The EAU Annual Congress 2012 in Paris began with a special ICUD-EAU session: the 5th International Consultation on Incontinence (ICI). The International Consultation on Urological Diseases (ICUD) organised the 2012 International Consultation on Incontinence (held every 4 years) this time jointly with the EAU as a special session and not as a separate conference as in the past.

Professor Paul Abrams emphasised to delegates that the different ICI committees ultimately produce consensus statements, not to be confused with guidelines produced by a number of societies. The various committee chairs presented their preliminary reports in Paris, after which they will be fine-tuned before being published as chapters in book and CD format. Further information about ICUD can be found on its website: http://www.icud.info/futureconsultations.html, where previous ICI Incontinence books can be downloaded, including the last one published in 2009 with its chapter on Bladder Pain Syndrome.

**5TH ICI: COMMITTEE 19: BLADDER PAIN SYNDROME**

*Committee members: P. Hanno (chair) (USA), P. Dinis (Portugal), A. Lin (Taiwan), C. Nickel (Canada), J. Nordling (Denmark), A. van Ophoven (Germany), T. Ueda (Japan).*

The last ICI conference was held in 2008 and it is perhaps rather discouraging that Committee 19 on Bladder Pain Syndrome, chaired once again by Philip Hanno, MD, reported on 24 February 2012 that few advances have been made since the previous ICI in the field of new treatments, while despite many discussions and debates on the controversial topic of nomenclature and definitions, there is still no international agreement. Indeed, far from there being global consensus, Professor Hanno reported that there is a substantial difference of opinion with the East Asian countries of Japan, Korea and Taiwan which have their own approach to taxonomy and nomenclature. These countries take an approach which keeps all urgency-frequency syndromes in the picture, with or without pain, and have introduced the term hypersensitive bladder syndrome. While Committee 19 noted that Hunner’s lesion is a subtype that should be treated differently to non-lesion, there was unfortunately as yet little progress to report in the field of subclassification or phenotyping which are likely to play an important role in selection for specific types of treatment in the future. It is hoped that more progress will be made in the coming four-year period before the next ICI and that we will see results coming from the NIDDK MAPP project before too long. We will provide more detailed information on the report of Committee 19 and its recommendations when it reaches its final version and is published. *There was regrettably no patient advocate on this ICI committee.*

**EAU SCIENTIFIC PROGRAMME**

**ESU COURSE ON PAINFUL BLADDER/CHRONIC PELVIC PAIN AVAILABLE ON TTMED UROLOGY WEBCASTS**

While relatively little attention was paid to IC in the EAU main scientific programme, with just a few posters being presented, an excellent ESU Course 11 was nevertheless provided, chaired by Professor J.J. Wyndaele, which made it all worthwhile. TTMed Urology webcasts happily included most of the
ESU courses and everyone can therefore benefit from the excellent **ESU Course 11 on Painful bladder/chronic pelvic pain in men and women**, chaired by Professor J.J. Wyndaele from Antwerp, Belgium. Others speakers were Professor J.C. Nickel from Kingston, Canada and Dr R. Posch-Zimmermann from Salzburg, Austria. Topics covered: Neurophysiology of chronic pelvic pain, causes and confusable diseases, Chronic Prostatitis and chronic pelvic pain in men, Clinical picture, diagnosis and classical treatment, Bladder Pain Syndrome BPS/IC clinical picture and diagnosis and finally Innovative treatment.


**FYI: BOTULINUM TOXIN TYPES**

Bearing in mind that several abstracts on IC presented at the EAU congress (see below) concerned botulinum toxin, it is perhaps useful to mention here that the 5th ICI Committee 8 on Drug Treatment clarified the different types of botulinum toxin now on the market, in case you are puzzled by the different names. The various botulinum toxins possess individual potencies, and care is required to assure proper use and avoid medication errors. Recent changes to the established drug names by the FDA were intended to reinforce these differences and prevent medication errors. The products include the following:

**Botulinum toxin A**
- Onabotulinumtoxin A (onabotA: Botox®)
- Abobotulinumtoxin A (abobotA: Dysport®)
- Incobotulinumtoxin A (incobotA: Xeomin®)

