Interstitial Cystitis - Current Concepts and Controversies

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Objectives

• To review some of the current concepts in Interstitial cystitis
• To discuss some interesting controversies regarding this condition
• To review some current research ideas in I.C.
• To understand the need for a multidisciplinary center for pelvic pain syndromes
• Future Prospects MAPP
Historical Overview

- 1808- Philip Physick- bladder ulcers
- 1836-Joseph Parish-Tic Doloureux of bladder/stone
- 1839- Louis Mercier- ulcer perforation
- 1887-Alex Skene-mucosal lesions-IC
- 1907-M. Nitze-IC condition
- 1914- Guy Hunner-Bladder ulcers
- 1949- John Hand-clpnical series-223 pts-204 female
- 1970-K. J. Oravisto-uncommon condition
- 1978- Messing and Stamey-ulcer vrs non ulcer
- 1980- Larrian Gillespie and Pamela Sue Martin
- 1981- L. Parsons-GAG-layer

- 1984- Vicki Rattner ICA
- 1987-NIDDK
- 2006- Essic
- 2008-NIDDK-MAPP
Definition of IC

- Multiple definitions over the years
- Historical review-skene and Nitze
- 2002-ICS-PBS
- Disease {local or systemic} vrs syndrome
- IC is a clinical condition associated with frequency, urgency, pain and suprapubic discomfort in the absence of UTI or other pathology
- No specific marker test or pathognomonic finding
- Clinical Dx based on Hx, PE and urinalysis

Nomenclature and Terminology

- I.C
- P.B.S
- B.P.S
- H.B.S
- Urethral syndrome
- Interstitial cystitis syndrome
- Pelvic pain syndrome
- IC/PBS
- Hypersensitive Bladder syndrome – east Asian Society
- NIH/NIDDK-1998
- PBS -2002
- Female hysteria-Historical
- Multiple Terminologies-CONFUSION
- Need for clarification of terminology and classification
Clinical Phenotyping and IC

2009-D.Shoskes and C.Nickel
UPOINT-classify IC with relevant domains
Snowflake hypothesis-M. Pontari June 2008 NIH Pelvic pain workshop
Urinary-100%
Psychosocial-34%
Organ specific-96%
Infection-37%
Neurological/Systemic-45%
Tenderness-48%
TNM Classification
Direction of multimodal therapy and outcome improvement
NIH and MAPP

NIIDDK{1997}

- Research trials recruitment
- Criteria for diagnosis and to compare research patients
- ICDB-424 patients
- Controversy too restrictive-60% would not have disease
- NIH-NIDDK-2008
- Multidisciplinary panel of experts
- Recent epidemiological evidence – GU pain disorders occur simultaneously with other non GU chronic pain syndromes
- Research definitions of IC/PBS and CP/CPPS need to be re-evaluated
- New aspects of chronic pain
- Mapp
Prevalence of IC

- Very rare
- Uncommon
- Hunner ulcer
- Hunner patch
- Atypical ulcer
- 1997-300,000 - USA
- 2009-Rice-up to 6% USA {18,000,000}
- 25-30% women at some time have pelvic pain

Etiology and Pathogenesis

- Infection
- Leaky urothelium and GAG layer deficiency
- Mast cell activation
- Immunologic mechanisms
- Neurogenic inflammation
- Consolidating theories - Campbell-Walsh
Neural upregulation in IC

- 1949-J. Hand – neurogenic Inflammation
- 1993-Substance p and c-fibres
- 1999-nerve growth factor and chronic pain
- 2002-M. Saban-gene upregulation
- 2007-G. Sant-mast cell activation
- Upregulation- multiple agents
- Neural upregulation and symptoms of IC
- Chronicity of symptoms

Neurogenic Inflammation

- 1997-A. Elbadawi
- Pathological evaluation
- Multifactorial pathogenesis
- C-fibres
- Substance P, neurokinin, calcitonin gene related peptide-mast cell activation-epithelial cell permeability and injury and release of potent mediators
- Neuropeptide release from sensory nerve stimulation
- Activation of mast cells and mediator release
- Vasoactive effect-leukocyte adhesion-tissue edema = neurogenic inflammation
- Neuropregulation and neurogenic inflammation
- IC
- Urothelial injury and gag layer def and leaky urothelium secondary
- Neurogenic inflammation found in IBS and other chronic pain conditions
Mechanisms of chronic Pain

