

REVIEW OF THE 46TH ANNUAL MEETING OF THE INTERNATIONAL CONTINENCE SOCIETY (ICS)

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The annual meeting of the International Continence Society (ICS) 2016 was held in Tokyo, Japan and was chaired by Professor Yukio Homma from Tokyo. While this was a long trip for delegates from western countries, it was a home game for the East Asian and Australian-Pacific countries. The 2,146 registered delegates this year included a record 464 from Japan, with many physicians, physiotherapists and nurses from countries in the region such as Korea, Thailand, China, Taiwan and Australia and more besides.

In recent years, the International Continence Society (ICS) has become a hub for discussion of chronic pelvic pain, including interstitial cystitis/bladder pain syndrome and hypersensitive bladder, together with presentation of new research in this field.

Perhaps appropriate to mention here that the ICS Standardisation Steering Committee's working group on chronic pelvic pain was published "early view" online at *Neurourology & Urodynamics* just before the meeting:

*Doggweiler R, Whitmore KE, Meijlink JM, Drake MJ, Frawley H, Nordling J, Hanno P, Fraser MO, Homma Y, Garrido G, Gomes MJ, Elneil S, van de Merwe JP, Lin AT, Tomoe H. [A standard for terminology in chronic pelvic pain syndromes: A report from the chronic pelvic pain working group of the international continence society](#). *Neurourol Urodyn*. 2016 Aug 26. doi: 10.1002/nau.23072. [Epub ahead of print].*

This new-style multidisciplinary standardisation document provides an overview of chronic pelvic pain syndromes together with known associated disorders. It systematically looks at the whole person and all organ systems in 9 domains: lower urinary tract, female genital, male genital, gastrointestinal, musculoskeletal, neurological aspects, psychological aspects, sexual aspects, and comorbidities. With regard to terminology and definitions, it notes that "Inappropriate and unclear coding and definitions have negative effects not only on diagnosis, but also on the patient's ability to obtain appropriate treatment, reimbursement, and social benefits". This is a welcome approach, particularly for IC/BPS/HSB patients, bearing in mind that many guidelines and standards have failed to take account of the wider impact on the patient of changes in both terminology and definitions.

INTERNATIONAL CONSULTATION ON INCONTINENCE (ICI) COMMITTEE 19: BLADDER PAIN SYNDROME

This year, the ICS annual meeting was combined with the 6th International Consultation on Incontinence (ICI). Over the last 12 years, the International Consultation on Incontinence (ICI), currently chaired by Professors Paul Abrams, Linda Cardozo, Alan Wein, and Adrian Wagg, has published international guidelines on the management of urinary and faecal incontinence for over 12 years. Committees are formed for specific chapters which are then presented in a book of

recommendations and guidelines. The committees that presented in Tokyo will each be contributing a chapter to the latest ICUD Incontinence book.

ICI Committee 19 on Bladder Pain Syndrome was chaired and presented by Philip Hanno, MD with committee members Paulo Dinis, MD, Jorgen Nordling, MD, Arndt van Ophoven, MD, Alex Lin, MD, Tomohiro Ueda, MD, Curtis Nickel, MD, Mauro Cervigni, MD.

It was clear that terminology continues to be as confused and confusing as ever with bladder pain syndrome, painful bladder syndrome, interstitial cystitis, hypersensitive bladder and a variety of terms for Hunner lesion currently being used in all possible combinations and often with differences in meaning. Professor Hanno noted that there was still unresolved dissonance between ICI nomenclature/definitions and the Asian nomenclature/definitions where pain as such is not a requirement for diagnosis and has been replaced by “hypersensitivity”. [However, it should be noted here that there is a trend by other organisations and societies towards following the example of the AUA in using the more patient-friendly IC/BPS which helps to ensure that patients have access to reimbursement of treatment and social security benefits. In some countries, using BPS alone has led to patients being denied this access.]

Prevalence figures are still unreliable and vary greatly around the world, depending on which diagnostic criteria they are based on. In some countries – including some European countries – it is classed as a rare disease, while in others considered fairly common. The percentage of patients diagnosed with Hunner lesion also varies hugely, but may depend on urologists’ experience in this respect, while there could potentially be regional variations. A further problem with prevalence figures is that Hunner lesion and non-lesion patients have often bundled together in earlier studies.

