

# A review of the SENSORY BLADDER MEETING

Les Pensières, Fondation Merieux, Veyrier du Lac, France  
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Around 95 expert speakers and participants from 13 different countries gathered in the breathtakingly beautiful setting of Les Pensières on the bank of Lake Annecy in France, against a picturesque backdrop of snow-capped Alps, to discuss many different aspects of the “Sensory Bladder” during a multidisciplinary meeting organised by Professors G. Amarenco and E. Chartier-Kastler. Honorary President of this special meeting was Professor Clare Fowler. The meeting with 25 speakers focused on sensory disorders and the urinary bladder, from anatomy to therapeutic strategies, including the latest information on imaging of the brain and generated a huge amount of information. The organisers are to be congratulated for this welcome and useful initiative which enabled all participants to obtain a more complete picture of the sensory bladder.



Since the meeting language was English only, this international event provided a unique opportunity for particularly French research and ideas to reach a wider audience, instead of being published exclusively in the French language as is so often the case. Our review gives a brief look at aspects of particular interest in our field.

## What is sensory bladder?

Sensory bladder disorders include disorders involving abnormal sensations resulting from many diseases of the urinary bladder. In a proportion of patients no cause can be found and if pain or pelvic pressure is a part of the symptomatology, they are labelled as having IC/BPS (see *Nordling J. Sensory bladder disorders. Int J Clin Pract Suppl. 2006 Dec;(151):38-42*).

According to Professor Xavier Fritel, from Poitiers University Hospital, looking at epidemiology, sensory bladder disorders represent a wide field for which there is still no precise definition. We can include in this field, he said, the overactive bladder (OAB) syndrome, sensory symptoms as increased, reduced, or absent bladder sensation, painful bladder syndrome, and some voiding and postmicturition symptoms.

## Voiding: A reflex? A habit? A pleasure? A pain?



Many different disciplines were represented at this meeting and it became clear right from the start that different disciplines often have different views when Professor R. Robert – speaking on Bladder and Sensory Neurological Pathways - explained the nervous system from the point of view of the neurosurgeon and anatomist and clearly had a rather different concept of afferent nerves than the neurourologists. This led to a lively and very interesting discussion later in the day.

Voiding is basically a reflex, he explained, consciousness is mostly not required. Voiding can become a habit and social behaviour also plays an important role in our voiding. When you need to void, it is a pleasure or relief, but it can also become a painful experience, he said.

Looking at the urothelium cells, he explained that once upon a time the urothelium was believed to be nothing more than a urine-proof barrier. However, we now know that its cells do in fact have neuron-like properties, respond to chemical and mechanical stimuli and secrete neuromediators such as NO, ATP and prostaglandins. He explained that the sympathetic system of sensory fibers insures passive continence, while the

parasympathetic (no sensory fibers) and somatic system (sensory fibers) organise the micturition-continnence cycle.

The nervous fibers are: A-Delta fibers: smooth muscle (muscular stretching), C-Fibers: stretching of the endothelium, Silent C-fibers: no sensitivity to distension.

When everything is running normally, the cortex in the brain is not informed, he explained, but as soon as pain occurs, the upper centres of the nervous system become involved and the normal function of the urinary tract changes.

Professor Robert summarised by saying that the bladder evolves throughout our life, from birth onwards. It works mostly by itself, but it must be socially controlled. When we are stressed, our bladder can be emotionally affected and we may need to keep running to the bathroom. But when things go wrong, it may lead to severe pain.

He ended by quoting an ancient Chinese proverb which says that “the bladder is the mirror of the soul”, which might be a rather alarming thought for IC patients!

### Terminology issues

Many speakers lamented the fact that terminology and definitions are often inconsistent and sometimes downright confusing. Speaking on Sensory Receptors and Afferent Signal Modulation, Professor Dirk de Ridder (Belgium), a former chair of the ICS Standardisation Steering Committee, said that there is a lack of discipline concerning correct terminology regarding receptors. Everyone is using different terms and this hampers literature searches and makes it impossible to compare studies. This also applies to the layers of the bladder wall. The mucosa of the bladder is composed of the GAG-layer, the urothelium, the lamina propria where the interstitial cells are, and the muscularis mucosae, surrounded by the detrusor, adventitia and serosa. But in reality many other different terms are commonly in use.

