

REVIEW OF THE INTERNATIONAL CONTINENCE SOCIETY (ICS) ANNUAL SCIENTIFIC MEETING RIO DE JANEIRO, BRAZIL, 20-24 October 2014

Jane Meijlink

This year's annual scientific meeting of the International Continence Society (ICS) was held in Rio de Janeiro, Brazil, thereby giving many health professionals from Latin America access to this multidisciplinary conference for the first time. Brazil is a vast country with hugely differing regions and a population varying from super-rich billionaires to the poorest tribal populations living in the Amazon jungle. As we crisscrossed Rio in the shuttle buses, the ever present *favelas* (slums or shanty town) of Rio de Janeiro – a city of 10 million inhabitants - showed clearly that urban areas are also still plagued by extreme poverty. This naturally presents overwhelming problems in the field of disease and healthcare and gave delegates to the 2014 ICS annual scientific meeting much to reflect on, as well as nagging feelings of guilt that we ourselves were privileged to be returning every evening to clean, comfortable hotels and meals on the table!

Pelvic floor dysfunction and pain

In recent years, those involved in IC/BPS and chronic pelvic pain have been aware that less and less space is being devoted to this in many of the urology and urogynaecology conferences. However, I am happy to report that the ICS is an exception and that at this year's meeting a number of workshops were presented in this field, as well as dedicated podium sessions and many posters. Since the ICS multidisciplinary field of activity covers pelvic floor dysfunction in a wide sense, including bowel/rectal dysfunction as well as the urinary tract, along with neurological aspects, and is seen from medical, physiotherapy, nursing and patient advocate points of view, it provides a more comprehensive picture of dysfunction and pain in the pelvic floor. A great deal of research into IC/BPS and hypersensitive bladder is being done in East Asia, including Japan, Taiwan, South Korea and China, as can be seen from the research presented at this meeting. Taiwan is also an important centre for research into ketamine cystitis.

There is still some confusion in studies presented regarding what type of patient they are referring to: whether it concerns Hunner lesions or non-lesion IC/BPS. Some studies refer only to "refractory IC patients" without giving further details, while a number still have patients diagnosed on the basis of the old NIDDK criteria. The latter is particularly the case in retrospective studies. This makes comparison of studies confusing if not impossible.

Workshops

W6: SEX, NEUROMODULATION, SELF-HELP, GUT MICROBIOME AND IC.

Speakers: Dr Ragi Doggweiler, Switzerland (chair), Dr Kristene Whitmore, USA, Dr Michele Spinelli, Italy, Mrs Barbara Mündner-Hensen, Germany (Patient Advocate), Dr Elke Heßdörfer, Germany.

The aim of this workshop was to discuss the importance of a multimodal approach in the treatment of patients with chronic pelvic pain (CPP). It has been the persistent endeavours of Dr Whitmore worldwide that has placed sexuality and chronic pelvic pain firmly on the conference map in recent years and radically changed the approach by professionals to sexuality and sexual dysfunction in all chronic pelvic pain and bladder hypersensitivity patients, including of course IC/BPS. Making intimacy issues discussable has also given patients more confidence to broach the subject with their doctor. Following an introduction to pain and the brain by Dr Doggweiler, Dr Whitmore looked at sexual pain and chronic pelvic pain syndromes. The field of CPP syndromes is complex and includes: lower urinary tract, male genital pain, female genital pain, gastrointestinal pain, musculoskeletal pain, neuropathic pain, psychological overlay, sexual pain, extra-pelvic comorbidities.

Important points about sexual pain, she emphasized, are that the pain is real, that it greatly impacts the quality of life of the patient and partner, that history taking and an accurate diagnosis are key aspects, expectations must be realistic and a multi-disciplinary approach is necessary. The patient perspective was provided by patient advocate Mrs Barbara Mündner-Hensen from Germany, while Dr Elke Heßdörfer, also from Germany, spoke about the gut microbiome, emphasizing the importance of evaluating gut microbiome and discussing the possibility of auto-vaccination in the treatment of IC. (Further information on microbiome can be found at: <http://en.wikipedia.org/wiki/Microbiome> for those who are not yet familiar with this term).

W19: FINAL FRONTIER IN LUTS; TARGETING THE UROTHELIUM TO TREAT OAB, IC/BPS, HYPERSENSITIVE BLADDER AND KETAMINE CYSTITIS.

Speakers: Dr Hann-Chorng Kuo, Taiwan (chair), Dr Lori Birder (USA), Dr Yao-Chi Chuang, Taiwan, Dr Michael Chancellor, USA, Dr Chun-Hou Liao, Taiwan.

The aim of this workshop with its eminent speakers was to help participants to select appropriate intravesical treatment for urothelial associated lower urinary tract dysfunction. It is believed that urothelial dysfunction may play a role in the abnormality of expression of sensory receptors or release of transmitters in the suburothelial nerves or interstitial cells. The epithelium receives and transmits signals to submucosal neurons. Afferent nerves are found within the urothelium and in a nerve plexus just below the basal cell layer. The urothelium may communicate bladder fullness to the underlying nervous system through a paracrine signalling pathway involving ATP release, according to Dr Y-C Chuang. Consequently, intravesical treatment to inhibit receptor expression or transmitter release may provide good therapeutic effects in the treatment of sensory urgency, IC/BPS and OAB. While intravesical pharmacotherapy is commonly used for treating OAB and IC/BPS, an important obstacle to the success of intravesical drug delivery arises from the low permeability of bladder epithelium.

It was noted in this workshop that street ketamine is the 5th most popular recreational drug in Taiwan and approximately 20-30% of abusers suffer from lower urinary tract symptoms. In powdered form, it can be insufflated, injected or placed in beverages. The peak age for ketamine abuse is 16-35 years. Other than ketamine withdrawal, treatment may include pain treatment, steroids, intravesical instillation of hyaluronic acid and intravesical botulinum toxin, with bladder augmentation or even cystectomy in severe cases. Also discussed in this workshop was the use of botulinum toxin injections for IC/BPS and the use of liposomes. An immense amount of research is being done in Taiwan into the whole field of hypersensitive and painful bladder, including IC/BPS and the increasing problem of ketamine cystitis.

W22: SETTING THE STANDARDS; DEVELOPING NEW ICS STANDARDS IN THE ERA OF EVIDENCE-BASED MEDICINE. STANDARDISATION STEERING COMMITTEE ACTIVITY.

Speakers: Dr Marcus Drake, United Kingdom (chair), Dr Peter Rosier, Netherlands, Mrs Jane Meijlink, Netherlands, (Patient advocate)

The "Standards" are one of the key initiatives of the ICS. The ICS Standardisation Steering Committee has modernised the approach to developing ICS standards, using the principles of evidence-based medicine. The new approach has been designed to develop relevant practical and up-to date standards in a concise manner. What was completely new here was having a patient advocate (Jane Meijlink) to speak on the impact of new or changed terminology and definitions on the patient and why it is important to involve patients in the whole process of developing terminology and definitions.

Standardization has an impact on every link in the healthcare chain, directly affecting the patient with regard to diagnosis, treatment, eligibility for reimbursement, social benefits and care. Official recognition of a condition is vital, so coding must be correct and uniform across all authorities. Particularly important for the patient is that official recognition of the condition means eligibility to receive: reimbursement of treatment, unemployment benefits, disability benefits and a whole range of social services and care.

Patients should be involved in the standardization process to ensure that all aspects of a condition are covered and no patients or symptoms are excluded. Patient organizations can provide standardization professionals with supplementary information, helping to create a comprehensive picture of each condition and everything this involves along the healthcare chain.

The speaker gave two examples showing how terminology and definitions have had an adverse effect on groups of patients. She therefore urged health professionals to ensure that patient representatives are given every opportunity – and training if necessary - to play a full role in national or international discussions on guidelines, taxonomy, definitions and nomenclature, including of course the International Classification of Diseases version 11 (ICD-11) to ensure that these are a true reflection of all the key components of a disease or complaint, that they make practical sense, and do not cause the patient any harm in any way.

The topic of patient participation in standardization and guidelines has been dealt with fully in the Scottish SIGN Guideline handbook, available online, in Chapter 10 on involving patients and their representatives. <http://www.sign.ac.uk/pdf/sign50.pdf>

A SELECTION OF RESEARCH ABSTRACTS AT ICS 2014 WITHIN THE FIELD OF IC/BPS, HYPERSENSITIVE BLADDER, CHRONIC PELVIC PAIN AND KETAMINE CYSTITIS

Abstract #5

INVESTIGATION OF AN ACUTE ROLE FOR NON-NEURONAL CELLS IN PELVIC PAIN AND BLADDER DYSFUNCTION IN A NOVEL MOUSE MODEL OF EXPERIMENTAL AUTOIMMUNE CYSTITIS (EAC).