One of the big issues today is the question as to whether Hunner lesion should be removed from BPS and stand as a separate disease. This has been discussed for several years and was again raised in several IC/BPS presentations at ICS. While it seems that most people want to do this, nobody has as yet taken the definitive step. So the interesting question is going to be whether ICI Committee 19 will take this step.

There is virtually no change where treatment is concerned. Certainly nothing new here for the patients. The level of recommendation of specific treatments tends to change from year to year but whether these recommendations are very meaningful is questionable since much of the evidence comes from studies based on old criteria and included a mixed bag of patients who varied from study to study. Due to absence of reliable studies, many treatments which are commonly used and have proven to be successful in groups of patients receive relatively low levels of recommendation. Treatment is still trial and error and will continue to be so until we have better phenotyping or sub-classification. A flexible approach should be taken to guidelines.

All in all, it paints a somewhat depressing picture. Too little has changed in the last decades. Research directions outlined today were no different a decade ago. The question is: why not?

And this issue was raised during question time when Professor Christopher Payne (USA) proposed that the reason that we have made so little progress and have mostly grade C & D recommendations is that we've been doing it wrong for 40 years. “If we were starting over today”, he said, “we would never combine ulcerative interstitial cystitis with Bladder Pain Syndrome. Ulcerative interstitial cystitis is its own specific disease. If we separate it out and research it independently we can treat it successfully and maybe find a cure. Bladder Pain Syndrome is not a disease. It is a syndrome comprising a heterogeneous group of patients. We won't be able to make progress in Bladder Pain Syndrome until we start identifying and researching defined phenotypes”. This comment from Professor Payne really summed up the thoughts of many delegates. It is time for concrete action now and maybe we do need to start all over again.

However, not all is doom and gloom since we are seeing a welcome surge in research taking place in East Asia with a new generation of doctors and researchers, hopefully with a new, fresh vision and ready and willing to listen to the individual patients, because that is what is now urgently needed.

This presentation by Professor Hanno and Committee 19 can be read in detail when the new edition of Incontinence is published.

WORKSHOPS

Two ICS workshops were related to the field of IC/BPS/HSB.

W11 HOLISTIC APPROACH BY BIO-PSYCHO-SOCIAL MODEL TO PATIENTS WITH IC/BPS

Presented by: Ming-Huei Lee, MD (Chair), Christopher Payne, MD, Alex Teng-Lung Lin, MD, Yukio Homma, MD, Chiu-De Chiu, MD. Three patient speakers: Tomiko Shinozaki (Japan), Jane Meijlink (Netherlands), Yu-Chen Lan (Taiwan)

This workshop presented both East and West concepts of IC/BPS and hypersensitive bladder and included an interactive patient/physician forum in the second half with patient speakers from Japan, Taiwan and the Netherlands.

Dr Alex TL Lin emphasized the importance of multidisciplinary holistic care in a disease that may be accompanied by many comorbidities or non-bladder syndromes.

Discussing patient phenotyping (subtyping) in IC/BPS, Dr Christopher Payne once again emphasized that while Hunner lesion is a disease, BPS is a syndrome. Therefore, it is wrong to combine the two and they need to be approached in completely different ways. Dr Payne believes that BPS cannot be treated without making a more specific diagnosis, in other words: phenotyping (subtyping). He mentioned some common BPS phenotypes: bladder phenotype, myofascial phenotype, pudendal neuropathy phenotype, systemic pain phenotype. He suggested that care algorithms are too general for heterogeneous patient populations and that treatment must be individualized to the particular patient's disease.

This was reiterated by Professor Yukio Homma (Japan) who said "we should not treat the patients as a single entity because of similar symptoms". Professor Homma explained the East Asian Hypersensitive Bladder (HSB) concept in which HSB and non-lesion IC are hypersensitive bladder disorders while Hunner lesion IC is an immuno-inflammatory disease.