**Botulinum toxin B**
- Rimabotulinumtoxin B (rimabot B: Myobloc®)

**POSTER SESSION 23:**
**CHRONIC PELVIC PAIN SYNDROME**

271


Noting that the results of recently published studies demonstrate the efficacy of BTX-A in the treatment of painful bladder symptoms, Dr Kasyan explained that the aim of this study from Moscow was to evaluate the efficacy and safety of BTX-A in patients with Hunner’s lesions. 76 female patients with bladder pain syndrome/interstitial cystitis (BPS/IC) were screened for the study. Hunner’s lesions were found in 51.3% (39/76) of cases, which is certainly a very high percentage. 32 patients were randomised into an experimental (Group 1) and a control group (Group 2). The patients from Group 1 (15 patients) were given injections of 100 U of BTX-A diluted in 10 ml 0.9% NaCl. The injections were performed under spinal anaesthesia using a cystoscope with a flexible needle in the trigone of the bladder only. The patients from the Group 2 received standard hydrodistension under spinal anaesthesia (17 patients). The O’Leary–Sant symptom index and problem index scores were used for validation of subjective complaints from the BPS/IC patients. Pain intensity was scored using a 10-point visual analogue scale (VAS). Quality of life (QoL) was evaluated using question 8 of the International Prostate Symptoms Score. Uroflowmetry followed by postvoid urine volume
measurement and kidney ultrasound were performed after treatment. The study team found that a trigonal injection of 100 U BTX-A results in similar efficacy compared to conventional bladder hydrodistension. There were no significant increases in the amount of residual urine, no decrease in uroflowmetry rate and no upper-urinary tract retention. Therefore, they believe that longer-term follow-up studies are warranted.

272

This study from Portugal looked at the differences between ulcerative and non-ulcerative Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) patients, who had failed to respond to first line treatment, with regard to lower urinary tract symptoms and clinical response to intra-trigonal injection of Onabotulinum toxin A (OnabotA). Pain intensity in a 10 points Visual Analogue Scale (VAS), frequency and nocturia in a 3-day voiding chart, O’Leary-Sant Score (OSS) and QoL from IPSS were evaluated in 10 ulcerative and 14 non-ulcerative BPS/IC patients, at presentation and 1 month after intra-trigonal injection of OnabotA (100 U). The average age of the patients in the non-ulcerative group was 53.9±15.4 years and 44.5±14 years in the ulcerative group. BPS/IC ESSIC classification was: 2a (3), 2b (5), 2c (6) in the non-ulcerative group and 3a (1), 3b (3) and 3c (6) in the ulcerative group (see ESSIC classification table http://www.essic.eu/pdf/ESSICconsensus2007.pdf). Although pain, frequency and nocturia were numerically slightly superior in the ulcerative group, the study team found that the differences between the two groups were not significant. All patients reported subjective improvement following OnabotA. Decreases in pain score, urinary frequency, OSS and QoL after 1 month of treatment are shown in Table 1 (no statistical significant differences were found). Symptomatic relief lasted for a period between 9-10.5 months with no differences found between the two groups. The Portuguese study team concluded that the traditional point of view that ulcerative BPS/IC patients have more severe symptoms cannot be sustained by the analysis of the present group of patients, characterized by ESSIC criteria. In addition, the duration of symptom relief brought by OnabotA was similar in both groups. However, they suggest that the ulcerative form may affect a substantially younger population.

273

This was a study from Nijmegen, in the Netherlands that reflected much of the research currently being undertaken – and presented in Paris - into the bladder lining (urothelium) which was long considered to be a relatively inert structure, but has now been found to be a veritable hive of activity with multiple structures creating a barrier against toxins and waste products contained in the urine. The glycosaminoglycan (GAG) layer is believed to be involved in the bladder protective layer. The structure and negative charge of the GAG-layer enables it to bind H2O-molecules into a gel-like form that creates a barrier between the urine and the urothelial cells. Examples of GAG’s are chondroitin sulfate (CS), heparin sulfate (HS) and dermatan sulfate (DS). GAG-replenishing therapies are widely used for chronic bladder inflammation, including IC. However, there is a lack of scientific evidence that GAG’s play an important role in the barrier of the bladder. The aim of this study was therefore to investigate the distribution of different GAG’s in the bladder and to evaluate the contribution to the bladder barrier. They found that chondroitin sulfate is localized on the luminal surface of the urothelium and contributes to the bladder protective barrier; that the GAG-layer normally recovers from mild damage within 24 hours and that replenishing the GAG-layer as a treatment for bladder inflammation is based on a sound principle.
Intravesical epinephrine preserves uroplakin II expression in urinary bladder from cyclophosphamide-induced rat cystitis. Lee G.H., Song J.M. Eur Urol Suppl 2012;11;e274

The apical membrane in the bladder mucosa contains uroplakin (UP) that represents one of the tightest impermeable barriers in the body. In this rat study from South Korea, Lee and colleagues investigated the attenuated effect of intravesical epinephrine (EPI) on uroplakin II (UPII) expression in the bladder of cyclophosphamide (CYP)-induced cystitis in a rat model. They found that CYP induced severe cystitis and decreased mRNA levels of UPII. The obstructed groups showed much more cellular loss compared with the control group. The mRNA levels of UPII in the CYP injected groups were significantly decreased 24 hr after CYP injection compared with the control group. It was concluded that CYPO-induced cystitis actively induces the down-regulation of UPII genes in the rat urinary bladder and that intravesical instillation of epiphrine preserves UPII expression and attenuates the toxic responses in the bladder in CYP-induced rat cystitis.