Bicer F, Huang W, Daneshgari F, Hanna-Mitchell A.

This study group from Cleveland reported that the underlying pathophysiology of PBS/IC is poorly understood and, unfortunately for millions of patients suffering from this debilitating disease, therapeutic strategies for treatment have failed to produce clinically significant results. Characterizing the impact of urothelium-directed autoimmunity on urothelial and spinal cord glial (microglia and astrocytes) physiology will provide valuable mechanistic information about the underlying pathophysiology of PBS/IC and provide a new perspective on clinical management of this chronic pain syndrome.

Abstract #13

FACTORS THAT AFFECT THE TREATMENT OF REFRACTORY INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME USING INTRAVESICAL THERAPY WITH A HYALURONIC ACID SOLUTION: RESULTS FROM A PROSPECTIVE MULTICENTER STUDY ON 103 PATIENTS.

Hung M.

Intravesical therapy with a hyaluronic acid (HA) solution is an effective treatment for IC/BPS, however with varying degrees of success. This was a prospective multicentre study from Taiwan that aimed to evaluate factors that may have associations with treatment outcomes. They found that intravesical HA is an effective and safe treatment for refractory IC/BPS. However, according to this study, the treatment seems to be more effective in reducing bladder pain compared to urinary symptoms. Those patients who reported lower pain scores and reduced functional bladder capacity before treatment may have sub-response to the treatment.

Abstract #14

A RANDOMIZED, OPEN-LABEL, MULTICENTRE STUDY OF EFFICACY AND SAFETY OF INTRAVESICAL HYALURONIC ACID AND CHONDROITIN SULFATE (HA 1.6% AND CS 2%) VS. DIMETHYL SULFOXIDE (DMSO 50%) IN WOMEN WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS (BPS/IC).

Cervigni M, Sommariva M, Porru D3, Ostardo E, Tenaglia R, Giammò A, Pappagallo G.

The aim of this study from Italy was to evaluate the efficacy and safety of intravesical instillations with high concentration HA 1.6% and CS 2.0% versus DMSO 50% in female patients with diagnosis of BPS/IC. While at the end-of-treatment visit, the response to treatment in terms of pain decrease from baseline was statistically significant in both groups, there was a higher proportion of patients with adverse events in the DMSO (30.56%) than in the HA/CS (14.86%) group. The results from voiding diaries and the questionnaire scores were consistent with pain reduction. They concluded that on the basis of their results, treatment with intravesical instillations of HA/CS appears to be effective in improving pain, voiding frequency, urinary symptoms and quality of life in women with BPS/IC.

Abstract #15

AUTONOMIC RESPONSES DURING BLADDER HYDRODISTENTION REFLECT THE SEVERITY OF SYMPTOMS IN PATIENTS WITH IC/PBS.

Kim S W, Jee S H, Kim J Y, Moon S Y, Lee J S, Choi J H, Seo J T, Kim J H, Hyeon C S.

Previous studies have demonstrated elevated indices of sympathetic activity in patients with interstitial cystitis/painful bladder syndrome (IC/PBS). Kim and colleagues from South Korea examined autonomic responses, including changes in blood pressure (BP) and pulse rate (PR) in IC/PBS patients during bladder hydrodistention in order to evaluate the correlation between symptom severity and autonomic responses. They investigated 32 IC/PBS patients who underwent bladder hydrodistention from March 2012 to June 2013. The anaesthesia techniques were as follows: general 25 patients, spinal 6 patients, while 1 patient underwent both anaesthesia in separate distentions. 25 patients who underwent holmium laser enucleation of the prostate (HoLEP) under general anaesthesia were used as controls. They found that autonomic responses including BP and PR during hydrodistention under general anaesthesia were associated with the severity of symptoms in patients with IC/PBS, which could be used as a clinical marker of IC/PBS

Abstract # 16

APPLICATION OF SODIUM ALGINATE FOR PROLONGATION OF INTRAVESICAL EFFECTS OF LIDOCAINE AND OXYBUTYNYN IN TREATMENT OF BLADDER PAIN SYNDROME.

Mirkin Y, Karapetyan A, Shumoff S, Oltarzhevskaya N.

Intravesical instillations of lidocaine and/or oxybutynin are widely used to reduce pain and frequency in treatment of BPS. The main disadvantage of this method is short duration since soon after urination all symptoms return. Prolongation of effect can be achieved by using a mixture of lidocaine and oxybutynin with a polar molecule, such as sodium alginate. This can increase adhesion of composition to the urothelium. This study estimated the efficacy of sodium alginate with lidocaine and oxybutynin in comparison with lidocaine and oxybutynin only. Mirkin et al from Russia found that lidocaine/oxybutynin with sodium alginate works longer than without. They are therefore of the opinion that this mixture can be used for intravesical administration to prolong the effect of lidocaine, oxybutynin or some other drug.

Abstract # 17

A SURVEY ON CLINICAL PRACTICE OF INTERSTITIAL CYSTITIS IN JAPAN

Homma Y, Yamada Y, Igawa Y, Nomiya A, Ito T, Tomoe H, Takei M, Ueda T.

Homma and colleagues from Japan conducted a questionnaire survey among the members of the Society of Interstitial Cystitis of Japan (SICJ), to explore the number of IC patients, and diagnostic and therapeutic modalities commonly used in Japan. The survey was conducted in February, 2014. A questionnaire was sent to 169 members belonging to 114 medical institutions of SICJ via e-mail, addressing the number of IC patients on follow up, the number of new patients in 2013, diagnostic methods used, and the treatment employed such as medicine, intravesical therapies, and surgery. Completed questionnaires were returned from 62 institutions (20 university hospitals, 26 general hospitals and 16 clinics). The response rate was 54% (62/114). The total number of patients was 4531. Seven institutions had more than 100 patients, while 14 institutions had less than 10 patients. The average number of patients per institution was 73 (median 20). The total number of new patients in 2013 was 1214. Two institutions had more than 100 new patients a year, while 20 institutions had less than 5 patients. The average number of new patients per institution was 20 (median 7). Of the 4531 patients, 2066 (45%) patients had Hunner lesion and 1720 (38%) patients had glomerulations on hydrodistension. The percentage of Hunner type IC was highly variable among the institutions. Since this survey covered the majority of high volume IC centres in Japan, it is presumed that the results reflect the actual clinical practice of IC in Japan. While assessment methods are relatively homogenous for clinical tests and symptom evaluations, the rate of patients with Hunner lesion was highly variable among the institutions. This suggests that the criteria of Hunner lesion are far from being unified and substantial numbers of patients are not properly diagnosed and/or treated.

During the presentation of this paper in Rio, Professor Homma explained that it was clear that there was apparently a considerable difference in levels of expertise between physicians with regard to their ability to

diagnose Hunner lesion and that clearly more education is needed. And this certainly applies worldwide and indicates that an education programme is also needed worldwide.

Abstract #18

WHAT CAN URINE TELL US ABOUT INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME? PRELIMINARY DATA FROM PROTEOMIC COMPARATIVE STUDY.

Moitinho R, Barretto L, Bertolla R, Bertuccez F, Camargo M, Souza G, Silva C, Almeida F.

Interstitial cystitis/painful bladder syndrome (IC/PBS) has a large spectrum of clinical presentation and sometimes the diagnosis is not an easy task. Many patients suffer for long periods without a proper diagnosis. The main problem is the lack of reliable marker or test that could help clinicians to identify the disease. In this study from Brazil, Moitinho and colleagues performed a shotgun proteomics study to show the difference between the urinary protein profile in control subjects and patients with IC/PBS to identify possible specific proteins and networks associated with IC/PBS. According to the authors, this preliminary study demonstrated that urinary proteomic could help to identify significant difference in urinary proteins. The Brazilian study indicates a significant qualitative and quantitative difference in urinary proteins between women with and without IC/PBS. In the near future, it may be applied as a new technology to determine biomarkers and help understanding IC/PBS physiopathology.

Abstract #128

ADAPTATION TO THE BRAZILIAN CULTURE OF THE QUESTIONNAIRE "RICE BLADDER SYMPTOM IMPACT SCALE – BSI-6" FOR QUALITY OF LIFE EVALUATION OF PATIENTS WITH INTERSTITIAL CYSTITIS.

Fernandes M, D'Ancona C, Silva A, Lúcio A, Lopes M H.