Dr Ming-Huei Lee from Taiwan told us about development and evaluation of an E-system for IC patients. Having looked at both text-based and video-based telecare, using the mobile phone as a tool, they found that the video-based approach outperformed the text-based approach in consolidating good lifestyle, improving quality of life and alleviating disease symptoms. The telecare system was found to be easy and relevant, and simple to use and understand by IC patients. They also found that the telecare system can enhance communication between patients and physicians outside the hospital itself. This work is backed up by the work of the Taiwanese patient support group TICA which also helps with the social aspect of care.

Psychological aspects were discussed by Dr Chiu-De Chiu from Hong Kong looking at IC as a functional somatic syndrome.

After the break, there was an interactive patient/physician forum with presentations by three patient/physician pairs: Professor Yukio Homma and Tomiko Shinozaki from Japan, Professor Christopher Payne (USA) and Jane Meijlink (Netherlands), Dr Ming-Huei Lee and Yu-Chen Lan from Taiwan.

We heard about the activities of the Japanese and Taiwanese patient organizations. They are very active and very enthusiastic, working hand in hand with health professionals in their countries.

Below left is a photo of the “Western” team: Professor Christopher Payne and IPBF chair Jane Meijlink and on the right a photo of the patient advocates attending this workshop from Italy, Netherlands, Japan and Taiwan.



W2 OVERACTIVE PELVIC FLOOR (Pelvic Pain Syndromes / Sexual Dysfunction)

Presented by: Anna Padoa (Chair), Melanie Morin, Mauro Cervigni, Marc Beer Gabel

The purpose of this workshop was to understand the definition, pathophysiology and clinical presentation of an overactive pelvic floor and its relation to chronic pain conditions and psychosocial issues. It included a presentation on Bladder Pain Syndromes, chronic pelvic pain, voiding dysfunction and overactive pelvic floor by Professor Mauro Cervigni from Italy. He also underlined the need for change, quoting Albert Einstein: “let’s not pretend that things will change if we keep doing the same things”.

ROUND TABLE:

INTERSTITIAL CYSTITIS REVISITED (LOCAL VS SYSTEMIC PATHOPHYSIOLOGY)

Hann-Chorng Kuo (chair), Philip Hanno, Yukio Homma, Lori Birder

Can epidemiology and individual history help us understand BPS? A close look at Phenotyping.

Professor Philip Hanno (USA), discussing phenotyping, said that regardless of what we call this disease or how we define it, phenotyping may hold the key to improving treatment outcomes and facilitating research. The only proven phenotype in 2016, he said, is the Hunner lesion, which defined the disease 100 years ago. He noted that there are few if any documented examples of a non-Hunner lesion patient assuming this phenotype. Pathology and visual appearance is virtually diagnostic. The patient population seems to be different from non-Hunner patients. Response to fulguration, excision, steroid injection, cyclosporine is characteristic.

What should a phenotype do? Professor Hanno is of the opinion that early adoption of unproven phenotypes in a clinical setting does us no favours. Proving the utility of a phenotype is a critical step.

The term “Phenotype” refers to the observable physical properties of an organism: including the organism’s appearance, development and behaviour. To be useful when referring to a disease, it could improve diagnosis, prognosis. Therapy selection, prevention, pharmaceutical research and suggest new treatment pathways. For a symptomatic syndrome, a phenotype could ultimately prove to be a self-contained disease.

The speaker put forward his own suggestions for some potential, possibly useful phenotypes of BPS:

- Hunner lesion: most likely the original interstitial cystitis and a separate, easily identifiable disease, localized to the bladder but subject to central sensitization if not adequately treated; responsive to analgesic therapies as well as lesion-directed therapy.
- Absence of bladder inflammation, localized symptoms, no associated disease...
- Absence of bladder inflammation, diffuse symptoms, but with non-bladder syndromes (associated disorders or “comorbidities”)...
- Chronic non-localized bladder inflammation...
- Natural history: progressive symptomatology...
- Natural history: stable or improving over time...
- Bladder capacity under anaesthesia...

Professor Hanno suggested that an international patient registry might be able to help us find answers.

Pathology Revisited; Hunner Type IC Is a Distinct Inflammatory Disease with Clonal B-Cells Expansion.