Professor de Ridder explained that signals pass not only from the inside of the bladder outwards, but also vice versa. He looked at the role of TRPs as cellular sensors in some detail. Sensory receptors are an expanding field in urological research, he said. This is an area of research under development, but much knowledge has already been gained. The more you go into it, the more complicated it becomes!

He summed up by saying that modulation of the afferent signals occurs at several levels and is very complex and poorly understood at the moment. Good scientific research is needed where morphological and functional data are combined. On conclusion, he emphasised that extrapolation of findings in cell cultures or normal animals to humans with a specific disease is a giant leap of faith and should be done with some caution. A number of other speakers were to endorse this view.

### Painful Bladder

On the topic of Sensory Bladder, Definition, Syndromes, Symptoms, Epidemiology, Professor Christopher Chapple looked at the history of IC/BPS criteria and current definitions and criteria, which vary from East to West. He noted that in the past existing criteria were clearly felt to be too restrictive and this ultimately led to less attention being paid to objective findings, with diagnosis becoming more dependent on expert opinion. Recent new definitions have really been pulling together the strands developed over the past decades, he felt.

On the topic of diagnosis, he stressed the following:

- Diagnosis is based on symptoms and exclusion of other diseases
- Stratification can be based on many factors including presence or absence of Hunner’s lesion, urodynamics, associated chronic pain syndromes (e.g. IBS, FM), histology
- Potassium sensitivity testing has neither specificity nor sensitivity to be used in diagnosis
- Glomerulations are non-specific for IC/BPS
- Hunner’s lesion can change the treatment algorithm.

He reminded everyone that a number of autoimmune diseases are known to be associated with bladder pain problems. He also noted the overlap in a limited number of patients with associated OAB-dry with underlying detrusor overactivity, but emphasised that in his view IC/BPS and OAB are not interchangeable concepts, although others have suggested that this may be the case, he added.

Professor Chapple went on to explain that it is thought that afferent mechanisms are important in OAB, and clearly they must also be so with IC/BPS, as pain is a sensation. Both lead to urgency: a painful bladder associated with urgency due to pain, and OAB urgency for fear of leakage. It is not clear what the discrete mechanisms are which lead to different afferent sensation producing a different end result for the OAB symptom complex versus the painful bladder symptom complex, although clearly there is an overlap at times between the two. There is evidently plenty of scope for research here.

He also outlined the East Asian concept of **hypersensitive bladder syndrome** which can be with or without pain. This formed an appropriate introduction to the next speaker who presented the French proposals for hypersensitivity.

#### French voiding study

Dr J.J. Labat (neurologist) from Nantes, France, continuing with IC/BPS patients, began by presenting the results of a French study using voiding diaries to compare IC/BPS patients with and without cystoscopic abnormalities, showing significant differences in voiding frequencies during the day and the night. It was concluded that in the case of IC/BPS with abnormal cystoscopy, we are talking about a pathological bladder wall or in other words a disease of the bladder wall. In this group, voiding diaries showed that voiding volumes remain fairly constant from one void to the next and that voiding frequency is increased both during the day and at night. In the second group: IC/BPS with normal cystoscopy, it is believed that this indicates “hypersensitivity” with alterations in bladder sensitivity suggesting neuronal dysfunction. Voiding diaries showed variation in volumes voided and frequency.

Looking at sensory alteration in IC/BPS, he focused attention on the following aspects:

- Alteration in the urothelium
- Neurogenic inflammation
- Central sensitisation
- Organ cross-talk
- Visceral organ hyperalgesia/allodynia
- Pelvic sensitisation

#### French hypersensitivity proposal

He then presented the French **hypersensitivity** proposal. Previously, this was presented in French at the Convergences PP meeting in Nimes, but now he presented this interesting concept in English with English slides, allowing everyone to obtain a clearer picture of this proposal which is not unlike the East Asian/Japanese concept of hypersensitive bladder syndrome (HBS).