As it is important to evaluate the quality of life in patients with interstitial cystitis using a validated questionnaire and there is none available in Portuguese, it is necessary to translate and validate questionnaires developed, tested and used in other countries. Therefore, the aim of this study was to translate and adapt the questionnaire "Rice Bladder Symptom Impact Scale – BSI-6" to the Brazilian culture, which evaluates the quality of life of patients with IC/BPS. The methodological process of cultural adaptation aims at the acquisition of an instrument true to the original, but adapted to the culture of the country where this version will be applied. A feature of this questionnaire is that it is self-reported and due to this all of the items needed to be changed to achieve cultural equivalence, in order to make the instrument more understandable to the target audience. The changing of all items demonstrated the necessity of adapting the questionnaires developed in other countries. As the questionnaire is simple and takes little time to be applied, the authors believe that it can be useful for healthcare professionals in different practice scenarios to promote multidisciplinary action.

Abstract #148

IN WHAT TYPE OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME IS DMSO INTRAVESICAL INSTILLATION THERAPY EFFECTIVE?

Tomoe H.

There are two types of IC/BPS: with or without Hunner lesions. Hydrodistension followed by transurethral resection (TUR) and fulguration is known to be an effective means of treating lesions. While the recommendation level of intravesical instillation of dimethylsulfoxide (DMSO) as a method of intravesical instillation therapy is high, which type of IC/BPS it is effective against has been rarely reported. According to the author from Japan, hydrodistension followed by transurethral coagulation (TUC) has been performed to treat IC/BPS with Hunner lesions at their hospital since 2005. They therefore conducted a retrospective study of consecutive cases of IC/BPS in which hydrodistension had been performed in 2003–2004, when TUC was not being performed. They combined DMSO with hydrodistension in 2003 and from 2004 they performed hydrodistension alone. It was concluded that DMSO intravesical instillation therapy did not have any particular efficacy in the treatment of IC/BPS without Hunner lesions, but it was useful in both maintaining and improving the effectiveness of hydrodistension in IC/BPS with Hunner lesions. The small number of cases, the fact that the data analysis of only recurrence-free cases may not have reflected the true situation, and the fact that it was a retrospective study were limitations of this study.

Abstract #154

ELEVATED SERUM IMMUNOGLOBULIN E AND BLADDER EOSINOPHILS INFILTRATION SUGGEST HYPERSENSITIVITY MIGHT CONTRIBUTE TO THE PATHOGENESIS OF KETAMINE CYSTITIS.

Jhang J, Jiang Y, Kuo H.

The number of ketamine related cystitis (KC) cases is increasing, but the pathogenesis of KC is still unclear. Previous studies revealed bladder mast cell and eosinophil cell increased infiltration in patients with KC. Mast cell and eosinophil in tissue usually suggested hypersensitivity. This study from Taiwan investigated the possibility of hypersensitivity as pathogenetic mechanism of KC. The KC patients had higher serum IgE than the patients with IC/BPS, acute bacterial cystitis and normal controls. The bladder biopsy specimen also showed eosinophil infiltration in almost every patient. The serum IgE and submucosal eosinophil is correlated with clinical symptoms. This evidence suggests that hypersensitivity might contribute to the pathogenesis of KC.

Abstract #155

DEVELOPING A CHRONIC IN-VITRO MODEL FOR BLADDER PAIN SYNDROME.

Rozenberg B, Heesakkers J, Schalken J.

In bladder pain syndrome (BPS), the barrier of the urothelium is compromised. This enables solutes from the urine to leak into the bladder wall and cause irritative symptoms. Different models are being developed to achieve a better understanding of this disease and to test therapies. Many animal models use different irritants such as acids to directly damage the lining of the bladder wall. Rozenberg and colleagues from Radboud university medical centre in the Netherlands report that in their previous studies they used protamine to damage the urothelium and create a deficient barrier. In order to set up a chronic protocol, they instil this enzyme repeatedly for longer periods of time. This could possibly interfere with glycosaminoglycan (GAG) replenishment therapies which they want to evaluate with this model. They set out to prepare a chronic model in-vitro for urothelium with a deficient barrier. In this study they aimed to evaluate the effects of lipopolysaccharide (LPS) on barrier function in-vitro and compare this to protamine. They evaluated the effect of protamine and LPS in search of the ideal chronic model in-vitro for inflamed urothelium with a deficient barrier. Protamine shows a nice decrease in TEER while the cells stay viable. The disadvantage of protamine is that it should be instilled daily because of the natural recovery of urothelium to a certain extent. Continuous instillation with this enzyme will possibly interfere with therapeutic instillations they want to test on this model. Through measuring TEER, no negative effect of LPS could be detected for barrier function. The authors are of the opinion that, for now, protamine is their best option to decrease the barrier in-vitro. These results prove the principle for animal experiments in which protamine is used to create a deficient barrier.

Abstract #156

IMMUNOHISTOCHEMISTRY STUDY OF KETAMINE RELATED CYSTITIS – A CORRELATION WITH CLINICAL CHARACTERISTICS WITH UROTHELIAL DYSFUNCTION AND CHRONIC INFLAMMATION.

Tsai Y, Lee C, Jhang J, Jiang Y, Kuo H.

Ketamine related cystitis (KC) is a recently emergent bladder disease characterized by severe bladder irritative symptoms, bladder pain, small voided volume and upper urinary tract deterioration after long-term ketamine abuse. The changes of the bladder histology have not been well elucidated to explain the disease progression of this disease. In this study from Taiwan, Tsai and colleagues compared the urothelial dysfunction, chronic inflammation and expressions of sensory proteins in the bladder urothelium and tried to correlate these parameters with the clinical characteristics. Significantly increased inflammation, increased urothelial apoptosis and decreased junctional protein expression were noted in KC bladders. These IHC results correlated with severe bladder pain, irritative symptoms and reduced bladder capacity in severe KC bladders. The authors concluded that inflammation leading to urothelial dysfunction and upregulation of M3 receptors was evident in KC bladder and causes bladder symptoms.

Abstract #157

PAINFUL BLADDER SYNDROME / INTERSTITIAL CYSTITIS AND HISTAMINE INTOLERANCE – IS THERE A LINK?

Heßdörfer E.

In this retrospective case collection from Germany, the role of histamine overproduction is highlighted. A total of 33 women with diagnosed interstitial cystitis were surveyed. Histamine in faecal samples was measured with a commercially available ELISA kit. Additionally, vaginal swabs were analysed for histamine producing bacteria of the Enterococcus family. In 25 of the 33 analysed women, elevated histamine levels were found in faecal samples. In 16 of the 25 women, the presence of Enterococcus spp. in vaginal swabs was also detected. In a further 4 women, only the presence of Enterococcus spp. was found. Only 4 women showed neither elevated histamine levels nor the presence of Enterococcus spp. in vaginal swabs. Elevated histamine levels and the presence of histamine producing bacteria were therefore found in the majority of women with diagnosed Interstitial Cystitis. Histamine intolerance is a poorly described disease which may be responsible for a variety of symptoms (e.g. digestive complaints and non-allergic food hypersensitivity). Histamine overproduction may mimic a mast cell burst, thus explaining the symptoms of interstitial cystitis.

Abstract #158

URINARY DIVERSION FOR INTRACTABLE INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME: WHETHER THE TRANSVAGINAL URETHRECTOMY CAN PLAY A PART.

Yang T, Luo D, Hu X, Shen H.

This study from Sichuan University, China retrospectively evaluated the history, intraoperative, and postoperative outcomes of patients choosing major surgery as the final IC/BPS treatment. Furthermore, because ileal conduit urinary diversion with cystectomy or cystourethrectomy was selected in the majority of cases, Yang and colleagues compared the therapeutic benefits and risks of the procedures involving transvaginal urethrectomy. The medical records of the urology department outpatients experiencing frequent and painful urination for a long duration were reviewed. Patients reporting no improvement or exacerbation of symptoms were considered surgical candidates and eligible for the study. The ability of surgical candidates to endure the procedure was evaluated individually. The uncertain surgical outcome, as well as risks and benefits, were discussed with each patient. The main surgical options were urinary diversion with cystectomy or cystourethrectomy and orthotopic ileocystoplasty because of their low re-operation rate. A classical ileal conduit urinary diversion, i.e. Bricker conduit, was performed transabdominally with cystourethrectomy where the bladder was excised from the trigone to the pubourethral ligament and the urethrectomy was performed transvaginally when possible. An orthotopic ileocystoplasty was performed transabdominally with supratrigonal cystectomy where the excision did not include the trigone or the ureteral orifices. Intraoperative and postoperative medical records were retrospectively reviewed. The patient's satisfaction was considered the main standard of successful operation. Surgical outcomes were assessed on the basis of a repeated voiding diary, visual analog scale (VSA), the Chinese edition of the MOS (medical outcomes study) item short form health survey (SF-36). The surgical outcomes were remarkable in all 14 patients. Management of the ileal conduit urinary diversion was feasible using a urine collection device. Patients reported improved social function and mental condition postoperatively due to a decreased urinary frequency. Although urethra-localized pain is associated with a worsened prognosis for substitution enterocystoplasty, few studies confirm whether the transvaginal urethrectomy can play a part. In the present data, five cystectomy and eight cystourethrectomy with ileal conduit urinary diversions were performed. Urethrectomy was performed transvaginally only as a radical operation. There was no significant association between the outcomes with urethra involvement and the transvaginal urethrectomy incidence. Hence, the urethra may not be a source of IC/BPS symptoms. Histopathologically, glandular urethritis with squamous metaplasia was the primary finding in the urethral epithelium, but typical ulceration lesions or interstitial change is absent. Furthermore, in the present study, transvaginal urethrectomy was associated with postoperative delayed healing at the transvaginal incision. The authors concluded that based on the present understanding and available therapy for interstitial cystitis/bladder pain syndrome, major surgery cannot be completely avoided. A careful and thorough evaluation weighing the individual benefits and risks is required. Overall, surgery resulted in favorable subjective and objective outcomes in the selected patients. Transvaginal urethrectomy was not recommended as an initial surgical technique.