Professor Yukio Homma (Japan) took a brief look at the confusing multitude of different names but concentrated on the East Asian concept in which Japan, Taiwan and Korea participate. He is particularly concerned about the inconsistencies in the definition.

A new term from East Asia is mucosal bleeding after distension (MBAD) instead of the term glomerulations. Since nobody knows what causes this or what it means, they are carefully recording which patients develop this on distension.

Looking at pathology of the bladder, Professor Homma explained that Hunner IC features inflammation (possibly with a specific immune response) and sensory hyperactivity. Non-Hunner IC has no inflammation but it does have sensory hyperactivity.

The clinical implication is that:

- Hunner IC is an immuno-inflammatory disorder
- Both Hunner IC and non-Hunner IC present with bladder hypersensitivity.

(Note: Hypersensitive bladder symptoms consist of either pain or pressure or discomfort in the bladder usually with urinary frequency day and night and an urgent need to void)

Useful reference:

Homma Y, Ueda T, Tomoe H, Lin AT, Kuo HC, Lee MH, Oh SJ, Kim JC, Lee KS. Clinical Guidelines for Interstitial Cystitis and Hypersensitive Bladder updated in 2015. Int J Urol. 2016 Jul;23(7):542-9. doi: 10.1111/iju.13118. Epub 2016 May 24. PMID: 27218442

How Do Findings in IC/BPS Animal Models Provide Insight into The Human Condition?

Professor Lori Birder (USA) emphasized that diagnosis of most bladder disorders is symptom based, while their pathophysiology remains controversial and incompletely understood. Chronic pain in humans is not constant and is a complex experience rather than a reflex response to an acute stimulus. Animals can be used to test hypotheses covering etiology, pathophysiology, natural history and therapy for the disease.

Challenges and needs today include:

- A need to identify major pain mechanisms and targets that participate in producing clinical symptoms (consider additional factors – gender/age)

- Few if any agents tested in induced models of chronic abdominal and pelvic pain syndromes have been translated into effective clinical therapies
- Therefore, reverse translational approaches may be a better strategy rather than relying solely on the traditional approach of predicting human efficacy from limited rodent models.

A SELECTION OF RESEARCH PRESENTATIONS AND E-POSTERS

Abstract 23

INCREASED MRNA EXPRESSION OF CONNEXINS AND TRANSIENT RECEPTOR POTENTIAL CHANNELS IN THE UROTHELIUM OF PATIENTS WITH INTERSTITIAL CYSTITIS: POSSIBLE BIOMARKERS

Mitsui T, Tsuchiya S, Sawada N, Ihara T, Kira S, Miyamoto T, Nakagomi H, Takeda M

Signal transmission of sensation in the bladder of IC patients could be changed through the increase of Cxs and TRPs in the urothelium. Further investigations of connexions and TRPs in the urothelium have a potential to develop new biomarkers to diagnose IC and effective therapeutic interventions for IC patients.

Abstract 25

TRANSIENT RECEPTOR POTENTIAL C1 AND C4 IN INTERSTITIAL CYSTITIS - IMMUNOHISTOCHEMICAL ANALYSIS OF THE BLADDER TISSUE

Nomiya A, Niimi A, Akiyama Y, Fujimura T, Hukuhara H, Enomoto Y, Igawa Y, Homma Y.

The results of this study support the hypothesis that TRPC1 and TRPC4 have some role in the pathogenesis of IC. Further research is required to elucidate the function of TRPC1 and TRPC4 in the bladder mucosa in connection with pathogenesis of IC.

Abstract 26

EXPRESSION AND LOCALISATION OF CONNEXINS 43 AND 45 AND THEIR INVOLVEMENT IN MEDIATING ATP RELEASE IN PORCINE BLADDER

Sana-Ur-Rehman H, Mansfield K, Moalem-Taylor G, Moore K H, Liu L.

