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Khasriya R[1], Bhome R[1], Khan S[1], Bignall J[1], Ali V M[1], Malone-Lee J[1]
1. *UCL*

URINARY INTERLEUKIN-6 AND PYURIA IN PATIENTS WITH SYMPTOMS OF OAB

Hypothesis / aims of study

The study of OAB has started to focus on the pathophysiology of the urothelium, particularly in relation to ATP signalling through the puringergic system. In the human lower urinary tract, ATP has not been found to play the major role that has been described in other animals. However, it is known that if an inflammatory response affects the human urothelium, then ATP is produced in large amounts [1]. Recently, an inflammatory response in the urine of patients with OAB symptoms has been described. However, the method necessary to detect the offending white cells requires light microscopy of a fresh, unspun urine sample in a haemocytometer. This is not an easily applied method and would struggle to achieve widespread acceptance. In addition, the detection of pyuria on its own may not be clinically relevant and corroborating data is necessary before significance be accepted.

Interleukin-6 is an immune protein in the hematopoietins family. IL-6 stimulates the acute-phase reaction, which enhances the innate immune system and protects against tissue damage. It is released very early in the inflammatory response and has a short half-life so its detection reflects on recent events. IL-6 is expressed by the urothelium in response to infection, in addition to IL-8 and platelet derived growth factor (PDGF). IL-6 has been studied in urinary infection and interstitial cystitis but not OAB [2]. The detection of IL-6 expression in urine in association with OAB symptoms would support the hypothesis of a urothelial inflammatory response as part of the pathophysiology.

We tested the hypothesis that urinary IL-6 expression in the urine of patients with OAB would be increased in association with pyuria.

Study design, materials and methods

This was a blinded, observational cohort study. Women with symptoms of the OAB were asked to give consent to participate and provide catheter specimens of urine (CSU) for the study. Their symptoms were recorded using a validated questionnaire. A CSU was obtained by inserting a Lofric (in and out) size 12 Fr catheter into the urinary bladder under aseptic conditions. Urine specimens were collected into a sterile container and a 4ml aliquot was taken immediately. The aliquot was centrifuged at 2000 revolutions per minute for five minutes and frozen at -80 ^{o}C. A sample of 0.9µl was taken in order to effect a count of white blood cells using a light microscope and a haemocytometer.

The samples were thawed and analysed in batches, blinded, once weekly. Human urinary IL-6 concentrations were determined using a commercial high sensitivity ELISA with a limit of detection of 0.09pg/ml with an inter and intra assay coefficient of variation of less than 10% (R&D Systems, Oxon, UK).

The study was powered at 87% to detect a clinically significant difference in IL-6 of 1 pg/ml given a standard deviation of 1.5 with 40 patients in each group.

The between group differences in IL-6 were tested by use of the t-test for independent samples. Correlations between IL-6 and log pyuria were examined by means of Pearson's R

Results

104 women with symptoms of the Overactive Bladder gave their consent to participate and provided catheter specimens of urine for the study. Their mean age was 56 (sd=17).

Because of the exponential nature of increasing pyuria the log of the urinary white cell count was calculated. There was a significant difference in IL-6 levels between those with pyuria and those without (95% CI of difference -2.9 to -0.11, p=0.34, t=-2.1) Figure 1

It was found that there was a correlation between the log white cell count and IL-6 Pearson R = 0.5, p=0.001 (Figure 2). There was no relationship between IL-6 and symptoms of urgency, frequency and incontinence.

Figure 1 Mean Il-6 and 95% CI comparing pyuria against no pyuria

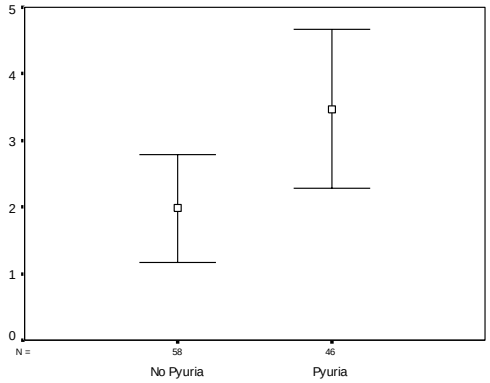
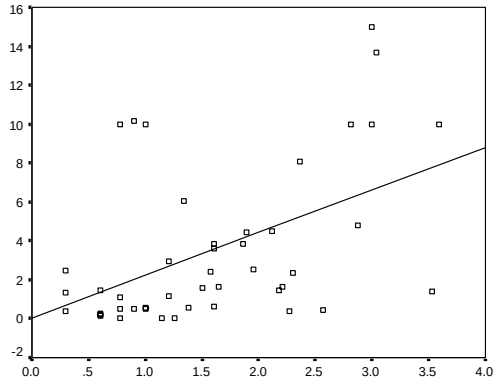


Figure 2 Scatter plot of Il-6 and log urinary white cell count showing correlation



Interpretation of results

The pyuria found in these patients with OAB was associated with an alternative marker of inflammation, namely IL-6. This provides some additional independent verification of the significance of pyuria detected by microscopy of fresh unspun specimens of urine. Whilst there was a correlation between the pyuria and IL-6 this was not sufficiently strong to encourage the view that IL-6 might prove to be a useful surrogate marker of pyuria.

Concluding message

Pyuria in patients with OAB symptoms is associated with urinary expression of the acute phase cytokine IL-6. This finding is supportive of the view that OAB symptoms in some patients are associated with a urothelial inflammatory reaction.

References

1. J Urol. 166(5), 1951-1956. 2001
2. Urology 68(4), 702-706. 2006

Specify source of funding or grant	**The Whittington Hospital NHS Trust**
Is this a clinical trial?	**No**
What were the subjects in the study?	**HUMAN**
Was this study approved by an ethics committee?	**Yes**
Specify Name of Ethics Committee	**The East London Ethics Committee**
Was the Declaration of Helsinki followed?	**Yes**
Was informed consent obtained from the patients?	**Yes**