- Pelvic pain syndromes
- Allan Basbaum PHD
- Neuropathic and inflammatin-neurogenic inflammation-tissue injury
- Hyperalgesia and alldynia- heightened sensitivity –sensitization
- Molecular and structural changes in nerve cells-generate pain signals in absence of envirn input
- Activation c- fibers
- Receptor activation
- Rewiring of nerve connections
- K channel deactivation
- Central sensitivation
- Neuroupregulation
- Chronic pain
- William Steers-2001-common neurological mechanisms assoc with chronic pain
- Neuropathic and nerve growth factor
- Inflammatory

Pelvic Pain Syndromes

- GYN
- GU
- GI
- Overlap Between Syndromes-K Whitmore 2009
- Dorsal horn neuron activation –substance P release of histamine nitric oxide and neurogenic inflammation
- High tone pelvic floor muscle dysfunction
- A. Bernstein - PFM dysfunction - chronic pain
Muscular Abnormality

• A.Bernstein 1991
• IC symptoms
• Pelvic floor muscle abnormality
• Chronic pain
• Secondary anxiety
• Biofeedback
• Neuromodulation

Pelvic Pain Classification
Philippe Zimmern- 2008 AUA

• GU
• IC
• IC Syndrome
• PBS
• Overactive bladder
• Urethritis
• Urine retention
• Neurogenic bladder
• Menopause /atrophy/estrogen deficiency
• Battered bladder syndrome
• Urethral masses
• Muscular
• Psychological
• GYN
• GI
Pelvic pain syndromes overlap

- CP/CPPS
- IC/PBS
- High tone pelvic floor muscle-overactive muscular contraction
- Chronic pain
- Emotional abuse
- Pudendal nerve entrapment
- K. Whitmore

Medical conditions associated with IC

- Allergies-40.6-22.5
- IBS-25.4-3.2
- Fibromyalgia-12.8-3.2
- Similar genetic or environmental risk factors
- Organ crosstalk
- Same disease- Collagen disease
- IC systemic rather than local disease
Organ Crosstalk

- Fiorentino PM et al
- Arthritis
- Nerve processing of pain
- Joint transfer of inflammation
- Worsening arthritis
- Interleukin 1-beta
- Nervous system spreads inflammation
- Interference reversal
- Pelvic organ crosstalk
- Colonic organ crosstalk
- MAPP network

Antiproliferative Factor

- Susan Keay
- Bladder epithelial protein
- Secreted urine in IC
- Inhibits bladder lining growth
- Marker for IC
- Future treatments-hyrodistension-decreased activity
Office Consultation

- Hx
- PE and Pelvic/rectal examination
- Urinanalysis
- Voiding diary
- Symptom score
- Cysto
- Intravesical testing
- K test

Symptom Scores

- University of Wisconsin {UW-IC} -1994
- Oleary Sant {ICSI and ICPI} -1997
- Pelvic pain and urgency{PUF}-2002
- Validation
- Sant no single ideal symptom scale
- Role in diagnosis IC and other voiding disorders
- Follow symptoms
K Test

• L. Parsons -1998
• C. K. Chambers-1999
• L. Parsons ad P. Hanno JUROL-2009
• LUDE versus neurogenic Inflammation
• Syndrome versus disease

Disease or syndrome

• Controversial
• PBS terminology
• CPP/CPPS
• C.Nickel
• M.Pontari
• L.Parsons-LUDE
Cystoscopy

- Cystoscopy
- Cystoscopy and bladder biopsy-
- Cystoscopy and urethral dilatation
- Cystoscopy and hydodistension
- Cystoscopy and fulguration
- Cystoscopy and bladder instillation
- Cystoscopy and botex injection
- Cystoscopy and ulcer injection

Downregulation in IC

- Alkalinization treatments
- T. Ueda citrate therapy
- Neural hyperactivity
- Neuronal cross talk
- Dynamic urothelium
- Other medical treatments
- Hydodistension
- Intravesical therapy-downregulation sensory nerves
  - Other Treatments
Diet Modification

- Food triggers
- Diet regime
- Role of dietician
- Prelief-calcium glycerophosphate-K. Whitmore-1998
- Books on diet

Allergy

- 85% allergic component
- 40% food allergy
- Patch testing
- Bladder hydrodistension and biopsy
- Mast cells and histamine
- Histamine blockers-Atarax{hydroxizine} cimetidine and tagamet
- Elimination-challenge diet
- Allergy treatment
Intravesical Cocktails

- **Philip Hanno**
- DMSO (Rimso 50) 50 cc
- Sodium bicarbonate 44 meq (one ampule)
- Kenalog 10 mg
- Heparin sulphate 20,000 IU