Abstract #160

A PROSPECTIVE RANDOMIZED CONTROL TRIAL OF BOTULINUM TOXIN A (BOTOX A) INJECTION FOR INTERSTITIAL CYSTITIS

Akiyama Y, Nomiya A, Niimi A, Yamada Y, Suzuki M, Fujimura T, Igawa Y, Homma Y.

Akiyama and colleagues from Tokyo, Japan report that intravesical injection of BTX-A has been recently introduced as a new treatment for refractory interstitial cystitis (IC). However, the efficacy of this treatment is still controversial. A total of 34 IC patients (25 women and 7 men) were enrolled for this study. These were IC patients who had received hydrodistension at least once and one or more oral drugs for the relief of their symptoms yet remained symptomatic. Patients were randomly divided into two groups, Group A: immediate injection of BTX-A 100U after enrolment, or Group B: one-month delayed injection of BTX-A 100U after maintaining the conventional therapies for a month. As a primary endpoint, global response assessment (GRA) of seven grades was evaluated one month after assignment. Patients who rated the efficacy as better than +1 in GRA, which means “slightly improved”, “improved” or “remarkably improved”, were considered as responders to the BTX-A treatment. The authors are of the opinion that the results of this study indicated that intravesical BTX-A injection improved the symptoms and QOL impairment in patients with refractory IC. Predictive factors for better outcomes included a longer disease duration and a larger number of hydrodistension received. They concluded that intravesical BTX-A injection could be an alternative treatment option for the patients with refractory IC, especially for those who have received repeated hydrodistension.

Abstract #161

URINARY IMMUNOGLOBULIN CONCENTRATION IS NOT INCREASED IN INTERSTITIAL CYSTITIS

Yamada Y, Suzuki M, Saito Y, Nomiya A, Niimi A, Igawa Y, Homma Y.

A previous study has shown increased levels of urinary immunoglobulin G and A in interstitial cystitis (IC) patients, suggesting up-regulated immunological reactions in the urinary tract in IC. To confirm the promising results, Yamada and colleagues from Japan quantified urinary immunoglobulin concentrations in patients with Hunner type IC, non-Hunner type IC, and other conditions with lower urinary tract symptoms (LUTS). Patients visiting their institute in Tokyo from 2009 to 2013 were recruited for the study. Urine samples were collected from 110 patients with Hunner type IC, 35 patients with non-Hunner type IC, and 138 patients with other conditions with LUTS. All the IC patients were compatible with NIDDK research criteria and fulfilled three diagnostic requirements of IC recommended by clinical guidelines for interstitial cystitis and hypersensitive bladder syndrome. The diagnosis of the comparative group was benign prostatic hyperplasia, pelvic organ prolapse, overactive bladder, neurogenic bladder, stress urinary incontinence, genitourinary cancer, hydronephrosis, or urinary tract infection. The authors found that urinary immunoglobulin concentrations were less than the lower limit of quantitation in most of the patients. There were no significant differences in urinary immunoglobulin A and G levels among those 3 groups. No specific clinical features were identified for IC cases with positive urinary immunoglobulin. It was therefore concluded that urinary immunoglobulin concentration levels are not increased in IC. Further investigations are needed to confirm the results.

Abstract #162

OUTCOMES OF HYDRODISTENSION WITH OR WITHOUT FULGURATION FOR INTERSTITIAL CYSTITIS AND RISK FACTORS PREDICTING THERAPEUTIC FAILURE

Niimi A, Nomiya A, Yamada Y, Azuma T, Suzuki M, Fujimura T, Nakagawa T, Fukuhara H, Kume H, Igawa Y, Homma Y.

Hydrodistension is a first-line non-conservative therapy for interstitial cystitis (IC) without Hunner lesion. Hydrodistension accompanied by transurethral resection (TUR) is employed for IC with Hunner lesion. Unfortunately, however, symptoms are likely to recur after these procedures. The aims of this study were to evaluate the outcomes of hydrodistension with and without TUR and to identify risk factors for therapeutic failure. IC patients who underwent hydrodistension with or without TUR at this institute in Tokyo, Japan from 2007 to 2013 were retrospectively reviewed. All the patients were compatible with NIDDK research criteria and fulfilled three diagnostic requirements of IC recommended by clinical guidelines for interstitial cystitis and hypersensitive bladder: lower urinary tract symptoms, bladder pathology and exclusions of confusable diseases. The symptoms are characterized by bladder hypersensitivity, usually associated with urinary frequency, with or without bladder pain (hypersensitive bladder syndrome symptoms). A total of 191 patients

were recruited; 126 with Hunner type IC and 65 non-Hunner type IC. Failure free rate was higher in Hunner type IC within 15 months; however, it was higher in non-Hunner type IC thereafter and there was no difference between the two types of IC during the whole period. Hunner type IC is characterized by intense pro-inflammatory reactions in the affected lesion and the whole bladder, and TUR of Hunner lesion was reported to produce good outcomes. However our result showed that outcomes fared well until 15 months and fell back in a long term follow-up. In non-Hunner type IC, concomitant LCS and IBS were unfavourable factors. Association of chronic inflammation and comorbidities affecting pelvic sensory system with refractoriness to hydrodistension and/or TUR suggests sensory hyperactivity status in the IC bladder. It was concluded that the efficacy of fulguration of Hunner lesion did not last for a long period. Concomitant LCS and IBS are predictive of failure of hydrodistension with or without TUR. These factors should be taken into account in counselling with patients.

Abstract #163

SAFETY AND FEASIBILITY OF INTRAVESICAL INSTILLATION OF BOTULINUM TOXIN IN HYDROGEL-BASED SLOW RELEASE DELIVERY SYSTEM IN PBS/IC PATIENTS: A PILOT STUDY.

Stav K, Vinshtok Y, Jeshurun M, Ivgy-May N, Gerassi T, Zisman A.

PBS/IC persists as a challenging syndrome in urology. In the case of other treatment failure, intradetrusor injection of botulinum toxin A (BTX) may be administered. However, due to the seriousness and duration of adverse events (AE), BTX injections are only considered as a fifth line therapy. Common drug AEs include dysuria, the need for abdominal straining to void, large post-void residuals, and the need for intermittent self-catheterization that persists for one to three months. Intravesical instillation is an appealing alternative to injection of BTX. The efficacy of intravesical BTX instillation was only tested in a few open label trials for overactive bladder patients whereby the clinical improvement observed was short-lasting with a mean duration of 6.8 weeks. The short exposure duration of the urothelium to BTX could be one of the factors responsible for the lack of a sustained effect. Therefore, an extended release formulation or a mechanism through which the contact time between BTX and the bladder's urothelium is extended, may address this shortcoming. TCGel (TheraCoat) from Israel is a novel hydrogel with reverse thermal gelation properties. It has a high viscosity at body temperature and it is fluid-like at low temperatures. This allows for a simple instillation of the cooled liquid TCGel pre-mixed with BTX into the bladder where it solidifies and serves as a drug reservoir allowing for gradual release of the drug for 6-8 hours and thereby for its extended contact with bladder urothelium. Here Stav and colleagues from Israel report the results of a pilot clinical trial in which for the first time, the feasibility, tolerability, and safety of intravesical instillation of BTX mixed with TCGel was evaluated in patients with PBS/IC. This was an open label single arm pilot trial in which the feasibility, tolerability and safety of intravesical instillation of BTX mixed with TCGel was evaluated. This is the first clinical trial in which the effect of intravesical instillation of TCGel+BTX, allowing for a slow release of BTX, has been evaluated in patients with PBS/IC. The results of this trial suggest that intravesical instillation of TCGel+BTX is generally safe and well tolerated. The instillation procedure did not require any general or spinal anesthesia in contrast to the intradetrusor injection procedure. No serious drug-related AEs were reported. In contrast to intravesical injections, no discomfort or pain associated with the procedure was observed and no lasting adverse effects associated with the treatment were reported. Considering the high sensitivity of IC/BPS patients to invasive treatments, simple intravesical instillation of BTX appears to be well tolerated. The apparent sustained reduction of PBS/IC symptoms is difficult to interpret due to the small number of subjects. However, the results are encouraging and provide the basis for further exploration of the safety and efficacy of TCGel+BTX in a randomized placebo controlled trial.

