

DOES AN ALTERATION IN THE BALANCE BETWEEN PRO-INFLAMMATORY AND ANTI-INFLAMMATORY CYTOKINES EXPLAIN WHY PATIENTS WITH REFRACTORY DO ARE MORE PRONE TO RECURRENT UTI?Hypothesis / aims of study

Bacterial cystitis is known to occur in 40% of patients with refractory detrusor overactivity (DO). The bladder response to infection is determined by a balance between the pro-inflammatory and anti-inflammatory cytokines. In this study we have compared urinary levels of the pro-cytokine interleukin-1 α (IL-1 α) and the anti-inflammatory cytokine interleukin-10 (IL-10) in women with urodynamically diagnosed refractory DO, women with newly diagnosed DO, and controls who exhibited no urgency.

Study design, materials and methods

Midstream urine samples were collected, with careful labial toilet, by patients from a regional urogynaecology clinic. Any current UTI and history of previous UTI was noted. The presence of leukocytes in the urine specimen was determined by dipstick. Patients were divided into three groups: control (n=51, no current UTI and no history of UTI), newly diagnosed DO (n=39) and refractory Detrusor Overactivity (DO) (n=56). Patients were excluded if they had voiding dysfunction or a history of neurological dysfunction. Urinary levels of the cytokines, IL-1 α and IL-10, were quantitated by enzyme-linked immunosorbent assays following the manufacturer's instructions. Cytokine concentrations were compared based on the urological diagnosis, the presence of a current diagnosis of a urinary tract infection or a history of a urinary tract infection. Data are presented as median cytokine concentration (pg/mL) with interquartile range.

Results

As expected based on the current literature history of urinary tract infection was significantly more common in patients with refractory DO than in patients newly diagnosed with DO (P<0.001, Chi-square, Table 1). Similarly a current UTI was significantly more common in patients with refractory DO (P 0.005, Chi-square, Table 1). In patients with DO the presence of a UTI significantly increased secretion of both IL-1 α (P 0.04) and IL-10 (P 0.005).

Table 1: UTI symptoms and urinary cytokine concentrations (pg/mL) in the three patient groups.

	<i>Controls</i>	<i>Newly diagnosed DO</i>	<i>Refractory DO</i>
History of UTI	0%	32%	61%
Current UTI	0%	11%	31%
Leukocytes	21%	40%	61%
IL-1 α (pro-inflammatory)	51.9 (0-80.4) n=51	105.6 (35.8-229.7)* n=39	53.4 (9.4-132.3) n=47
IL-10 (anti-inflammatory)	4.6 (1.9-7.5) n=49	8.1 (6.3-13.9)*** n=37	8.1 (6.8-9.9)*** n=56

*statistically different to control, P<0.05, *** statistically different to control, P<0.001

NOTE: a current UTI or a history of UTI was an exclusion criteria in control patients.

We also examined whether leukocytes were more commonly detected in patients with refractory DO compared to controls and patients newly diagnosed with DO (Table 1). Similar to the results seen with UTI, leukocytes were more common in patients with refractory DO (p<0.0001, Chi-square, Table 1). The presence of leukocytes had no influence on the secretion of IL1a but was associated with significantly increased expression on IL-10 (P 0.045).

IL1 α was undetectable in approximately 15% of urine specimens, 12% of controls, 13% of newly diagnosed DO and 15% of refractory DO patients. The median concentration of IL-1 α was significantly elevated in women with newly-diagnosed DO compared to controls (P 0.015). The median concentration of IL-10 was elevated in both newly diagnosed DO and refractory DO compared to controls (P<0.001). The ratio of IL1 α to IL10 was significantly decreased in patients with refractory DO compared to the ratio in controls (P 0.03, Figure 1).

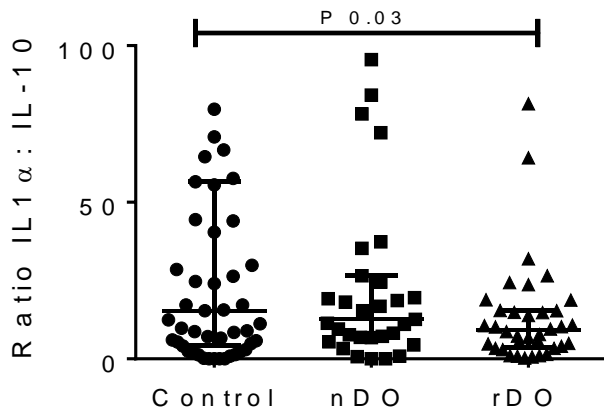


Figure 1: Ratio of IL1 α to IL10 in the three patient groups.

Interpretation of results

Patients with refractory DO were more likely than patients newly diagnosed with DO to have both a history of UTI and a current UTI. In addition these patients were more likely to have leukocytes detected in their urine suggesting the presence of an inflammatory response.

Both pro-inflammatory and anti-inflammatory cytokines (IL-1 α and IL-10 respectively) were seen to be elevated in patients with DO compared to controls. The ratio of Pro (IL-1 α): anti (IL-10) inflammatory cytokines was lower in patients with refractory DO, suggesting a suppression of the immune response in these patients relative to that seen in patients with newly diagnosed DO or control patients. This suppression of the immune response in patients with refractory DO may result in an increased prevalence of UTI in these patients.

Concluding message

It is well known that there is an increased prevalence of UTI in patients with refractory DO. The results of this study suggest that this may be the result of a suppression of the immune response whereby the anti-inflammatory response is relatively greater than the pro-inflammatory response in these patients. This alteration in the balance between pro and anti-inflammatory cytokines may play a role in the pathogenesis of DO and may predispose a patient to the refractory state.

Disclosures

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