Dr Labat illustrated the concept by showing 3 overlapping circles that form the French pelvic sensitisation clinical approach:

- **Non-painful visceral hyperactivity syndrome due to visceral hypersensitivity** (Bladder, Bowel)
- **Painful pelvic visceral hypersensitivity** (bladder, bowel, vulva, urethra, prostate)
- **Pelvic non-visceral hypersensitivity** (musculoligamentous trigger points, bone (bone tenderness), skin, mucosa (hyperpathia, superficial allodynia))

On the basis of this concept, they have drawn up a proposal (still under development and open to suggestions) for a pelvic pain diagnostic score from 0-10, which now needs to be evaluated, called

**The Pelvic Pain Sensitisation: Convergences PP Score** comprising 10 items:

#### Clinical interview: subgroup: non-painful visceral hyperactivity syndrome due to visceral hypersensitivity syndrome

1. Urinary symptoms (dysuria, frequency...)
2. Bowel symptoms (dyschezia, diarrhoea...)

#### Clinical interview: subgroup: painful visceral hypersensitivity

3. Pain worsened by bladder filling (bladder) or worsened after voiding (urethra)
4. Pain worsened by filling of the rectal ampulla and/or following defecation

5. Pain worsened during or after sexual intercourse
6. Hyperpathia or allodynia to superficial skin contact (clothes)

**Examination: subgroup: pelvic and perineal non-visceral hypersensitivity**

7. Myofascial pain
8. Pelvic bone tenderness
9. Vulvodynia or testicular tenderness

**Predisposition subgroup**

10. History of other types of functional pain.

BPS, he explained, is a form of pelvic sensitisation which, when only urological, may be considered a focal form of pain. But in the majority of cases, he noted, the patients present with multiple diffuse disorders.

Dr Labat concluded his presentation by noting that the concept of organ pain has been transformed into a concept of pain perceived to be in an organ. IC/BPS can be considered to be a form of functional pain involving peripheral neurological phenomena such as neurogenic inflammation and central sensitisation phenomena. He underlined that in future we need to define homogeneous subgroups of patients in order to improve treatment.

Dr Xavier Gamé from Toulouse, speaking on non-neurogenic male frequency, asked what is normal frequency and what is abnormal? He pointed out that descriptions of normal functioning are way too inadequate and this makes it difficult to assess what is abnormal.

He stressed that voiding diaries are important to determine the cause of the frequency and whether this is due to increased urine output or diminished bladder capacity.

Dr R. de Tayrac (Nîmes), speaking on the female point of view, looked at the increasing prevalence of overactive bladder and its cost for healthcare systems. While the cost in 2000 was estimated at € 4.2 billion, it is estimated that this will reach € 5.2 billion in 2020.

This speaker also said that the definition of OAB had recently been revisited and made more patient-friendly: *Complaint that micturition occurs more frequently during waking hours than previously deemed normal by the woman*. A number of speakers and many delegates in Annecy felt that the whole OAB syndrome needed to be re-examined and redefined.

Speaking on sensation, Professor JJ Wyndaele (Antwerp) said that sensation is by definition subjective. However, this does not mean that reporting of sensation by patients is unreliable. He emphasised that the patient does not only have symptoms while sitting in the consultant's office, but every single day, affecting every aspect of life. Evaluation should therefore focus on gathering information about the patient's lower urinary tract function from day to day. Voiding diaries can help provide this information. A bladder diary is used to document the symptoms and signs of lower urinary tract function in daily life; it gives objective and reliable information on the clinical signs and symptoms, grades them and puts patients' complaints into a proper perspective. It permits the clinician to document how sensory information from the bladder is used by the patient. Bladder sensation is the first guidance to use the involuntary lower urinary tract in an acceptable way. When using a voiding diary, the patient writes down what happens with the bladder function during a certain period, preferably also reporting on bladder sensations. A sensation-related diary gives both accurate and specific information on bladder sensation in daily life. Good patient compliance is needed which means that there has to be a clear explanation of what is expected. Regarding how many days are needed for a voiding diary, he said that to gain a good basic impression it should be done for at least 1 full day and night. To obtain consistency of events: 3 full days and nights; for research purposes, 7 days and nights; for training purposes at least 14 days and nights.

