urine is known to be a marker of bacterial infection, while IL-8 is said to be an unspecific marker of inflammatory reaction. IL-8 is produced by macrophages and epithelial cells and is supposed to be a major mediator of inflammatory response. It is not plausible that such an inflammatory response could have been induced by the transvaginal massage per se. It is however highly possible that the massage releases inflammatory mediators already present. Such an inflammatory reaction may be a part of the urgency symptoms. IL-8 is known to be a potent chemoattractant for neutrophils but may in these patients still be “hidden” in the epithelium and, by unknown mechanisms, activate nociceptors responsible for urgency.

### Concluding message

In spite of the absence of reaction in some of the cytokines known to be involved in inflammatory reactions, the presence of a reaction in IL-8 indicates that some sort of inflammatory reaction is present in the urethra of women with urgency. The nature of this inflammatory reaction is not known. It is known that other cytokines may activate nociceptors while this is not supposed to be a main mission for IL-8. A possible inflammatory reaction in the urethra should certainly contribute to our understanding of the mechanisms of urgency.

### References

1. Löfgren O NEUROLOGY AND URODYNAMICS 2009;28,812

### Disclosures

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