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Gill K[1], Jeyakumar A[1], Brenton T[1], Malone-Lee J[1]
1. *University College London Medical School, Whittington Archway Campus*

A URINE TEST FOR OAB

Hypothesis / aims of study

There is a growing interest in chronic cystitis as an important aetiological factor in the evolution of the overactive bladder (OAB) (1). urothelial damage by infection leads to the release of inflammatory mediators including platelet derived growth factor (PDGF), tumour necrosis factor-α (TNF-α), interleukin 6 (IL-6) and interleukin 8 (IL-8). *E.coli* infection has been well studied(2;3), in which a rapid cytokine response is observed. Cytokines play a key role in the innate defence. IL-6 may cause fever and trigger the acute-phase response, while chemokines such as IL-8 recruit inflammatory cells to the site of infection. Urinary cytokines are elevated in patients with UTI and epithelial cells have been identified as early producers of cytokines in the murine UTI but the epithelial cytokine response of the human mucosa in situ has not been investigated. Uroepithelial cell lines of bladder and kidney origin constitutively make IL-6 and respond with elevated IL-6 production to exogenous stimuli like bacteria or cytokines. Studies of patients with urinary tract infection have shown rapid increases in urine IL-6 levels after the onset of infection or instillation of bacteria into the urinary tract. There is very little data on the expression of inflammatory mediators in other lower urinary tract syndromes such as OAB. An increased IL-8 has been shown in Interstitial Cystitis but not in the overactive bladder. There are no studies investigating the IL-6 response in the overactive bladder syndrome. Il-6 is a particularly interesting target because it is produced very early in the inflammatory response and metabolised rapidly. Therefore Il-6 levels are footprints of very recent pathological activity. To analyse Il-6 in the urine a very high sensitivity assay must be adopted because low levels must be expected. There is a sandwich ELISA which is capable of measuring pg ml^{-1} concentrations of IL-6 and this was selected for the experiment. This study tested the hypothesis that urinary IL-6 concentration, assayed by a highly sensitive ELISA, would be a useful marker of disease activity in patients with OAB.

Study design, materials and methods

This was a blinded, controlled observational study. Patients with OAB provided a catheter specimen of urine and normal controls provided meticulous MSU samples. Pyuria was counted by immediate urine microscopy. Aliquots of urine were stored frozen at -80^{o}C. The samples were thawed and analysed. 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 power to test the null hypothesis that the population means were equal was calculated. The criterion for statistical significance (alpha) was set at 0.050. The test was 2-tailed. It was found that a sample size comprising 20 controls and 20 patients had a 80% power to detect 0.4 pg/ml^{-1} difference in IL-6 between patients and controls, given a population standard deviation of 0.4 pg/ml^{-1}. Statistical analysis of the data was conducted using ANOVA at the 95% level of confidence.

Results

172 patients (157=F, 15=M, mean age 57, sd=19) and 20 controls (9=F, 11=M, mean age=34, sd=11) were recruited. Of the 172 patients who had OAB symptoms, 99 (58%) had pyuria and 73 (42%) did not have pyuria. The Il-6 data were normally distributed and suitable for parametric analysis. There were significant differences in Il-6 concentrations between normal controls and patients with OAB (F=9, p=.003), see figure 1. These differences were related to the diagnosis of OAB. The presence or absence of pyuria did not alter the relationship, see figure 2 (F=3.2, p=.045)

Figure 1

Comparison of controls and OAB

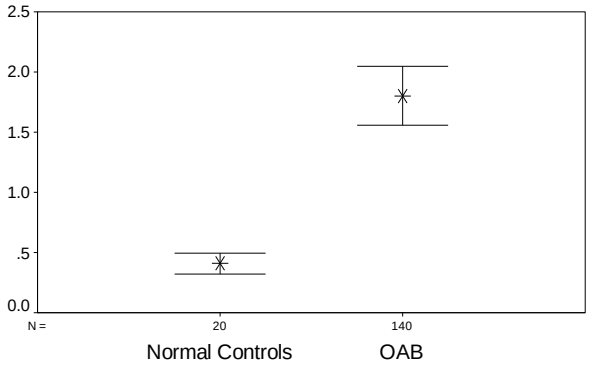
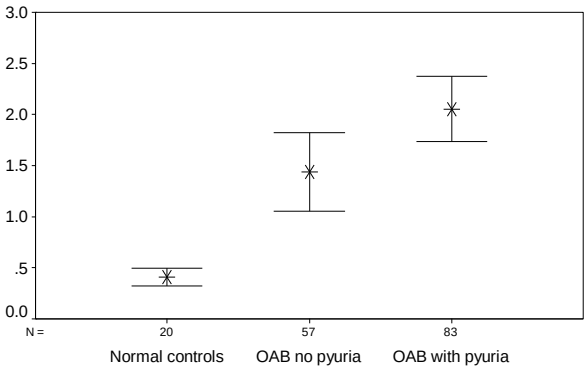


Figure 2

Comparisons based on pyuria



Interpretation of results

Levels of IL-6 were elevated in the urine of patients with OAB compared to controls. The differences in IL6 levels between groups were considerable and reflected the symptoms described. An important observation was that the cytokine levels seemed to be unrelated to the presence or absence of pyuria

Concluding message

The results of this investigation provide evidence to suggest that inflammatory pathophysiological changes are seen in sufferers of OAB, regardless of their pyuric state. These data support a bladder inflammatory reaction as key to the overactive bladder. They also suggest that IL-6 might be a very useful disease marker that is independent of pyuria. A suitable instant clinic assay is certainly feasible.

References

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