Discussing the electronic diary as opposed to the paper diary, he mentioned that actual compliance with an electronic diary was 94% (Stone *et al*, 2002). There is no difference in ease of use. However, there is a difference in the completeness of filling in the record if the electronic diary is used by the elderly. While the

electronic diary is useful in research with large sample sizes, the paper diary remains useful in daily practice. He emphasised that a voiding diary cannot be used for diagnosis, but may be considered a diagnostic aid.

### **Urgenturia?**

Professor Philippe Grise returned to the terminology issue, noting that words need to be precise and according to accepted international terminology. Research and new distinctions could require new expressions. At a meeting such as this, it was inevitable that the controversial term “urgency” should raise its head. He suggested “urgenturia” by analogy with dysuria, dematuria etc. This is in fact the term currently being used in France. Many more speakers had something to say on the inadequacies of the term urgency.

### **Listen to the patient!**

Professor Grise also suggested that physicians are not listening to the patients sufficiently and often underestimate the degree of bother for the patient. He underlined the importance of measuring the impact of an improvement in a medical condition from the patient perspective. It should not be forgotten that patient symptoms may change over time or after treatment.

He discussed the merits of various questionnaires and scores that assess sensory lower urinary tract symptoms. They evaluate a range of different and specific concepts: qualitative measurement of symptoms, symptom discomfort, symptoms related to quality of life, patient satisfaction to clinical outcome and treatment. He emphasised that symptom measurement remains the most important primary outcome, but the true impact on the quality of life is basically necessary to evaluate outcome of the pathology, and the benefit of the treatment. According to Professor Grise, there is a discrepancy in the patient's and the physician's perception of quality of life related to urinary symptoms, as physicians tend to underestimate the patient's degree of discomfort. This outlines the importance of measuring the impact of an improvement in the medical condition from the patient's perspective.

Dr R.J. Opsomer, Belgium, speaking on video-urodynamics, also stressed that when performing imaging and urodynamics, the doctors should try to remain as close as possible to the reality of the complaints of the patients and asked whether tests and investigations truly reflect the symptom experience of the patient.

### **Animal studies not automatically translatable to the human situation**

Speaking specifically on animals models in sensory bladder research, Professor K-E Andersson also gave a warning that animal studies are not automatically translatable to the human situation. Available models in fact have very limited translational value, he suggested. Many researchers reporting the results of animal studies assume that these can lead to better treatment in humans. This is not the case, he said. Micturition in rodents and humans differs considerably. Cystometric parameters in rodents are poorly defined and do not correspond to what is used in humans. However, despite many limitations, current animal models may give relevant information on bladder afferent functions. He raised the question as to what is needed? Careful standardisation of terminology, improved characterisation of models used, well-characterised new models, and finally general awareness of translational limitations.

Neurological evaluation of the sensory bladder was presented by Dr Marianne de Seze, from Bordeaux, noting that general and perineal neurological examination is an important step in the evaluation management of urinary disorders, and may help to attribute a neurological etiology in front of urinary disorders. She explained that the neurological examination includes clinical sensory, motor, reflexes and tone pathways. She pointed out, however, that current published data does not help in identifying the clinical symptoms and signs, which are most suggestive of perineal neurological abnormalities, and there is no evidence based on the value of the clinical examination in this area. No symptom or sign taken on its own can be adduced in favour of a neurological cause, resulting in the problem of nicturition. The combination of subjective and objective symptoms and signs, namely the association of urinary, anorectal and sexual disturbances, in a context compatible with such pathology may suggest a neurogenic cause, and encourage a search for it.

