

A REVIEW OF THE NIDDK INTERNATIONAL SYMPOSIUM 16-17 June 2008, Bethesda MD, USA DEFINING THE UROLOGIC CHRONIC PELVIC PAIN SYNDROMES – A NEW BEGINNING

The international symposium, “Defining the Urologic Chronic Pelvic Pain Syndromes - A new beginning”, organized by the National Institute of Diabetes and Kidney Diseases (NIDDK), was held 16-17 June 2008 at the Doubletree Hotel, Bethesda, USA.

Bearing in mind that a full report will be published by the NIDDK in the autumn, we will suffice here with simply highlighting a few interesting points and speakers and endeavour to explain the background to this symposium and its purpose.

Background

In the past two decades, much research has been carried out into interstitial cystitis and chronic prostatitis but has so far failed to lead to any real understanding of the pathophysiology and – most importantly for the patients – has failed to achieve any breakthrough in the field of treatment, let alone cure. It was felt by the NIH/NIDDK that a new approach was necessary. This symposium in Bethesda was a follow-up to:

1. A meeting of multidisciplinary advisory experts in the summer of 2007 to review the progress that has been made in understanding the pathophysiology and effective treatment and prevention of the major urologic chronic pelvic pain disorders: interstitial cystitis (IC) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). This panel concluded that there has been recent epidemiological evidence to suggest that these urological disorders occur simultaneously with other, non-urological, symptom-based chronic pain syndromes. These findings suggest that the initial NIDDK research definitions of IC and CP/CPPS need to be re-evaluated in the light of these findings.
2. A small round-table workshop meeting held in Baltimore in December 2007 comprising the above advisory panel plus an international consultation panel together with a small number of interested parties, including patient advocates.

It was concluded that future research studies need to be carried out that will:

- incorporate the basic diagnostic symptoms of the significant concurrent co-morbid disorders into the urologic diagnostic protocols;
- explore in more detail the relationship between these co-existing disorders; and
- develop diagnostic protocols that will allow disease identification by the generalist physician and not limit it to an organ-specific disease.

The international symposium held in June was an outcome of that round-table workshop and together these meetings formed a prelude to the NIH/NIDDK-funded holistic Multidisciplinary Approach to the Study of Pelvic Pain (MAPP) multicentre project which is currently at the starting blocks. This international symposium was

also the final brainstorming session before the NIDDK produces a draft definition for IC/PBS for research purposes.

Advisory Panel:

Members of the multidisciplinary advisory panel included: Drs Andrew Avins, Dedra Buchwald, Daniel Clauw, Philip Hanno, Michael Pezzone, Michel Pontari and Ursula Wesselman. The purpose of this panel was to discuss, delineate and ascertain all the issues related to understanding the chronic urologic pelvic pain syndromes using a holistic, systematic approach.

Multidisciplinary, multi-stakeholder attendance

The NIDDK symposium in Bethesda was attended by around 140 delegates from the USA and abroad. This included experts in urology, gastroenterology, internal medicine, rheumatology, epidemiology, behavioural science, anaesthesiology, pathophysiology, nursing as well as representatives from research centres, health organizations, the pharmaceutical industry and the patient world.

Patients and their representatives made welcome

Patients and their representatives from patient organizations in the field of IC and related disorders were made very welcome at this international meeting. The IPBF was represented by IPBF chairman Jane Meijlink from the Netherlands and co-board member Florentina Ferreyra, president of the Mexican IC support group. Also present were a number of patient advocates from the American ICA including Executive Director Barbara Gordon, Juergen Hensen CEO from ICA-Deutschland, Loredana Nasta from the Italian AICI, Mike Hennefent from the Prostatitis Foundation, Christin Veasley from the National Vulvodynia Association, Rae Marie Gleason from the National Fibromyalgia Association and others.

Dramas beyond our control!

Some unfortunate delegates on domestic flights alas never made it to Bethesda due to severe storms over several regions of the United States that prevented planes from taking off and landing, with many international planes being diverted from Washington to other airports. And as if that wasn't enough, just as we were preparing to start early in the morning on the first day, there was yet another drama when the hotel fire alarm went off and we all had to make our way outside down many flights of stairs. Fortunately it was a minor incident and the hotel did not burn down!

Introduction by the NIDDK

The very full schedule on the first day (from 8 am to 7 pm!) opened with a welcome by Dr Robert Star and an explanation of the purpose of the meeting by Dr Leroy Nyberg, both from the NIDDK. They explained that the meeting would include keynote speakers (with no discussion), speakers providing information on specific fields, expert panel discussion, a patient advocacy panel discussion and interactive brainstorming discussions with the audience. It would focus on re-characterizing the two main urologic chronic pelvic pain syndromes: chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) and interstitial cystitis (IC). This recharacterization will be utilized in future research studies to better define the clinical and other characteristics (phenotype) of patients suffering from these syndromes. The meeting would also examine the relationships and common factors between these disorders and

concomitant disorders and between the urologic pelvic pain syndromes and other chronic pelvic pain syndromes.

