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Lunawat R[1], Khasriya R[1], Bishara S[1], Maraj B[1], Falzon M[1], Malone-Lee J[1]
1. *UCL*

HISTOLOGICAL EVIDENCE OF UBIQUITOUS OCCURRENCE OF CHRONIC CYSTITIS IN UROTHELIAL BIOPSIES FROM PATIENTS WITH SYMPTOMS OF OVERACTIVE BLADDER AND NORMAL URINANALYSIS

Hypothesis / aims of study

The role of the urothelium in the pathophysiology of overactive bladder symptoms has gained some prominence (1). Whilst the physiological literature in this arena is growing there is a striking lack of an histopathological narrative. Recently the detection of inflammatory exudates of ≥10 wbc µl-1 in fresh unspun catheter specimens (CSU) of urine from around 35% of patients with overactive bladder (OAB) symptoms has been reported(2). Fresh urine microscopy is not a usual method for screening patients with OAB symptoms so there are sparse data available at the moment to inform on the veracity or significance of this phenomenon. Since 1968 it has been known that the best surrogate method of diagnosing urine infection, in symptomatic patients, is the identification of pyuria of ≥10 white blood cells (wbc) µL-1, counted by microscopic examination of fresh unspun urine in a haemocytometer. This does not necessarily mean that the pyuria associated with OAB implies bladder infection, although that remains one possible explanation. It is assumed that pyuria originates from inflammatory infiltration of the urothelium with white cells being shed into the urine. That assumption must be tested by histological examination of the urothelium. Since 1968 the association of pyuria with urinary infection has been further scrutinised and the relationship to urinary infection confirmed. The published literature certainly describe patients with pyuria whose urine fails to provide significant bacterial isolates. Nevertheless, current evidence opines that given pyuria, the most probable explanation would be bacterial cystitis. It would therefore be tautological to study the histology of the urothelium in patients with OAB symptoms, pyuria and demonstrable urine infection since any inflammatory reaction in the urothelium could be explained by a known or probable urine infection. The purpose of this experiment was to shed light on OAB. Since this diagnosis is contingent on the exclusion of urine infection it would be important to focus attention on those with a legitimate diagnosis of OAB who did not show any evidence urine infection, including pyuria. This would reassure on the veracity of the diagnosis of OAB in the sense that infection had been excluded by all reasonable means, not just urine culture. This experiment scrutinised uroepithelial histology in patients with OAB symptoms, requiring maximum antimuscarinic therapy, who were shown to have sterile urine with normal dipstick analysis and without pyuria on microscopy of a fresh unspun sample of urine in a haemocytometer

Study design, materials and methods

A blinded prospective observational design was adopted. Three groups of patients were studied;1) patients with OAB without pyuria. They were on maximum treatment doses of antimuscarinics, their urine was sterile and free of pyuria for at least twelve weeks and their symptoms merited Botox injections 2) patients with OAB symptoms and persistent pyuria and 3) normal asymptomatic controls. A CSU was collected and subjected to dipstick analysis and a haemocytometer count to evaluate pyuria. During cystoscopy a mucosal biopsy was obtained from the dome of the bladder. The biopsies were fixed in a paraffin block section and stained by H&E. The slides were interpreted by the researcher, the supervisor and a consultant histopathologist using light microscopy at x200 magnification (x20 objective and x10 eyepiece). The Fisher's exact probability test was used to compare groups. Because normal controls posed a serious recruitment challenge the power of the study was calculated *post hoc*.

Results

Normal controls were very hard to find nevertheless this study has over 80% power at alpha=0.05. 67 patients (15 male & 52 female; mean age 55, sd=15) Provided urothelial biopsy specimens. Three patients without symptoms and clear urine, undergoing cystoscopy as follow up for an episode of microscopic haematuria acted as controls. 50 patients had OAB, without pyuria and sterile urine. 11 patients had OAB symptoms but persistent chronic pyuria although sterile on culture. Three patients' tissue had to be rejected as it was inadequate for histopathological analysis. The groups were matched for age and sex. 45 (90%) of non-pyuric OAB patients and 10 (91%) of the pyuric OAB patients manifest all the uroepithelial features of chronic cystitis *viz*: (a) oedema, (b) mixed inflammatory cell infiltrate, and (c) urothelial hyperplasia (d) some urothelial shedding. The three controls showed normal urothelium without any features of inflammation. None of the patients had neurological disease nor any other cause for their overactive bladder symptoms. (Fisher $p<0.001$)

Interpretation of results

The ubiquitous finding of a chronic inflammatory infiltrate in OAB patients who had been free of pyuria and manifest sterile urine was a very surprising observation. It had been assumed at the outset that urothelial inflammation would manifest only in those with pyuria at the time of biopsy. These were a selected group of patients in the sense that they had not responded to maximum antimuscarinic treatment in the form of imipramine combined with CR Oxybutynin, or Solifenacin. Infection in those without pyuria had been excluded by every means available. The mixed lymphocyte and neutrophil infiltrate implies a chronic inflammatory response and the urothelial hyperplasia is clear evidence of significant chronic urothelial distress.

Concluding message

Chronic cystitis would seem to be an important aetiological factor in the overactive bladder symptoms of patients who cannot respond to antimuscarinic agents to the extent that they require Botox injection. We cannot be reassured that there is no cystitis when the urine proves free of infection or pus cells.

References

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