

INTERLEUKIN 8 IN URINE AS A MARKER FOR URGENCY IN THE OVERACTIVE BLADDER SYNDROME

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HYPOTHESIS/AIMS OF STUDY

THE OBSERVATION OF A COEXISTENT URETHRAL TENDERNESS IN WOMEN APPLYING FOR THE OVERACTIVE BLADDER SYNDROME (OAB-SYNDROME) RAISED A NEW INTEREST IN THE HYPOTHESIS THAT URETHRA PLAYS A MAJOR ROLE IN OAB. TENDERNESS OFTEN INDICATES INFLAMMATION BUT THE DEGREE OF INFLAMMATION IS DIFFICULT TO OBJECTIFY EVEN IN THE MICROSCOPE. THUS INFLAMMATION IS OFTEN DESCRIBED AS "SUGGESTED", "MARKED", "OBVIOUS" OR "SUBSTANTIAL".

CYTOKINES MAY, THEORETICALLY, BE USED TO QUANTIFY AN INFLAMMATORY REACTION. HIGH IL-6 AND/OR IL-8 CONCENTRATIONS ARE SUPPOSED TO REFLECT INFLAMMATION IN THE URINARY TRACT (1,2). THE CONCENTRATION, HOWEVER, DOES NOT TELL WHERE IN THE URINARY TRACT THE INFLAMMATION IS SITUATED.

IF AN INFLAMMATION IN THE FEMALE URETHRAL WALL CONTRIBUTES TO URGENCY – AND OAB - IT SHOULD BE POSSIBLE TO DEMONSTRATE IL-6 AND/OR IL-8 IN URINE AFTER TRANSVAGINAL URETHRA MASSAGE. THE FIRST PORTION OF URINE DELIVERED AFTER THE MASSAGE, SHOULD THEN CONTAIN A HIGHER CONCENTRATION OF INFLAMMATORY CYTOKINES THAN PORTIONS OF URINE DELIVERED LATER, AS CYTOKINES FROM THE URETHRA ARE EXPRESSED BY THE MASSAGE.

IF A LOCAL INFLAMMATION IS PRESENT, LOCAL ANTI-INFLAMMATORY TREATMENT SHOULD RELIEVE OR CURE THE SYMPTOMS.

STUDY DESIGN, MATERIALS AND METHODS

ONE HUNDRED CONSECUTIVE WOMEN APPLYING FOR OAB-SYMPTOMS WERE STUDIED. ALL WERE "TOILETTE MAPPING", HAD NEGATIVE URINE CULTURES AND WERE USING PADS TO FOR "SAFETY" REASONS.

URINE DIARIES WERE COLLECTED FOR 2 X 24 H BEFORE AND AFTER TREATMENT.

A CYSTOSCOPY WITH ESTIMATION OF BLADDER VOLUME WAS PERFORMED. IN 25 PATIENTS TISSUE WAS OBTAINED FROM THE URETHRA FOR MICROSCOPY. 11 OF THE SAMPLE WERE USED ALSO FOR IMMUNOHISTOLOGY TO SCREEN FOR T- AND B-LYMPHOCYTES.

TREATMENT WAS GIVEN WITH INTRAURETHRAL APPLICATION OF A GROUP-I-CORTICOSTEROID OINTMENT AND URETHRAL MASSAGE WITH AN INDWELLING UTERINE DILATOR (HAEGAR 7) WAS PERFORMED AT FOUR SESSIONS WITHIN TWO WEEKS.

IN 10 PATIENTS AFTER ADDITIONAL INFORMED CONSENT A "DRY" MASSAGE WITHOUT THE UTERINE DILATOR AND WITH A SEMI FILLED BLADDER, WAS PERFORMED BEFORE TREATMENT. THE PATIENTS URINATED IN TWO PORTIONS DIRECTLY AFTER THE MASSAGE. THE SAME PROCEDURE WAS PERFORMED IN 10 HEALTHY CONTROLS. THE URINE PORTIONS WERE ANALYZED FOR IL-6 AND IL-8.

RESULTS

TWO PATIENTS WERE EXCLUDED BECAUSE OF CONCOMITANT MEDICATION IN SPITE OF INFORMATION.