Dr Gilberte Robain looked at psychological evaluation of the sensory bladder, quoting the French psychiatrist Dr Jules Janet back in 1890 who noted that “the bladder has no anatomical capacity; the bladder has a physiological capacity; but most often our urinary habits induce a psychological capacity. In stressful life events, pollakiuria and urgency are frequent, as well as diarrhoea and urge defecation.” (*Les Troubles Psychopathiques de la Miction*). Dr Robain noted that psychological disorders such as depression and anxiety can be a

consequence of bladder disorders. They may also induce a bladder disorder. However, he added, there is no proof that chronic anxiety can induce urge incontinence.

### More Urgency

Professor Clare Fowler (UK) also took a look at “urgency”. She said that the main questions are:

- Is urgency a separate pathological sensation, or an extreme form of normal sensation?
- Does urgency always occur suddenly or can it result from a gradual build-up of sensation?
- Is urgency one uniform sensation or do different types or grades of urgency exist?

She emphasised that systematic studies are necessary, noting that it seems likely that the pathogenesis of extreme urge and urgency are different, but the two phenomena often coincide.

### Children

Professor Jacques Corcos (Canada) looked at pelvic floor disorders in children, noting that pelvic floor dysfunction mainly concerns incontinence (OAB, bed-wetting). Pelvic pain is usually included in abdominal pain, with the usual presentation being “tummy-ache”. It is only in the teenage years that complaints become more precise and pelvic pain starts to be mentioned in the literature. 92% of adolescent girls complain of dysmenorrhoea, but other causes in teenage girls include endometriosis, ovarian abnormalities, pregnancy and ectopic pregnancy, malignancies, IBS, Crohn’s disease and of course interstitial cystitis. Age at diagnosis of IC, he said, has been seen to range from 3-16 years (average 8.2). Symptoms appear to be slightly different from adults.

Pelvic pain in boys is mainly due to urological problems, but may also be caused by a foreign body, UTI revealing malformation, ureteral and bladder stone and malignancies. In cases of refractory pain, past abuse should be considered among the possibilities. Professor Corcos added that managing patients with chronic pain is intellectually and emotionally challenging. The patient’s problem is often difficult to diagnose: such patients are demanding of the physician’s time and often appear emotionally distraught.

Dr Xavier Deffieux (Paris), presenting on sensory bladder research, was another speaker who felt that better insight was needed into different types of urgency.

He felt that the definition of sensory symptoms is unclear. There is a need to describe normal bladder sensation more clearly for the patient and not as physician-derived terminology. He said that terminology for normal bladder sensations is limited and we don’t know which words are used to describe bladder sensation by patients and we don’t know where bladder sensations are located. The most challenging issue in clinical research is the definition of normal bladder sensations. There appear to be two types of urgency in OAB: a sudden absolute need to void and a slowly developing absolute need to void. This is not covered by the ICS definition. The speaker underlined that urgency is neither a well-defined nor commonly understood symptom.

### Take home messages

Summing up on the final day, Professor Chartier-Kastler reminded delegates that the lower urinary tract is controlled from our foetal period to old age through a complex neural system. On the subject of painful bladder, he noted that we don’t know very much about the pathological mechanism. He underlined the importance of voiding and sensation-related bladder diary. Speakers had shown that while animal models can provide relevant information on bladder afferent functions, the micturition type of rodents differs from that of humans. There is limited translational value and terminology in animals is not well defined. There is a great need for more cooperation between urologists and gastroenterologists for better understanding of overlapping syndromes. He thought that the topic of male and female sexual dysfunction could form a good topic for another meeting. Regarding bladder therapies: it seems that the properties of the urothelium are of major interest to find new targets for new types of treatment.

This is just a small sample of the many presentations which also included many aspects of treatment and on the second day a number of research presentations, including by young researchers.

### Webcasts

The presentations on the first day will be available as webcasts on the SIFUD PP website: <http://www.sifud-pp.org> and hopefully an official review will also be published in due course.

The programme and abstracts book of this meeting are still available on: <http://sbm2012.jimdo.com>.