The authors report for the first time that Cx43 and Cx45 are ATP release channels in response to physiological stretch in the bladder. This indicates that these channels are among several other channels, such as pannexin-1, that release ATP to initiate autocrine/paracrine signalling in response to bladder distension during the storage phase of micturition reflex. Cx43 channels are implicated in the initiation of inflammation through the activation of purinergic signalling pathways. Randomised clinical trials have shown that the application of Cx43 mimetic peptide gel reduces inflammation and accelerates wound healing in conditions such as chronic diabetic foot ulcers, and acute corneal wounds. Thus, Cx43 and Cx45 mimetic peptides may have the potential for the treatment of interstitial cystitis and other inflammatory bladder diseases.

Abstract 27

GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR IS RELEASED BY MOUSE BLADDER UROTHELIAL CELLS IN RESPONSE TO LIPOPOLYSACCHARIDES (LPS)

Li Y, Lu M, Alvarez Lugo L, Chen G, Chai T.

This is the first description of mouse bladder urothelial cells expressing GM-CSF as an early response to LPS. GM-CSF may be a potential regulator for mucosal signalling and bladder function.

Abstract 28

UROTHELIAL DYSFUNCTION AND SENSORY PROTEIN EXPRESSIONS IN PATIENTS WITH UROLOGICAL OR SYSTEMIC DISEASES AND HYPERSENSITIVE BLADDER

Ong H, Wu S, Jiang Y, Lin J, Kuo H.

In this study from Taiwan, patients with OAB or HSB showed increased urothelial inflammation and lower barrier protein expression. Increased M3/ β 3-AR or M2/ β 3-AR in the urothelium was associated

with OAB, whereas decreased M3/ β 3-AR or M2/ β 3-AR was associated with poor voiding efficiency and large PVR in LUTD.

Abstract 30

ROLE OF 5-HYDROXYTRYPTAMINE IN URINARY BLADDER AFFERENT SIGNALLING

Konthapakdee N, Daly D, Chapple C, Grundy D.

5-HT receptors have a modulatory action on peripheral bladder afferents. These mechanisms may underlie the hypersensitivity associated with a number of urological disorders. In addition, this is the first study to show that blocking 5-HT reuptake with citalopram, an anti-depressant, also peripherally affects bladder afferent function. Further studies are required to investigate the mechanisms involved.

Abstract 51

MULTIDISCIPLINARY SELF-MANAGEMENT TELECARE SYSTEM MAY IMPROVE QUALITY OF LIFE IN PATIENTS WITH INTERSTITIAL CYSTITIS / BLADDER PAIN SYNDROME (IC/BPS) – A RANDOMIZED CONTROLLED TRIAL

Lee M H, Wu H C, Chen W C, Chen Y F.

Changing lifestyle by health education is promising in improving the health status of the patients. The better effectiveness of video-based intervention suggests that patient's trust in physician or better physician-patient relationship can induce the reinforcing effect on preventing disease recurrence and improving QOL for BPS/IC patients. The intervention of video-based health education is effective in improving the QOL for BPS/IC patients. Moreover, video-based intervention outperformed the text-based intervention in consolidating good lifestyle, improving QOL, and alleviating disease symptoms.

Abstract 157

TRANSIENT RECEPTOR POTENTIAL MELASTATIN 2 (TRPM2) MEDIATES LIPOPOLYSACCHARIDE (LPS)-INDUCED INFLAMMATORY BLADDER PAIN AND FREQUENT VOIDING IN MICE

Kamei J, Aizawa N, Nakagawa T, Akiyama Y, Kaneko S, Homma Y, Igawa Y.

Intravesical instillation of LPS caused inflammatory bladder pain and frequent voiding in WT mice, but such changes were obscured in TRPM2-KO mice, suggesting that TRPM2 contributes to an inflammatory nociception in the mouse bladder.

Abstract 199

GAP JUNCTION REGULATES DETRUSOR ACTIVITY IN BLADDER INFLAMMATION.

Okinami T, Imamura M, Nishikawa N, Negoro H, Sugino Y, Yoshimura K, Kanematsu A, Hashitani H, Ogawa O.

Gap junction in the bladder might be an alternative therapeutic target for storage symptoms in bladder inflammation.

Abstract 237

THE RISKS OF INTERSTITIAL CYSTITIS AMONG PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS: A POPULATION-BASED COHORT STUDY

Wen J, Ho C, Wu M.