The meeting would provide a basis for the NIDDK to draw up a new research definition for interstitial cystitis and chronic prostatitis to enable the diseases to go forward. It was not the intention to discuss the controversial issue of nomenclature here – although several speakers did nevertheless take advantage of the occasion to push their preferred new terminology!

Brief review of selected speakers

First speaker of the day, Andrew Baranowski MD, pain consultant from the United Kingdom, spoke on the topic of “Redefining the Chronic Urologic Pelvic Pain Syndromes – is ‘phenotyping’ possible?” and presented the points of view of the European Society for the Study of IC/PBS (ESSIC) and the International Association for the Study of Pain (IASP). His first comment was that he would personally prefer to change the term ‘phenotyping’ in the title to ‘classification’. He gave the following explanation of his view of a pelvic pain classification system:

Phenotype: define the condition

Terminology: the words we use

Taxonomy: place the condition in relation to other conditions, create order

Classification: the combination of the above.

Concerning the question as to what we are trying to achieve by classification, he remarked that the aim was to achieve appropriate (best) assessment and management of the condition in its own right and of the patient as a whole.

Classification, he said, should serve as a basis for research while at the same time being usable by all parties: clinicians, researchers, patients, support groups and medical reimbursement agencies.

Where the patient representatives were concerned, the sensitive presentation on “The Perception of Chronic Pelvic Pain” by Alex Lin, MD, urologist from the National Yang Ming University in Taiwan, was undoubtedly one of the highlights of the symposium. Concerning the question “What is pain?” he explained that this may greatly differ in different cultures, different parts of the world and in different individual patients. Regarding whether the word “Pain” is required to diagnose IC/PBS, Dr Lin noted that it is not required in Taiwan, Japan and Korea nor was it an essential requirement in the NIDDK criteria.

While somatic pain is easier for a patient to communicate, bladder (visceral, organ) pain can be hard to describe. Patients may use a wide variety of words to describe the “pain” as they experience it. The same sensation may be described in different words by different individuals. In a Taiwanese study on pain in IC/PBS, data based on 316 patients indicated that 80% have pain while 20% have discomfort (not experienced as pain). The pain was described by patients in this study as: fullness/distension 54%, soreness 32%, sharp 22%, stabbing 21%, spasm 11%, dull 8%. The question regarding pain location in the Taiwanese study produced the following variations: low mid-abdomen 52%, suprapubic 23%, vagina 22%, left low abdomen 14%, right low abdomen 12%, left flank 11%, right flank area 10%, inguinal 9%, low back 8%.

The study of 316 patients showed that the duration of frequency and urgency symptoms (62 months) was significantly longer than that of the pain symptom (46 months). It was concluded from this Taiwanese study that patients may first experience urinary frequency only while pain may be a later presentation in IC/PBS.

Dr Lin discussed a number of cases of male patients with lower urinary tract symptoms and pain in different locations, asking the question: do these patients have IC/PBS or chronic prostatitis or do they have both? This was a question that cropped up time and time again during this symposium in connection with male patients.

On the subject of urgency versus pain: Dr Lin suggested that the sequence of the occurrence of pain or urgency in a micturition cycle might vary among patients and asked whether this could be a question of different neurotransmitters being involved or a different pathogenesis.

He emphasized the importance of assessing the negative psychological impact of pelvic pain and stressed that taking aspects such as depression and anxiety into account is particularly important in multi-disciplinary care.

In summary, he noted that there is a great variation in the characteristics of the symptom of pain. Whether such variations represent different subtypes of disease or are simply a reflection of an individual subjective feeling with the same pathological origin remains to be determined.

Dr J. Quentin Clemens, speaking on the topic of (My) Perceptions of Urologic Pelvic Pain, explained that afferent neurourology refers to the processing of sensory information in the genitourinary tract and in the female patient excludes gynaecologic organs. Abnormal processing of sensory information in the genitourinary tract results in distressing symptoms, as a consequence of which the patient is likely to seek help. Afferent neurourology disorders, he said, include IC/PBS/BPS (bladder pain/pressure/discomfort), CP/CPPS (penile pain, perineal pain, ejaculatory pain), OAB (urgency) and orchalgia/chronic epididymitis (distinct from CP/CPPS). Patients may manifest symptoms from more than one of these disorders. Afferent neurourology does not include: vulvodynia, nonspecific female pelvic pain, endometriosis, dyspareunia. These could be included in a broader term: Afferent pelvic disorders. He noted that afferent urologic symptoms should be viewed in the context of other urologic symptoms and disorders that may also be present. Afferent urologic symptoms/disorders are common. These symptoms have similar patterns in men and women. Afferent urologic disorders may be part of a systemic disease complex (to be further studied by the NIDDK MAPP Network). He concluded that while we appropriately focus on those with severe and refractory symptoms, study of the entire disease spectrum may provide additional insight into pathogenesis and prevention.