Abstract #164

EFFECT OF LOW-DOSE TRIPLE THERAPY USING GABAPENTIN, AMITRIPTYLINE, AND A NONSTEROIDAL ANTI-INFLAMMATORY DRUG FOR OVERACTIVE BLADDER SYMPTOMS IN PATIENTS WITH BLADDER PAIN SYNDROME

Jeong H J, Noh J H.

The primary purpose of this study from South Korea is firstly to identify the prevalence rate of OAB symptoms in patients with BPS/IC, secondly to identify changes in OAB symptoms after low-dose triple therapy, and

thirdly to build a theoretical foundation to improve quality of life for patients. The patients consisted of 3 men and 20 women, and their mean age was 61.9 years (41.0–83.2 years). According to the findings of Jeong and Noh, when values before treatment and at 4 and 12 weeks after treatment were compared, those of the ICSI, ICPI, OABSS, and VAS showed statistically significant improvement. However, when values at 4 and 12 weeks after low-dose triple therapy were compared, the ICSI and VAS showed contrasting results with the ICPI and OABSS. It was concluded that low-dose triple therapy in BPS/IC results in a clear decrease in OAB symptoms in the first 4 weeks after treatment, and additional treatment for 8 weeks had a partial effect with varied statistical significances depending on the questionnaires.

Abstract #167

EFFICACY AND SAFETY OF REPEATED INTRAVESICAL ONABOTULINUMTOXIN-A INJECTIONS FOR INTERSTITIAL CYSTITIS/PAINFUL BLADDER SYNDROME: LONG-TERM FOLLOW-UP

Lee C, Chung S, Kuo H.

Intravesical Onabotulinumtoxin-A (BoNT-A) injection is considered to be a safe and effective therapeutic option for interstitial cystitis/ bladder pain syndrome (IC/ BPS), though its sustainability after only one single injection remains unsatisfactory. The purpose of this study from Taiwan was to evaluate the long-term efficacy and safety of repeated Intravesical BoNT-A injections in the treatment of IC/ BPS. 100 U of BoNT-A was injected intravesically every 6 months for up to 4 times in 104 IC/ BPS patients who failed conventional therapy. At 6 months after the initial injection, patients could decide to remain in or quit study based on their subjective therapeutic effects. Those who received only one injection served as active controls. Out of 104 patients, 14 received single, 18 received two, 13 received three, and 59 received four injections, respectively. The mean of ICSI, ICPI, total scores, VAS, functional bladder capacity, and daytime frequency all showed significant improvement after repeated BoNT-A treatment with different injections. The occurrence of adverse events did not increase with increasing number of BoNT-A injections. The results of this study demonstrated that repeated intravesical injections of BoNT-A increased FBC and provided long-term pain relief in patients with IC/PBS who were refractory to conventional treatment. The long-term success rates of 3 or 4 repeated intravesical BoNT-A injections were better than a single or two injections. The incidence of adverse effects did not increase after repeat BoNT-A injections. Previous studies showed intravesical injections of BoNT-A have anti-inflammatory effect on IC/BPS, and current study also implies repeated BoNT-A injections might achieve long-term control of bladder inflammation. Repeated intravesical BoNT-A injections are safe and effective for pain relief and can increase bladder capacity and provide a better long-term success rate than a single injection for treatment of IC/PBS.

Abstract #168

SURGICAL OUTCOMES OF TOTAL CYSTECTOMY WITH ILEAL CONDUIT AND SUPRATRIGONAL CYSTECTOMY WITH AUGUMENTATION CYSTOPLASTY FOR END-STAGE INTERSTITIAL CYSTITIS.

Niimi A, Kimura N, Nomiya A, Yamada Y, Azuma T, Suzuki M, Fujimura T, Nakagawa T, Fukuhara H, Kume H, Igawa Y, Homma Y.

Clinical guidelines for IC/BPS published so far recommend a variety of treatment modalities, with cystectomy or augmentation cystoplasty mentioned as the last resort. However, few studies compared the outcomes of cystectomy and cystoplasty. The aim of this study is to compare surgical outcomes of these invasive surgical procedures indicated for end-stage IC. The single institutional data (the University of Tokyo, Department of Continence Medicine) were retrospectively analysed to evaluate outcomes of patients with refractory IC who received either total cystectomy or supratrigonal partial cystectomy with augmentation cystoplasty. Between 2002 and 2013, three patients received partial cystectomy with augmentation cystoplasty using ileal segment and five patients total cystectomy with ileal conduit. In this study, augmentation cystoplasty had no benefit for symptom improvement. Since the trigonal area of the bladder and urethra were conserved, remaining inflamed tissue could cause persistent symptoms. On the other hand, patients undergoing total cystectomy had no symptomatic recurrence and QOL index improved significantly. The authors concluded that augmentation cystoplasty is less invasive than cystectomy in terms of there being no need for urinary diversion, but may be less efficacious to resolve the symptoms. Total cystectomy rather than augmentation

would be indicated as the last resort for end-stage IC to relieve the intractable symptoms after thorough consultations with patients.

Abstract #170

LONG TERM OUTCOME OF SACRAL ROOTS NEUROMODULATION FOR THE MANAGEMENT OF BLADDER PAIN SYNDROME: SINGLE CENTER EXPERIENCE

Hernandez Hernandez D, Bernardez Tesouro R, Ortega González Y, Tamayo Jover M A, Gonzalez Perez L, Martinez Bustamante G, Concepcion Masip T, Castro-Díaz D M.

Hernandez and colleagues from the Canary Islands and Izola performed a retrospective evaluation of the results of sacral roots neuromodulation (SNM) of their patients with refractory BPS. After the failure of conservative therapy, 19 patients with BPS were tested with SNM following the Tinedlead procedure (2 stages with fully percutaneous lead implant) a variable period of time and then, if symptomatic improvement was higher than 50%, they were permanent implanted. In the group of implanted patients, 10 (of 15) were satisfied or very satisfied with SNM, and the same of them reported an improvement in QoL. Bowel and sexual function did not change in most of the patients. Five of the initial 15 responders to SNM developed late loss of effectiveness between 2-6 years after implant. They had no cases of infection, hematoma or lead migration, but had to explant the neuromodulator in 3 patients due to pain at local site of implantation and loss of effectiveness.

According to the authors, in their experience SNM plays a role in the management of patients with BPS because:

- It is a minimally invasive technique, performed under local anaesthesia and outpatient basis.
- Allows high degrees of satisfaction
- Improves QoL
- Could provide symptomatic long-term improvement in 1 in every 2 patients with refractory BPS, avoiding more aggressive/mutilating therapies.

Abstract #171

HISTOLOGY IN BLADDER PAIN SYNDROME PATIENTS, 5 YEARS IN RETROSPECT.

Rozenberg B, Heesakkers J.

The population of patients with bladder pain syndrome (BPS) or interstitial cystitis (IC) is very heterogeneous. This makes diagnosis of this condition quite difficult. Clear biomarkers are also unavailable. The diagnosis is mainly based on symptoms as chronic pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or frequency as stated in the ESSIC consensus. In addition, the consensus mentions further classification of BPS through cystoscopy and histology. When examining histology in these cases, the pathology department at Radboud University Medical Centre in the Netherlands mainly focuses on detrusor mastocytosis to support a clinical diagnosis. As found in the literature, mastocytosis is defined as 28 mast cells/mm² or more in the detrusor muscle. A number of 20-28 mast cells/mm² is a grey area. The aim of the present study was to evaluate the rate of histologic confirmation in the authors' BPS patients in the past 5 years. A second goal was to see if there is a difference in the number of mast cells between cases with and without a Hunner lesion. They looked into all patients who underwent surgical procedures for bladder pain syndrome in the past 5 years in their department. All the patients from whom bladder tissue was examined by the department of pathology were included. Cases with bladder malignancies were excluded. A total of 54 (11 males, 43 females) patients were included. In 46 of these patients histology was obtained through biopsy with cystoscopy, 8 other patients underwent a cystectomy because of functional conditions. In 39% a Hunner lesion was reported. When solely looking at histology and a true mastocytosis of 28 mast cells/mm² or higher, the diagnosis was confirmed in 43%. The number of mast cells was not statistically different when a Hunner lesion was present. The authors conclude that while mast cell count is regarded as the standard for histologic confirmation of BPS because it has standardized values, the drawback is the need for detrusor in the biopsy as in 20% of our cases no mast cell count was performed because detrusor muscle was absent. This shows the need for additional objective markers to confirm the diagnosis of BPS.