This concerned a population-based cohort study investigating the incidence of IC among patients with SLE in Taiwan. The authors note that to the best of their knowledge this is the first population-based cohort study investigating the incidence of IC among patient with SLE. Their result demonstrated a significantly higher risk of IC among patients with SLE than the general population and supported the postulation of interstitial cystitis being a disease originating from an autoimmune disorder.

Abstract 238

2016 COCHRANE REVIEW: INTRAVESICAL TREATMENTS FOR BLADDER PAIN SYNDROME/ INTERSTITIAL CYSTITIS

Ford A, Ballard P, Ramage C, Ogah J.

This most comprehensive and up-to-date review of RCT evidence of intravesical treatments for BPS shows that the evidence for their efficacy compared with placebo is at best guarded. There are few RCTs addressing this problem of which many have small sample sizes, moderate risk of bias, and poor outcome reporting. There are a large variety of both single agent and combination agent intravesical treatments in use and there needs to be adequate assessment through large clinical trials with high methodological quality addressing appropriate patient reported outcomes.

Abstract 243

INFLAMMATORY INFILTRATES SPECIFIC TO HUNNER TYPE INTERSTITIAL CYSTITIS

Akiyama Y, Maeda D, Niimi A, Nomiya A, Igawa Y, Fukayama M, Homma Y.

Historically mast cell infiltration has been recognized as a histological feature specific to HIC, but sceptical views toward the mastocytosis in IC have been recently reported. The authors concluded from this study that infiltration of inflammatory cells but not mast cells may be a feature of Hunner IC.

Abstract 269

AN ONCOLOGIC APPROACH TO ULCERATIVE INTERSTITIAL CYSTITIS: DEFINING COMPLETE REMISSION
Payne C.

Differential expression of chemokines in IC/BPS and CBC patients suggests that different chronic bladder inflammatory mechanisms are involved in two disease conditions. An increase in CXCL10 and a decrease in IL-1Ra may pathophysiologically be important for the development of IC/BPS with HL.

Abstract 272

EVALUATION OF A NOVEL PRECLINICAL MODEL FOR BLADDER BARRIER EVALUATION USING WHOLE PORCINE BLADDERS

Janssen DAW, Schalken JA, Heesakkers J.

This study shows that it is feasible to create a standardized preclinical model for the investigation of bladder barrier properties that is and very biocompatible with the human bladder, but does not have high cost or makes use of laboratory animals.

Abstract 554

ELECTRON MICROSCOPIC STUDY IN THE UROTHELIUM OF INTERSTITIAL CYSTITIS AND KETAMINE RELATED CYSTITIS

Jhang J, Wu S, Ong H, Kuo H.

The urothelium ultrastructure of KC and IC/BPS bladder were abnormal. The urothelium of KC was almost totally destroyed, and the submucosa collagen was exposed. The urothelium maturation and differentiation had disappeared in IC/BPS bladder, and it might result urothelial dysfunction in the patients.

Abstract 555

NARROW BAND IMAGING (NBI)-ASSISTED CYSTOSCOPIC EVALUATION OF NONHUNNER LESIONS OF INTERSTITIAL CYSTITIS/BLADDER PAIN SYNDROME (IC/BPS) IN 430 CASES.

Ueda T, Sengiku A, Ueda M, Yoshimura N.

By using the NBI system, the authors detected not only Hunner lesions, but also non-Hunner lesions that are characterized by spotty, neovascular mucosal lesions without bladder distension in the majority of IC/BPS patients who were diagnosed based on their symptoms (413 [191 Hunner+222 non-Hunner] out of 430 patients; 96%). The hypervascular, overstretched condition of the bladder mucosa and non-Hunner lesions with or without Hunner lesions found in the majority of IC/BPS patients may indicate that these patients have a hypersensitive condition of the bladder underlying IC/BPS symptoms. Thus, NBI-assisted cystoscopy under local anaesthesia would be useful to identify the

bladder-specific pathology for the tailored treatments such as bladder-targeting intravesical therapy for cases with non-Hunner lesions only or Hunner lesion-targeting fulguration therapy in IC/BPS.

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