The presentations on chronic pelvic pain by Drs Alex Lin and J. Quentin Clemens led to a discussion as to whether the perception of chronic pelvic pain is organ- and gender-specific and would any questionnaire need to be gender-specific due to both anatomical differences and potential differences between men and women in the perception of pain.

Dr Anthony Schaeffer spoke on Current Concepts and Etiology in the Treatment of Chronic Prostatitis/Chronic Pelvic Pain Syndrome. Most men with prostatitis fall under this heading. CPPS is associated with a greatly reduced quality of life similar to or greater than angina, congestive heart failure, Crohn's disease or diabetes mellitus. It is also associated with infertility. There are no issued guidelines for the management of either chronic bacterial prostatitis or CPPS.

Stress and the Bladder was the topic address by Dr Tony Buffington, paying specific attention to the Stress Response System (SRS). He explained that there are different types of stressor. They may be External (physical or environmental) or Internal (thoughts, feelings) and they may be acute or chronic. Quoting Bruce McEwen (*McEwen BS. Physiology and Neurobiology of Stress and Adaptation: Central Role of the Brain. Physiol Rev 87: 873–904, 2007; doi:10.1152/physrev.00041.2006.*), he noted: “The brain is the key organ of the response to stress because it determines what is threatening and, therefore, potentially stressful, as well as the physiological and behavioural responses which can be either adaptive or damaging.” Dr Buffington also discussed the paper by Walach & Jonas from Germany (*Walach H, Jonas WB. Placebo Research: The Evidence Base for Harnessing Self-Healing Capacities. J Altern Complement Med. 2004;10 Suppl 1:S103-12*) which argues that research involving placebo provides critical information regarding how the mind, body and culture heal. The speaker explained that establishing rapport with the patient, touching the patient, being clear, credible and confident about diagnosis and prognosis, helping the patient to understand what to expect, offering only treatments that both the doctor and patient fully believe in, creating realistic expectations from unhealthy or abnormal expectations and individualizing treatment for each patient can be the pathway to success. He summarized by saying that the SRS can affect the bladder, IC may be an “allostatic” illness and that developmental issues may play a role through epigenetics. This view opens additional avenues for basic and clinical research.

Dr Ragi Doggweiler, speaking on the Mind-Body Connection, quoted Plato (Charmides or Temperance, 380 BC):

“...that as you ought not to attempt to cure the eyes without the head, or the head without the body, so neither ought you to attempt to cure the body without the soul; and this is the reason why the cure of many diseases is unknown to the physicians of Hellas, because they are ignorant of the whole, which ought to be studied also; for the part can never be well unless the whole is well.... For this is the great error of our day in the treatment of the human body, that physicians separate the soul from the body.”

The possible relationship between stress and disease was a theme reflected in a number of presentations at this symposium. Dr Doggweiler noted that roughly 80% of all doctor’s office visits are related to stress and that current research indicates that between 70-80% of all health-related problems are either precipitated or exacerbated by emotional stress. On the dynamics between stress and disease, she explained that to understand the relationship between stress and disease, one needs to understand that several factors act in unison to create a pathological outcome, including: cognitive perceptions of threatening stimuli, activation of the sympathetic nervous system, engagement of the endocrine system and of the immune system. Giving an example of a stress situation, she described how the heart pumps harder, the sweat glands increase activity, the stomach starts to feel queasy: is this a mental or a physical phenomenon?

In relation to PsychoNeuroImmunology, there are many questions, said Dr Doggweiler: do psychological events have an effect on the immune system? If so, how, and are those effects relevant to health? Do those effects lend themselves to

interventions? Is there evidence for associations between stress, immune system functioning and risks for disease?

Dr Doggweiler also discussed the physical, emotional, cognitive, behavioural and spiritual signs of stress and how these are expressed in everyday life of people. What is beneficial for the immune system? According to the speaker this includes music, laughter, group support, counselling, writing and talking.