Abstract #172

GENE EXPRESSION PATTERN OF TRANSIENT RECEPTOR POTENTIAL C IN BLADDER TISSUE OF INTERSTITIAL CYSTITIS

Nomiya A, Niimi A, Yamada Y, Tagaya M, Homan T, Oyama T, Igawa Y, Homma Y.

The pathogenesis of interstitial cystitis (IC) is still unknown. A previous study demonstrated increased expression of genes involved in pronociceptive inflammatory reactions including TRPM2, TRPV1, TRPV2, TRPV4, ASIC1, NGF in Hunner type IC and different expression patterns in non-Hunner type IC. Recently, a specific increase in the expression of TRPC1 and TRPC4 in bladder-innervating sensory neurons and the sprouting of sensory fibers in the bladder mucosa was demonstrated in a rat cystitis model induced by repeated cyclophosphamide injections. However, few studies investigated expression of TRPC in human IC sample. In this study from the University of Tokyo, the difference of mRNA expression of TRPC was assayed and compared among bladder tissue of control, Hunner type IC and non-Hunner type IC. Patients with IC scheduled for hydrodistension or those with non-invasive bladder cancer undergoing transurethral resection (as controls) were enrolled. Diagnosis of IC was based on the clinical guidelines for IC and hypersensitive bladder. A total of 50 subjects (non-Hunner type IC, 17; Hunner type IC, 22; control, 11) were enrolled and all the IC patients were compatible with NIDDK criteria. This study demonstrated a different pattern of increased expression of TRPC genes among subtypes of IC. TRPC1 and TRPC3 expressions may link to the symptom severity in non-Hunner type IC, whereas in Hunner type IC, TRPC1, TRPC5 and TRPC6 expressions may do so. It was concluded by the authors that the results of this study support the hypothesis that TRPC family has some roles in pathogenesis of IC as well as other TRP families. Further research is required to elucidate the function of TRPC family in the bladder.

Abstract #293

ROLE OF TRPV3 IN URINARY BLADDER FUNCTION AND SENSATION

Lam M, Mann-Gow T, Zvarova K, King B, Moran M, Nelson M, Zvara P.

TRP channels have been shown to act as mechanosensory and pain receptors in a wide variety of organ systems. Despite their presence in the bladder, to date their pharmacologic modulation has not been shown to be effective in the treatment of overactive bladder and lower urinary tract symptoms. This study from the USA utilizes wild-type (WT) and TRPV3-knock out (KO) mice, coupled with novel drug compounds to clarify TRPV3's role in the regulation of bladder function and sensory signalling. The data presented suggest that TRPV3 is present and has a functional role in the urinary bladder. Similar to the effects of TRPV1-specific capsaicin, TRPV3-specific compounds may exert their effects through modulation of neurokinin release, such as substance P. Moreover, the fact that TRPV3 exerts a suppressive effect on bladder phasic activity in combination with TRPA1, but not alone, suggests that multi-target therapy may prove effective for the treatment of OAB.

Abstract #348

HIPPURIC ACID: A BIOMARKER FOR BLADDER PAIN SYNDROME

Bray R, Jimenez B, MacIntyre D, Cartwright R, Franklin-Nembhard L, Digesu A, Fernando R, Holmes E, Bennett P, Khullar V.

Bladder pain syndrome affects an estimated 3.3 million U.S. women. It is associated with profound physical and psychological impact, and significant economic costs. While the aetiology remains largely unknown, inflammation is thought to play an important role. Metabolites in urine represent the end products of normal and pathological cellular processes. The aim of this study from London was to evaluate the urinary metabolic profiles associated with bladder pain syndrome using ¹H-NMR spectroscopy. 288 women with a mean age 46 (SD 15.7) were recruited. OPLS-DA modelling of the urine metabolic data facilitated separation between cases and controls. Further analysis of the spectral data identified hippuric acid as a primary discriminatory metabolite between the two groups with levels consistently reduced in patients reporting bladder pain compare to controls. There were no significant differences in demographic characteristics between the groups.

Abstract #350

UROTHELIAL DYSFUNCTION AND CHRONIC INFLAMMATION IN PATIENTS WITH CHRONIC INTERSTITIAL CYSTITIS WITH AND WITHOUT HUNNER'S LESION

Chen S, Jhang J, Kuo H.

Interstitial cystitis/bladder pain syndromes (IC/BPS) can be classified into IC with Hunner lesion and non-ulcer IC subtypes. Cystoscopic hydrodistention usually can easily identify these two IC subtypes. Previous studies highlighted important clinical and histopathological distinctions between the two subtypes, which have been considered different disease entities. This study from Taiwan was designed to investigate the suburothelial inflammation and urothelial dysfunction between the two IC subtypes. Bladder mucosal tissues from 13 patients with ulcer type IC, 35 patients with non-ulcer type IC and 10 control subjects were analysed. The bladder biopsies were obtained randomly from the posterior wall in non-ulcer IC/BPS and the controls. Bladder biopsies were obtained from the margin tissue of the ulcerations in ulcer type IC/BPS. This study revealed the urothelial dysfunction markers, including tight junction protein E-cadherin and ZO-1, active mast cells, and TUNEL expression for apoptosis were all significantly different compared with the control group. When the authors compared the two IC/BPS subtypes, the apoptotic process was highly activated in the ulcer group. Their previous study had shown the urothelial cell apoptosis in patients with IC/BPS resulted from upregulation of inflammatory signals, including p38 mitogen-activated protein kinase and TNF- α . This study suggests the ulcer type and non-ulcer type IC/BPS might have different pathogenesis of inflammation and phenotype. It was concluded that bladder mucosal tissues from both ulcer type and non-ulcer type IC/BPS showed defective junction protein, increased suburothelial inflammation and increased urothelial cell apoptosis. In comparison of two IC/BPS subtypes, increased apoptotic cell was significantly higher in the ulcer type IC/BPS than the non-ulcer IC/BPS group.

Abstract #351

A NOVEL ANIMAL MODEL OF CHRONIC UROTHELIAL INJURY AND BLADDER PAIN HYPERSENSITIVITY INDUCED BY INTERMITTENT INFUSION OF PROTAMINE SULPHATE INTO THE BLADDER IN RATS: THE INVOLVEMENT OF PROSTAGLANDIN E2 AND EP1 RECEPTOR ACTIVATION

Okada H, Tyagi P, Kawamorita N, Majima T, Chancellor M B, Yoshimura N.

Although the aetiology of PBS/IC is multifactorial, urothelial dysfunction with increased urothelial permeability is considered to be a major pathogenesis of the disease. However, basic research into PBS/IC is hampered because there are no appropriate animal models of chronic bladder injury associated with increased bladder pain sensitivity. Previous studies showed that intravesical infusion of protamine sulfate (PS) in rats causes the urothelial damage, especially in the surface glycosaminoglycan layer and apical umbrella cells of the urothelium, leading to decreased transepithelial resistance and bladder inflammation, which mimic some aspects of urothelial dysfunction in human PBS/IC. Therefore, Okada and colleagues from the USA first attempted to develop a novel animal model of chronic urothelial injury with bladder pain hypersensitivity using intermittent PS infusion into the bladder in rats. PS-induced intermittent urothelial injury for 4 weeks resulted in bladder hyperactivity evidenced by spontaneous bladder contractions during the storage phase and increased bladder pain sensitivity shown by enhanced pain behaviours induced by nociceptive stimuli in the bladder, which were observed even after the remission of acute inflammatory changes in the bladder. Also, EP1 receptor activation by increased levels of PGE2 due to COX-2 upregulation in the bladder, afferent pathways, the spinal cord and/or the pons is likely to contribute at least in part to peripheral and central sensitization leading to increased bladder pain sensitivity in this model. It was concluded that rats with intermittent PS infusion are suitable for a chronic animal model of urothelial injury that exhibits bladder hypersensitivity, which could be used for the research identifying the mechanisms underlying bladder pain and dysfunction induced by urothelial damage that are often seen in PBS/IC patients. Moreover, EP1 receptor blockade may be a novel therapeutic option for controlling PBS/IC symptoms related to bladder pain hypersensitivity.