FREQUENCY AND LEAK;

37/98 (38%) REPORTED A "DRY" URGENCY FROM THE START. BLADDER CAPACITY AT CYSTOSCOPY WAS NORMAL IN ALMOST ALL PATIENTS. TREATMENT WITH TRANSVAGINAL URETHRA MASSAGE AND LOCAL CORTISONE DECREASED THE VOIDING FREQUENCY AND URGENCY IN 81/98 PATIENTS (83%). THE MEAN DECREASE WAS 2 SESSIONS /24H (RANGE 9 - -2) RESULTING IN A MEAN FREQUENCY OF 8,62 (SD2,59) SESSIONS/ 24 H AFTER TREATMENT. THE DECREASE, THOUGH BEING NUMERICALLY LOW, WAS STATISTICALLY HIGHLY SIGNIFICANT. FOUR PATIENTS REPORTED AN INCREASED MEAN FREQUENCY OF 1-2 SESSIONS/24H, WHILE 13 PATIENTS REPORTED NO CHANGE OF FREQUENCY. OUT OF THE 17 PATIENTS REPORTING INCREASED OR UNCHANGED MEAN FREQUENCY, 12 PATIENTS (70%) REPORTED LARGER URINE VOLUMES AFTER TREATMENT THAN BEFORE.

18/61 PATIENT WHO REPORTED INITIAL LEAK STOPPED LEAKING (30%) WHILE ANOTHER 42/61 LEAKING PATIENTS (69%) REPORTED FEWER PROBLEMS.

THE ONLY PATIENT WHO REPORTED MORE LEAK AFTER TREATMENT THAN BEFORE, COUNTED FEWER SESSIONS AFTER TREATMENT (17 AND 14 SESSIONS BEFORE AND AFTER RESPECTIVELY - MEAN OF 2 X 24 H COUNTS).

MICROSCOPY ;

IN 22/25 PATIENTS MICROSCOPY OF TISSUE FROM THE URETHRA SHOWED MILD OR MODERATE INFLAMMATORY REACTION. THREE SAMPLES SHOWED SQUAMOUSE CELL METAPLASIA. IN 7/11 PATIENTS THERE WAS A DOMINATION OF T CELLS, IN 5 PATIENTS THE DOMINANT LYMPHOCYTE WAS OF B-TYPE. 2/11 PATIENTS PRESENTED ABOUT THE SAME AMOUNT OF BOTH CELL TYPES.

1/3 PATIENTS WITHOUT ANY SIGN OF INFLAMMATION HAD A LOW BLADDER VOLUME (85ML).

CYTOKINES;

THERE WAS NO SIGNIFICANT DIFFERENCE IN CONCENTRATION OF IL-6 IN THE TWO URINE PORTIONS IN EITHER PATIENTS OR CONTROLS. THE CONCENTRATION OF IL-6 WAS NORMAL (<15 NG/L) IN ALL BUT ONE PATIENT (20NG/L) AND ONE CONTROL (22NG/L).

THERE WAS A SIGNIFICANTLY HIGHER CONCENTRATION OF IL-8 IN THE FIRST URINE PORTION COMPARED TO THE SECOND IN 8/10 PATIENTS. THE CONCENTRATION WAS HIGHER THAN THE NORMAL VALUE FOR URINE (<200NG/L) IN 8/10 PATIENTS IN THE FIRST URINE PORTION. ALSO IN THE SECOND PORTION THE CONCENTRATION OF IL-8 WAS ABOVE NORMAL VALUES IN 5/10 PATIENTS.

IL-8 WAS SIGNIFICANTLY HIGHER IN THE FIRST PORTION IN 4/10 CONTROLS, BUT THE LEVELS WERE GENERALLY MUCH LOWER THAN FOR THE PATIENTS AND ONLY IN 3/10 CONTROLS DID THE CONCENTRATION EXCEED THE NORMAL VALUE IN THE FIRST SAMPLE. IN THE SECOND URINE SAMPLE THE CONCENTRATION WAS NORMAL IN ALL CONTROLS.

INTERPRETATION OF RESULTS

FREQUENCY AND LEAK;