In this study from Beijing (not presented), Liu and colleagues noted that although mast cell and T cell infiltration is commonly seen in the tissue of interstitial cystitis, the role of mast cell-T cell interaction and which cytokine mediates this interaction is still a mystery. IL-9 has been previously shown to mediate regulatory T cells-mast cell interaction in a tolerant allografts model (Li-Fan Lu, et al. 2006). The aim of this study was to discover whether IL-9 is also involved in mast cell-T cell interaction in interstitial cystitis. Bladder tissues of patients with interstitial cystitis were obtained by biopsy during a cystoscopy under anaesthesia with bladder distension. They found that although IL-9 expression is very low, IL-9R is strongly expressed in the bladder tissue of interstitial cystitis, both in mRNA and protein level. Increased IL-9R mRNA and protein expression were observed in interstitial cystitis compared with that in normal bladder tissues and prostate tissues. The histamine level increased in the co-culture system with the presence of IL-9, while the histamine level decreased in the co-culture system by adding IL-9 antibody. T cells secrete IL-9 evidenced by flowcytometry analysis in co-culture system. Mast cell from cystitis model expressed the IL-9R both in mRNA and protein level, at the same time CD4+ T cells expressed IL-9 in protein level. They concluded that IL-9 mediates the mast cell-T cell interaction in interstitial cystitis. IL-9 may therefore be a new target for the treatment of IC.

LUTS: CAN WE IMPROVE THE ACCURACY OF THE DIAGNOSIS?


While a number of biomarkers for interstitial cystitis (IC) have been proposed, none of them is approved as a definitely useful biomarker for diagnosing IC or predicting responses to a specific treatment. Recently, up-regulation of CXCR3 and its binding chemokines, CXCL9, 10 and 11, and the helper-T-cell related cytokines IFN-γ and TNFSF14 was demonstrated in the bladder urothelium of patients with ulcer type IC (U-IC)[J Urol 183: 1206-12, 2010]. In this study from Tokyo, Igawa and colleagues evaluated urinary levels of CXCL10, TNFSF14, and other proposed markers, NGF, PGE2 and MIP1α in U-IC and non-ulcer type IC (NU-IC) patients and healthy controls, and compared among the three groups. They also analysed association of these markers with symptom severity. Urine
specimens were collected from 31 healthy volunteers, 25 NU-IC patients and 41 U-IC patients. The diagnosis of IC was based on the clinical guidelines for IC and hypersensitive bladder syndrome [Homma et al., Int J Urol 16: 597-615, 2009]. Urinary CXCL10, TNFSF14, NGF, PGE2 and MIP1α concentrations were measured by ELISA and normalised by urinary creatinine (Cr) concentration. The symptom severity was assessed by the O’Leary-Sant symptom index (OSSI) and problem index (OSPI). They found that the urinary CXCL10 level was elevated in ulcer type IC, and that the level positively correlated with symptom severity in ulcer type IC, suggesting that urinary CXCL10 may be a promising marker for ulcer type IC.

997


Pinto and colleagues from Porto, Portugal observe that the role of the sympathetic system in the development of Bladder Pain Syndrome/Interstitial Cystitis (BPS/IC) has been ignored during the last few years in favour of other pathologic mechanisms. However, the sympathetic system plays a role in some forms of chronic pain, such as the chronic regional pain syndrome. High levels of urinary catecholamines have been reported in BPS/IC patients, indicating sympathetic nervous system overactivity. In this study, urinary and serum noradrenaline were assessed in patients with BPS/IC before and after treatment with intra-trigonal injection of Onabotulinum toxin A (OnabotA). Noradrenaline, 24-hour urinary excretion (u-NA) and serum levels (s-NA), was evaluated in 18 women with BPS/IC (ESSIC classification: 2a (2), 2b (2), 2c (6), 3a (1), 3b (2) and 3c (5). See ESSIC classification table http://www.essic.eu/pdf/ESSICconsensus2007.pdf). Ten patients had non-ulcerative and 8 had ulcerative forms of BPS/IC. Samples were collected at baseline and 1 month after intra-trigonal injection of OnabotA, 100 U. Pain as evaluated by Visual Analogue Scale (VAS), frequency and nocturia in a 3-day voiding chart, O’Leary-Sant Score (OSS), QoL from IPSS were evaluated at the same time periods. Ten age and body mass index matched healthy women were used as controls. According to Pinto and colleagues, this study showed that OnabotA decreased u-NA without changing s-NA, indicating that the toxin caused a direct effect on bladder sympathetic fibers. Consequently, they believe that an increase in the activity of bladder sympathetic nerves in patients with BPS/IC is probable. These findings may be relevant to the understanding of the mechanism of BPS/IC.