Abstract #352

RECOVERY OF UROTHELIAL BARRIER FUNCTION BY REBAMIPIDE

Funahashi Y, Yoshida M, Yamamoto T, Matsukawa Y, Takai S, Gotoh M.

Rebamipide is used orally for treatment of gastritis, as eye drops for dry eye, and as an enema for inflammatory bowel diseases. Its mechanism of action includes inhibiting inflammation, accelerating wound healing, and protecting the mucosa. For these pharmacological effects, high local concentration has to be achieved in the target tissue. Funahashi and colleagues from Japan subsequently hypothesized that topical treatment with rebamipide might be effective for urothelial repair. In this study, they examined the healing effects of intravesical application of rebamipide on a damaged urothelium using a chemically induced cystitis rat model. This study revealed five major findings. Firstly, rebamipide administered inside the bladder directly permeated the bladder wall. This effect was more pronounced in the cystitis model than normal rats. Importantly, a pharmacologically effective concentration of rebamipide persisted for >6 h in the cystitis model. Secondly, intravesical application of rebamipide accelerated the healing of damaged urothelial cells and tight junctions. Thirdly, it enhanced the recovery of urothelial permeability, which resulted in decreased submucosal inflammation. Fourth, the protection of the urothelial barrier resulted in reduced pain reactions against bladder nociceptive stimuli. Finally, rebamipide was also effective for bladder overactivity. Intravesical administration of rebamipide relieved bladder overactivity and nociception in a hydrochloride-induced cystitis model, which was accompanied by accelerated urothelial repair. This could be a novel strategy for the treatment of patients with IC/PBS.

Abstract #353

A NOVEL CYSTOMETRY METHOD COMBINED WITH BLADDER ULTRASONOGRAPHY REVEALS RAPID DECREASE OF BLADDER CAPACITY AND COMPLIANCE IN MICE LPS-INDUCED CYSTITIS

Takezawa K, Kondo M, Kiuchi H, Soda T, Takao T, Miyagawa Y, Tsujimura A, Nonomura N, Shimada S.

Takezawa and colleagues from Osaka hypothesized that bladder filling and emptying were physically inhibited by catheters conventionally implanted in bladder apex but not by catheters implanted in bladder anterior wall. Moreover, they thought that transabdominal ultrasonography (US) would be useful for analysing mouse bladder function and the effect of bladder catheter. The aim of this mouse study was to examine the efficacy of transabdominal bladder US for analysing mouse bladder function and establish the most reliable cystometry method. The authors believe that this study demonstrates the usefulness of transabdominal bladder US on analysis of mouse bladder function and the validity of a new cystometry method with the bladder catheter in bladder anterior wall. In addition, rapid decrease in bladder capacity and compliance in mice LPS-induced cystitis are revealed by combination of bladder US and a new cystometry method. They conclude by noting that they have established a combination of bladder US and a new cystometry method. This new method will become a powerful tool for analysis of mouse bladder function.

Abstract #354

PROTEOMICS OF KETAMINE CYSTITIS AND INTERSTITIAL CYSTITIS – A WAY TO SEARCH FOR DIFFERENT PATHOPHYSIOLOGY BETWEEN DISEASES WITH SIMILAR BLADDER SYMPTOMS

Yang H, Wang C, Zhai W, Jiang Y, Kuo H.

Although similar suburothelial inflammation and histological symptoms in interstitial cystitis/painful bladder syndrome (IC/PBS) and ketamine cystitis (KC) were found, the level of urothelial dysfunction and apoptosis are different. More severe urothelial dysfunction and increased apoptosis, which correlated with more severe clinical symptoms, was found in KC. Furthermore, some KC progressed into the end-stage bladder manifested with contracted bladder and bilateral obstructive uropathy which were rarely observed in IC/PBS. This study from Taiwan was designed to identify significantly differentially expressed proteins between patients with IC/PBS and KC with the use of proteomic techniques. Three patients each with KC and IC/PBS undergoing partial cystectomy and augmentation enterocystoplasty were enrolled consecutively. At the same time, 3 patients with bladder cancer or prostate cancer undergoing radical surgery who never had episode of urinary tract infection or irritative bladder symptoms were also included and serve as controls. A total of 62 proteins were significantly different between IC/PBS and KC bladders and these proteins were connected by protein-protein interaction network. 27 of these proteins were up-regulated in KC and 35 of these proteins were down-regulated in KC. From the protein-protein interaction network, CFL1, GSN, Lmna, MYL, and CNN1 are associated with caspase 3 which is an apoptosis associated protein. Furthermore, CNN1 is also associated with necrosis and leads to inflammation. This study demonstrated that the etiology of IC/PBS and KC might be

mediated by multiple signalling pathways. The identified proteins contributing to the spectrum of IC/PBS and KC bladders may be used to elucidate the etiology of IC/PBS and KC and as candidate biomarkers for a diagnostic test.

Abstract #355

REDUCED EXPRESSION OF ESTROGEN RECEPTOR- α IN PATIENTS WITH BLADDER PAIN SYNDROME/INTERSTITIAL CYSTITIS

Furuta A, Suzuki Y, Kimura S, Egawa S, Yoshimura N.

It has been reported that chronic inflammation and epithelial cell apoptosis are prevented by 17 β -estradiol replacement due to the estrogen receptor- α (ER α) activation. This study from Tokyo and Pittsburgh examined the expression of ER α in bladder biopsy specimens from patients with BPS/IC. Bladder mucosal biopsies were obtained from 11 BPS/IC patients (male; 6, female; 5) with Hunner's lesion (HL) and in 8 BPS/IC patients (male; 2, female; 6) with non-Hunner lesion (NHL) after hydrodistention. Normal bladder mucosae were obtained from 11 patients (male; 6, female; 5) who underwent surgeries for stress urinary incontinence or benign prostatic hyperplasia (control). Their results demonstrated that: (1) BPS/IC with HL is associated with chronic bladder inflammation indicated by increased CD3 expression, (2) reduced expression of ER α is associated with chronic bladder inflammation (i.e., increased CD3 expression) in BPS/IC specimens, especially those with HL, (3) E-cadherin in the urothelium is reduced in the HL-type of BPS/IC patients, whose bladders often show thinning or denudation of the urothelium, and (4) reduced expression of ER α is also associated with urothelial dysfunction (i.e., decreased E-cadherin expression). The authors concluded that because ER α stimulation is known to prevent chronic inflammation and epithelial cell apoptosis, the reduced expression of ER α in urothelial and suburothelial layers could contribute to impaired urothelial function and chronic bladder inflammation, which are the important pathogenesis of BPS/IC. Thus, ER α expression could be a useful marker for the pathological detection of BPS/IC, especially in the HL type.

Abstract #372

LIPOSOME-BASED INTRAVESICAL THERAPY TARGETING NERVE GROWTH FACTOR (NGF) AMELIORATES BLADDER HYPERSENSITIVITY IN RATS WITH EXPERIMENTAL COLITIS

Kawamorita N, Yoshikawa S, Tyagi P, Chancellor M B, Yoshimura N.

The complex pathophysiology of chronic pelvic pain syndrome (CPPS) and bladder pain syndrome/interstitial cystitis (BPS/IC) could be interrelated. It has recently been proposed that pelvic organ "cross sensitization" contributes to the clinically overlapping symptoms in CPPS such as irritable bowel syndrome (IBS) and BPS/IC. Previous animal studies also demonstrated that experimental colitis evokes bladder overactivity evidenced by frequent urination in association with hyperexcitability of afferent neurons innervating the bladder although it has not been investigated whether this colitis model exhibits an increase in bladder pain sensation. Meanwhile, overexpression of nerve growth factor (NGF) in the bladder is thought to be one of the key factors in the symptom development in BPS/IC patients. Kawamorita and colleagues from Pittsburgh recently reported that instillation of liposome conjugated with antisense oligonucleotide (OND) targeting NGF into the bladder suppressed bladder overactivity in a rat model of acute cystitis. Therefore, this study was planned to explore whether bladder hypersensitivity induced by experimental colitis and NGF overexpression in the bladder are induced after colitis and whether intravesical liposomal-OND treatment can suppress bladder hypersensitivity and NGF expression in a rat model with experimental colitis. Their results in this study show that the rat model of experimental colitis is useful to study the mechanism inducing bladder hypersensitivity such as pain behaviour in addition to changes in bladder activity. The liposome-based antisense treatment targeting NGF in the bladder could be a new, effective modality for the treatment of bladder pain and overactivity in CPPS patients including those with BPS/IC and IBS, in whom the pelvic organ "cross sensitization" mechanism is involved in overlapping symptoms from different pelvic organs.