THE FREQUENCY OF PATIENTS WITH "DRY" URGENCY WAS LOWER THAN REPORTED BY OTHERS (3). THE NORMAL BLADDER CAPACITY AT CYSTOSCOPY IS A PUZZLING FACT THAT MAY BE CRITICISED AS THE FILLING MAY BE REGARDED AS "UNPHYSIOLOGICAL". HOWEVER THIS IS THE CASE IN MOST URODYNAMIC SITUATIONS AND THE RESULTS MAY BE USED AS AN ARGUMENT AGAINST THE THEORIES BEHIND OAB. LOCAL ANTI-INFLAMMATORY TREATMENT OF THE URETHRA DECREASED THE FREQUENCY WHILE THE "REST VALUE" OF 8,62 SESSIONS /24 H IS A LITTLE HIGHER THAN THE COMMON VIEW OF < 8 SESIONS/24H AS NORMAL. 30% OF WOMEN WHO REPORTED LEAK STOPPED LEAKING. ONLY 17 PATIENTS REPORTED LOW BENEFIT FROM THE TREATMENT. 70% OF THESE, HOWEVER, REPORTED LARGER VOLUMES AFTER TREATMENT THAN BEFORE, WHICH MAY HAVE CONTRIBUTED TO THE HIGHER OR UNCHANGED FREQUENCY.

MICROSCOPY:

AT DIRECT QUESTION THE PATHOLOGIST CONFIRMED THE PRESENCE OF DISCRETE OR CHRONIC INFLAMMATION IN 18/25 PATIENTS WHILE ADDITIONAL FOUR PATIENTS SHOWED METAPLASIA AND OTHER CHANGES CONGRUENT WITH INFLAMMATION. IMMUNE-HISTOLOGY SHOWED BOTH B- AND T-CELLS. THIS MAY INDICATE SOME SORT OF AUTOIMMUNE REACTION THOUGH THE CONCENTRATION OF LEUCOCYTES WAS NOT VERY MARKED.

CYTOKINES;

THE CONCENTRATION OF CYTOKINES IN URINE DEPENDS ON THE METHOD USED. NORMAL AND STABLE VALUES FOR IL-6 WERE CONGRUENT WITH NEGATIVE URINE CULTURES. HIGH IL-8 CONCENTRATIONS IN PATIENTS COMPARED TO CONTROLS INDICATED THE PRESENCE OF AN INFLAMMATION IN THE URETHRA TISSUE. THE SIMULTANEOUS PRESENCE OF T-LYMPHOCYTES MAY INDICATE SOME SORT OF AUTOIMMUNE INFLAMMATION OF THE ENDOTHELIA. PRESENCE OF AN INFLAMMATORY REACTION SHOULD BE OF GREAT INTEREST FOR THEORIES ON THE ORIGIN OF OAB- SYMPTOMS. THE RESULTS MUST BE HOWEVER BE VERIFIED BY TESTING A LARGER MATERIAL OF WOMEN, BOTH WITH AND WITHOUT URGENCY.

CONCLUDING MESSAGE

IT IS HIGHLY POSSIBLE THAT A LOW GRADE INFLAMMATION IN THE URETHRA IS THE ORIGIN OF URGENCY IN THE OAB-SYNDROME. THE TRUE NATURE OF THE INFLAMMATION REMAINS TO BE STUDIED BUT IT IS SEEMS INTIMATELY CONNECTED TO THE VOIDING REFLEX. TREATMENT OF URGENCY INCONTINENCE SHOULD FOCUS ON THIS INFLAMMATORY REACTION. INTERLEUKIN 8 APPEARS TO PLAY A MAJOR ROLE, AND MAY FUNCTION AS A NOCICEPTOR STIMULATOR, STARTING THE VOIDING REFLEX. THEORETICALLY IL- 6 AND/OR IL-8 IN URINE MAY BE USED AS A TEST TO VERIFY, QUANTIFY OR CONTRADICT INFLAMMATORY ORIGIN OF SYMPTOMS IN WOMEN WITH OAB-SYMPTOMS. IT IS EVEN POSSIBLE THAT IL-8 MAY BE USED TO SELECT PATIENTS WITH URGENCY SUITABLE FOR LOCAL ANTI-INFLAMMATORY THERAPY. HOWEVER, ANY SUCH RECOMMENDATION REQUIRES VERIFICATION FROM FURTHER AND LARGER STUDIES.

References

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Specify source of funding or grant	NO DISCLOSURES NO GRANTS
Is this a clinical trial?	Yes
Is this study registered in a public clinical trials registry?	No
Is this a Randomised Controlled Trial (RCT)?	No
What were the subjects in the study?	HUMAN
Was this study approved by an ethics committee?	No
This study did not require ethics committee approval because	The study is summary of results obtained for clinical reasons after informed consent including written information and according to the rules of the Helsinki declaration. The Ethical Committee of the University of Lund has let known that an expanded study, including a larger control group, may be judged as a drug trial. An application has been prepared for such a study
Was the Declaration of Helsinki followed?	Yes
Was informed consent obtained from the patients?	Yes