Intravesical Cocktails

- **Kristene Whitmore**
- Heparin 10,000 units/ml-2ml's
- Solucortef 125 mg
- Gentamicin 80mg/2ml-2ml's
- Sodium Bicarbonate 8.4% -50ml's
- Marcaine 0.5% -50 ml'sHeparin 10,000 units/ml-2ml's
Intravesical Cocktails

- C. Lowell Parsons
  - Heparin sulphate 40,000 IU
  - Lidocaine 2% 8 mL
  - Sodium bicarbonate 8.4% 3 mL
  - To reach a total fluid volume of 15 mL

Intravesical Cocktails

- Robert Moldwin
  - 1:1 mixture of 0.5% Marcaine and 2% Lidocaine jelly – about 40 cc total.
  - To this solution are added:
    - Heparin sulphate 10,000 IU
    - Triamcinolone 40 mg
    - Gentamycin 80 mg or a post-procedural prophylactic antibiotic.
Pain Drugs

- Elavil
- Elmiron
- Lyrica and gabapentin
- B and O suppositories
- Pyridium
- Marijuana/Cannabinor
- Memantine
- Chinese herbs / aconitine
- Bladder instillations
- Botox

Hydrodistension

- Diagnosis and staging
- IC versus PBS/BPS
- Ulcers – Hunner / patch / atypical
- Therapeutic response
- Indian IC/PBS
- Hanno and Homma
- PJM and HNF experience
- Botox - Muscle relaxation
Neuromodulation

• Sacral nerve stimulation
• 1878-M. Saxtorph-urine retention
• 1959-F. Katona-intraluminal electrotherapy
• 1954-W. Mcguire-bladder stimulation
• 1963-W. Bradley-implantable stimulator
• 1963-K. Caldwell-implantable pelvic floor stimulator
• 1971-B. Nashold-spinal cord stimulation
• 1979-R. Schmidt and E. Tanagho-sacral root stimulation

Neuromodulation

• 1983-Medtronic and Intrel
• Interstim
• Sacral nerve stimulation
• Micturition reflexes
• Modulation
• Urinary growth factors and antiproliferative factor
• IC and pelvic pain syndromes
• Tibial nerve stimulation S. Kabay 67% response
• Pain releife –stimulation afferent myelinated nerves and activation segmental inhibitory nerves
• Mast cell Interaction
• APF decrease
Multidisciplinary Center

- Clinical - Diagnosis and treatment
- Teaching
- Research
- Multisdisciplinary
- Multiple other examples
- Non Medical model - Continence nurse advisor

Multidisciplinary Center

- Urology
- Gynecology-urogyn and pelvic pain
- GI
- Nursing-consultation and Intravesical instillation
- Physiotherapy-Biofeedback, peroneal relaxation and physical therapy
- Dietitian
- Chronic pain management
- Alternate therapies
- Multimodal treatment
Multidisciplinary Center

- Research opportunities-
- Nerve Regulation
- Bladder Receptors
- Targeted Therapy
- IC markers
- New antiinflammatory agents
- Innate defence regulators and immune response Modulation

Alternative Treatments

- Herbal
- Accupuncture
- Neuromodulation
- Biofeedback
- Physical therapy
- Diet
MAPP

- Multidisciplinary Approach to Pelvic Pain
- NIH
- Research network projects
- 5 years

Mapp

- The Multidisciplinary Approach to the Study of Chronic Pelvic Pain (MAPP) Research Network is conducting collaborative research on urological chronic pelvic pain disorders—specifically, interstitial cystitis/painful bladder syndrome (IC/PBS) and chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS).

The MAPP study design looks beyond simply the bladder and prostate for the causes of disease. This national research network includes six Discovery Sites that will conduct multidisciplinary research studies, a Data Coordinating Core (DCC) that will coordinate data collection and analysis, and a Tissue Analysis and Technology Core (TATC) that will coordinate and analyze tissue samples and provide technical support.

- The MAPP Research Network Discovery Sites include:
  - Northwestern University, Chicago, IL
  - University of California at Los Angeles, Los Angeles, CA
  - University of Iowa, Iowa City, IA
  - University of Michigan, Ann Arbor, MI
Mapp

- Epidemiology of Disease / Phenotyping
  - This area of research examines how and why patients develop disease and how their disease changes over time. This area also looks at genetic, behavioral/lifestyle, environmental, and other factors as contributors to disease.