Abstract #436

ROLE OF WNT PATHWAY ON MESENCHYMAL STEM CELL THERAPY TARGETED TO INTERSTITIAL CYSTITIS

Song M, Park J, Park W H, Kim K S, Park S, Han J, Choo M.

According to Song and colleagues from South Korea, stem cell therapy could be an option to manage interstitial cystitis. This study evaluated the therapeutic potency of using human umbilical cord-blood derived mesenchymal stem cells (UCB-MSC) to treat IC in a rat model and investigate its responsible molecular mechanism. This is the first report that provides an experimental evidence of the therapeutic effects and molecular mechanisms of MSC therapy to IC using an orthodox rat animal model. The authors are of the opinion that their findings not only provide the basis for clinical trials, but also advance understanding of IC pathophysiology.

Abstract #437

BENEFICIAL EFFECTS OF GOSHA-JINKI-GAN AND GREEN TEA EXTRACT IN RATS WITH CHEMICAL CYSTITIS

Yamada S, Nasrin S, Ito Y.

Yamada and colleagues from Japan note that many reports have described the efficacy and safety of phytotherapeutic natural products for urinary dysfunction. However, the use of these agents in the treatment of lower urinary tract symptoms due to IC has been limited by a lack of scientific knowledge underlying the possible mechanism of pharmacological action. Gosha-jinki-gan (GJG) is a traditional Japanese medicine used for urinary disorders, and is composed of 10 crude drugs in fixed proportions. GJG has been shown to decrease the frequency of urination in patients with urinary disturbance, while the mechanism of pharmacological action of GJG is not yet clear. The medicinal value of green tea is well known and reportedly contains the highest concentration of powerful antioxidants called polyphenols, also known as green tea catechins. Green tea polyphenolic compounds present in the green tea extract (GTE) have antioxidant, anticarcinogenic, antiinflammatory, and antimicrobial properties in human, animal, and *in vitro* studies. This study with rats aimed to characterize pharmacological effects of GJG and GTE, on urodynamic parameters, bladder receptors, and urinary cytokines in rats with CYP-induced cystitis. It is the first study to demonstrate that GJG and GTE may improve bladder overactivity in rats with CYP-induced cystitis. Previous studies showed that treatment with CYP caused a decrease in the number of muscarinic and purinergic receptors in the rat bladder. Therefore, urinary cytokines and pharmacologically relevant bladder receptors may serve as direct therapeutic targets or potential biomarkers for the development of targeted therapy designed to prevent chronic bladder inflammatory conditions such as IC. The down-regulation of muscarinic and purinergic receptors in the bladder and an elevation of cytokines in urine of CYP-treated rats were effectively attenuated by repeated treatment with these phytotherapeutic agents, suggesting a viable alternative in the pharmacological treatment of cystitis. The authors concluded that GJG may be a potential therapeutic agent for improving clinical symptoms of cystitis. GTE also appears to have some ameliorative effects on the altered parameters observed in CYP-treated rats.

Abstract #460

INCREASED URINE LEVELS OF MACROPHAGE MIGRATION INHIBITORY FACTOR IN PATIENTS WITH ACUTE CYSTITIS AND INTERSTITIAL CYSTITIS

Lee K W, Kim Y H, Doo S W.

Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine that is associated with inflammatory process in acute cystitis, but not clear in interstitial cystitis. Lee and colleagues from South Korea measured MIF levels in urine of patients with acute cystitis and interstitial cystitis. Urine samples were collected from 30 healthy female volunteers (control group), 40 patients with acute cystitis, and 40 patients with interstitial cystitis. Quantitative measurement of urine MIF level was analyzed using Human MIF DY289 ELISA kit, and adjusted by urine creatinine level. Mean level of urine MIF adjusted by urine creatinine was 0.91ng/ml in control group, 14.41ng/ml in acute cystitis, and 7.10ng/ml in interstitial cystitis, They found that urinary MIF was increased in patients with acute cystitis and interstitial cystitis compared with control group. It was concluded that MIF is a precursor of an inflammatory reaction and it acts by reacting with many inflammatory cytokines. The authors are of the opinion that their data indicate that MIF may participate in the pathogenesis of not only acute cystitis but also interstitial cystitis.

Abstract #560

THERAPEUTIC EFFECTS OF INTRAVESICAL ONABOTULINUMTOXINA INJECTION ON IC/BPS REFRACTORY TO CONVENTIONAL TREATMENT - A RANDOMIZED, DOUBLE BLIND, PLACEBO CONTROLLED STUDY

Kuo Y, Lee C, Jiang Y, Kuo H.

Intravesical onabotulinumtoxinA (BoNT-A) injection has been demonstrated to be beneficial for the treatment of interstitial cystitis/bladder pain syndrome (IC/BPS) yet the therapeutic efficacy has not been validated by a placebo controlled study. Kuo and colleagues from Taiwan conducted a randomized, double blind, placebo controlled trial to elucidate the effects of intravesical BoNT-A injection on IC/BPS. Patients with IC/BPS refractory to conventional treatment for at least 6 months were recruited in this study. Patients with Hunner lesion were excluded. A total of 53 patients (6 male, 47 female) including 36 in group B and 17 in group N were enrolled in this study. At 8 weeks after intravesical injection, significant differences in VAS, ICSI, ICPI, OSS, GRA, FBC, frequency, nocturia and PVR could be observed in group B while only significant improvements in ICSI, ICPI and OSS could be revealed in group N when compared with those at baseline. Moreover, a significantly greater decrease in VAS and increase in PVR could be demonstrated in group B than those in group N after 8 weeks follow-up. The overall successful rates of intravesical injection for treating IC/BPS were 59.3% in group B versus 46.7% in group N by VAS and 70.4% in group B versus 53.3% in group N by GRA. There was no significant difference in prevalence of AE between the two groups. The significant improvements in ICSI, ICPI and OSS after normal saline injection disclosed the remarkable influence of placebo effects on subjective symptoms. Although the overall successful rate seemed higher in group B than in group N, the current study failed to generate a significant difference due to its small sample size. It was concluded that the results of this randomized, double blind, placebo controlled trial demonstrated single intravesical injection of BoNT-A is effective to release the pain symptom in patients with IC/BPS refractory to conventional therapy. The adverse events are acceptable according to the authors. Large scale studies are warranted.

Abstract #581

COMBINED INTRAVESICAL TRIGONAL AND URETHRAL INJECTIONS OF ONABOTULINUMTOXINA IN THE TREATMENT OF PATIENTS WITH HYPERSENSITIVE BLADDER AND VOIDING DYSFUNCTION – A PILOT STUDY

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Hypersensitive bladder (HSB) is characterized as urinary frequency and small voided volume without urgency or urgency urinary incontinence. Voiding diary recording usually confirms decrease of voided volume and small functional bladder capacity (FBC). In urodynamic studies, reduced cystometric bladder capacity and an early first sensation to void were noted in patients with HSB. However, patients with HSB will not develop glomerulation after cystoscopic hydrodistention, which is different from that of interstitial cystitis. Because of small voided volume, HSB patients usually complain of difficult urination. Recently, HSB has been implicated with overexpression of TRPV1 mRNA. There is still no consensus regarding the treatment of HSB, and it is usually managed like IC/PBS or overactive bladder. Combined hypersensitive bladder and voiding dysfunction is a complicated condition which greatly affects QoL. This study from Taiwan was designed to investigate the therapeutic efficacy of onabotulinumtoxin A (BoNT-A) in the treatment of patient with combined HSB and voiding dysfunction. A total of 15 patients (including 8 men, 17 women) who presented with HSB and voiding dysfunction proved by videourodynamic study (VUDS) were enrolled from July, 2013 to January 2014. Inclusion criteria included mean micturitions >8 per day, and functional bladder capacity (FBC) <200 mL, first sensation to void <100ml. Patients with detrusor overactivity, bladder outlet obstruction due to benign prostate hyperplasia and bladder neck dysfunction detected in VUDS were excluded. The authors report that in this pilot study they did not prove that intravesical trigonal and urethral BoNT-A injections can effectively improve voiding symptoms and uroflow parameters in patients with combined hypersensitive bladder and voiding dysfunction, only the quality of life index was significantly improved in this small pilot study series. The advantages and disadvantages of BoNT-A injections should be carefully weighed up in patients with complicated low urinary tract dysfunction.

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