Dr Michel Pontari's presentation on: Common Features and Dissimilarities of Urologic and Other Chronic Pain Syndromes: CP/CPD gave an update on CP/CPDS, comparing demographics, and raising the question: does CP/CPDS have a common pathophysiology with other syndromes. He concluded that compared to other pain syndromes CP is similar in many aspects of demographics and associated medical conditions. There appears to be a similar overactivity of the sympathetic nervous system and there may be a different pattern of cortisol response.

Vulvodynia was discussed by Dr Robert Moldwin, including associated disorders with a special look at vulvodynia and interstitial cystitis. While its etiology is still unclear, vulvodynia may affect up to 6 million women, pathology is found at end organ and possibly systemic and genetic levels, like IC there are multiple associated disorders. Multimodal care is recommended.

Dr Niloofar Afari discussed the Review of the Evidence for Overlap between Chronic Pelvic Pain Syndromes and Other Unexplained Clinical conditions, a data review study she carried out together with Dr Maria Bullones and Dr Dedra Buchwald. She noted that many of these disorders share features such as fatigue and pain and asked whether these conditions could be different manifestations of the same underlying pathophysiological processes. Future directions should include collaborative research on systemic conditions, i.e. not organ-based, established research diagnostic criteria, large, rigorously-designed and well-controlled studies, longitudinal studies to examine temporal onset and risk of developing more than one condition.

Dr Philip Hanno gave an update on recent meetings and looked at the status of international consensus on definitions and symptoms. He specifically discussed the NIH perspective, the definition and perception of pain, frequency and urgency perceptions, the relationship between OAB and IC, IC and CP in male patients, diagnosis, and finally agreement, disagreement and conclusions.

Dr Curtis Nickel from Canada presented the results of a potentially valuable international pilot study on phenotypic associations between interstitial cystitis/painful bladder syndrome (IC/PBS) and irritable bowel syndrome (IBS), fibromyalgia (FM) and chronic fatigue syndrome (CFS) with 11 participating centres in the USA, Canada, Denmark and India. This pilot study was designed to determine the feasibility of examining the relationship, common symptomatology and psychosocial parameters between IC/PBS and three related conditions: IBS, FM and CFS. The study focuses on 4 broad domains: demographics, symptoms, suffering/coping, behavioural/social factors. This was an excellent example of how to conduct an international study on a shoestring.

Patient Advocacy Panel Session

The NIDDK had also arranged a patient advocacy panel session moderated by Wayne Shields, Association of Reproductive Health Professionals with Barbara Gordon (Interstitial Cystitis Association), Christin Veasley (National Vulvodynia Association), Jane Meijlink (International Painful Bladder Foundation), Rae Marie Gleason from the National Fibromyalgia Association and Mike Hennefent from the Prostatitis Foundation.

Key messages from the patient panel:

- In the end our work as researchers, educators, providers and patient advocates is about helping the patient to feel better.
- The advocacy community is a key partner to the research community and helps facilitate research: we all have important work to do together. The patient organizations are a potential mine of information – cooperation in research projects can make good use of this.
- It is essential to provide education for multiple disciplines and specialities. It is not enough to simply raise awareness in the urology world. While more awareness of associated disorders has to be created among urologists, awareness of IC has to be raised among specialists working in the field of associated disorders. We also have to ensure that those participating in multidisciplinary teams have more than just a superficial acquaintance with IC.
- Research and decision-making should take account of the different social, medical and ethnic cultures around the world. Many people – doctors and patient advocates – are unable to attend international meetings due to lack of money. Consequently their voice is seldom heard and if heard is seldom taken into account.

Photo:
Patient Advocacy
Panel Session



Meeting Summary

As mentioned in the NIDDK symposium programme, a general statement will be compiled by the Advisory Panel and following review by the International Consultation Panel will be issued as a summary of this symposium.

This document will:

- 1) Describe current knowledge about the relationship between the urologic chronic pelvic pain syndromes and other chronic pain syndromes, including irritable bowel syndrome, chronic fatigue syndrome, fibromyalgia and other related disorders.
- 2) Recommend the type of clinical, demographic and other patient-oriented information to be collected in research studies to better characterize patients with urologic chronic pelvic pain syndromes and to advance our understanding of the etiology, risk factors, and distribution of these syndromes and their relationship with other chronic pain syndromes.
- 3) Develop a format for phenotyping the urologic chronic pelvic pain disorders that incorporates the symptoms and other relevant criteria of the major co-morbid disorders.
- 4) Propose a new “working definition” of urologic chronic pelvic pain syndromes broad enough to be utilized in a wide range of future research studies. New detailed definitions of the organ-specific urological diseases would not be developed at this symposium. That is the responsibility of organ-specific clinical definition groups. The outcomes of those groups will be incorporated into these overall definitions when necessary.

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