  MAPP Network epidemiology studies will look at relevant participant groups over time and will involve the collaboration of all MAPP Network sites. The MAPP Network epidemiologists will identify who has IC/PBS and CP/CPPS and will answer questions on how disease develops and changes.

  Based on commonalities—such as gender, symptoms, genetics, and environmental exposures—the MAPP Network epidemiologists will address a series of research questions. Of note is the goal to develop participant groupings that may represent specific categories of urologic chronic pelvic pain patients. This may serve to enhance attempts to tailor treatment to different participants based on their unique disease profile.

  MAPP Network epidemiologists are working collaboratively with network scientists focused on the characterization of urologic and non-urologic disease phenotypes. Studies focused on participant phenotypes look at what makes your body unique and considers genetic, behavioral, and biological differences. MAPP Network investigators working in urological phenotyping are developing a “working definition” for specific categories of urologic chronic pelvic pain patients— or the series of tests and questions—used to determine if a participant has IC/PBS or CP/CPPS. These will be used for all MAPP Network studies. Network investigators who address non-urologic phenotypes are interested in assessing characteristics of participants with conditions not specific to urological systems (e.g., the bladder and prostate). These investigators are establishing a questionnaire survey and other tools to assess participant characteristics across a number of pain conditions potentially found in association with IC/PBS and/or CP/CPPS, such as irritable bowel syndrome, fibromyalgia, and chronic fatigue syndrome. The survey tools will attempt to address unexplained medical and psychological conditions, as well as specific disease symptoms, and behavioral and environmental factors. Once completed, each Discovery Site will employ this standardized assessment tool when assessing overlapping conditions for all participants recruited into MAPP Network studies.

  Collectively these investigators comprise the MAPP Network Epidemiology/Phenotyping Working Group. In addition to addressing disease changes over time and participant phenotypes, this group is developing research tools to standardize how participants across the MAPP Network are enrolled and characterized. This foundation serves to unify the numerous research projects being conducted in Discovery Sites by ensuring the various scientific approaches are looking at similar participant groups, which yields more reliable study findings.

Mapp

- Neuroimaging / Neurobiology
  - Tests that look at brain structure and function (e.g., neuroimaging studies) can help diagnosis and define certain pain conditions. Types of neuroimaging tests include computed tomography, magnetic resonance imaging (MRI), and positron-emission tomography. In pelvic pain conditions, functional MRIs may be used to confirm symptoms in patients suffering from painful conditions.

  The Neuroimaging / Neurobiology working group is identifying the possible neurological (i.e., based in the nervous system) causes of the urologic chronic pelvic pain disorders. The group is also working to understand how the neurology of patients may change based on disease symptoms and how patient neurology may differ if they suffer from additional, possibly related, disorders.
Biomarkers

Biomarkers are unique substances or features (e.g., proteins, genes, features of anatomy, etc.) found in people with specific conditions that serve to identify the presence of diseases. Identification of biomarkers can help us diagnose and predict disease and may lead to a better understanding of the underlying causes of disease. Also, biomarkers can help physicians and researchers sub-group patients for more targeted treatments or research studies.

The Biomarkers working group will identify biomarkers that help to describe the causes and symptoms of urologic pain syndromes and will assess how such biomarkers can change during disease and when additional, possibly related, disease conditions are present.

Organ Cross-Talk / Pain Pathways

In some cases, patients with urologic pelvic pain syndromes may also suffer from additional or “co-morbid” conditions such as irritable bowel syndrome. The pelvic organs (bladder and urinary system, reproductive organs, and bowel) are assumed to contribute to these syndromes. Importantly, these organs share neural pathways (or “neural circuits”) in your body. The shared neural pathways and demonstrated co-occurrence of pelvic disorders in chronic pelvic pain syndromes suggest the possibility that “crosstalk” exists between pelvic organs, meaning that one pelvic organ influences another. Several research studies have demonstrated pelvic organ crosstalk. Animal studies reveal that stimulating a single spinal nerve can affect both the bladder and the bowel. Stimulating the bowel can also contribute to bladder inflammation and enhance bladder-associated pelvic pain.

This working group will look at how the urologic chronic pelvic pain disorders might relate to other conditions through human studies, as well as studies in a number of animal models of disease.
Mapp

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Summary

• Common condition
• Neurogenic Inflammation
• Syndrome or disease
• NO TEST
• Chronic pelvic pain
• Other pain syndromes
• Multidisciplinary approach
• Multimodal therapy
• Mapp