

## IL- 8 IN URINE AFTER TRANSVAGINAL URETHRAL MASSAGE; AN ADDITIONAL STANDARD FOR OBJECTIVE ESTIMATION OF URGENCY IN WOMEN?

### Hypothesis / aims of study

Since some years, indications of a low grade inflammation in the urethra have been presented as a source of urgency contributing to symptoms in the Over Active Bladder syndrome (OAB)(1). It has i.a., been shown that, IL-8 is elevated in the first portion of urine delivered after a transvaginal urethral massage in patients applying for OAB. It has also been demonstrated that IL-8 in urine, after transvaginal urethra massage, is higher in patients with urgency than in healthy controls. IL-8 is known to stimulate angiogenesis in inflammation and tumors.

The current study was performed to evaluate if OAB- symptoms are connected to an inflammatory reaction in the urethra, and if patients with urgency and high IL-8 in urine, after successful treatment, presented normal levels of IL-8. If so, IL-8 might be used in diagnosis of female urine urgency and maybe also used to estimate an objective degree of urgency.

### Study design, materials and methods

25 consecutive patients were all applying for OAB-symptoms, all with negative urine cultures, wearing pads for security reasons and toilette mapping. The concentration of IL-6 and IL-8 in two consecutive portions of urine after an initial transvaginal urethra massage with a semi filled bladder was compared to the number of sessions registered ( mean of 2 x24/h) before the standard treatment. Treatment was given with a group-I-cortisone ointment (Terracortril- Polymyxin B) as an injection of 3 ml into the urethra after four additional massage sessions. The patients were urged not to evacuate within 20 min after the injections. The massage treatments was completed within a fortnight. The patients registered urine diaries 2x24 h before and after treatment.

In ten patients a "dry massage" with semi filled bladder and fractionated micturition for cytokine measurement was performed also after the treatment.

### Results

10 patients reported < 9 sessions and 15 patients reported > 8 sessions, (mean of 2x24h). In the group with < 9 sessions 2/10 patients had a higher than normal concentration of IL-8 in the first portion of urine while in the group with > 8 sessions 11/15 patients had an IL-8- level higher than normal. IL-6 was normal in all patients and in all portions. IL-8 levels were lower in the second than in the first portion of urine in all but two patients – both in the group reporting > 8 sessions/24h.

In 10 consecutive patients where "dry massage" was performed also after treatment, 9/10 patients experienced a decrease of the number of sessions from a mean of 10,4 sessions to a mean of 7,75 and a subjective normalization with no urgency symptoms after treatment. Simultaneously there was a decrease in IL-8 from pathological high levels to normal - or almost normal- levels.

The decrease of IL-8 was significant in all patients except one. This patient also reported more sessions after treatment than before (10 compared to 8, initial urgency- not frequency- being the dominating symptom). The patient reported no urgency after treatment but to exclude urinary infection a sample was obtained by catheterization. The culture showed a rich growth of bacteria. IL-6 was normal in both samples.

One patient had very low levels of IL-8 both before and after treatment (54 and 70 ng/L). She presented diaries with 14,5 and 8,5 sessions respectively and volumes of 23 and 20 dl /24h (mean of 2x24h both before and after treatment)

### Interpretation of results

The decrease in voiding sessions in patients with OAB-symptoms after local treatment of the urethra with a mild cortisone ointment indicates an inflammation in the urethra, maybe with sensitization of the voiding reflex.

This support earlier finding that urgency is initiated from a hypersensitive urethra rather than a primary result of synchronization of oscillatory contractions in the bladder detrusor.

An increase of both IL-6 and IL-8 in urine is well known in urinary tract infections. The absence of bacteria in cultures, a normal IL-6 and a simultaneously elevated IL-8 indicates other underlying causes for an inflammatory reaction than infection. IL-8 is known to be a mediator of immune reactions, and a potent angiogenic factor in both tumors and inflammation. It is highly probable that IL-8 is involved in the initiation and sensitization of nociceptors for urgency.

The dominance of high levels of IL-8 in patients with urgency and > 8 sessions/24 h compared to the normal levels of IL-8 in patients without urgency and < 9 sessions/24 h support the conception that IL-8 might be used as an objective measure of this symptom. The decrease of IL-8 from higher than normal levels during urgency to normal levels after treatment, with a concomitant normalization of the number of sessions, adds to this support.

The discovery of a higher level of IL-8 in the second portion of urine in two patients was supposed to be the result of confusion of tubes, though a delayed secretion of IL-8 might be possible although not very likely.

The infection in the patient who reported more sessions and a higher IL-8 level after treatment than before, was probably iatrogenic as the treatment per se includes small but obvious risk of introducing bacteria into the bladder. This asymptomatic

bacteriuria was not accompanied by elevation of IL-6 but was revealed by culturing urine from a sterile catheterization. This further indicates a usefulness of IL-8 in the diagnosis of urgency.

The very low levels of iL-8 in the patient with urgency because of high liquid intake, shows that IL-8 also can be used to reveal "false" urgency.

#### Concluding message

It seems highly possible that low grade inflammation in the urethra initiates urgency in the OAB-syndrome. The cause of the inflammation is not infectious but remains to be revealed. Treatment of urgency incontinence should be focused on this inflammation and the afferent neurons from the urethra.

IL-8 seems to act as a sensitizer and/or trigger for nociceptors inducing urgency.

IL-8 concentrations reflect the degree of urgency and may have a role as an objective and additional tool at routine examination. The concept of the OAB – syndrome and the rationales for treating "OAB-symptoms" with muscarine inhibitors should be questioned.

#### References

1. 1. Löfgren O. Neurology and Urodynamics 2009;28,812

#### Disclosures

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