Bladder and urethral signaling dysfunction as an underlying contributor to Lower Urinary Tract Symptoms (LUTS)

Urethral and bladder sensation play a key role in the development of LUT complaints. Both a lack of sensation and an excess of sensation can lead to storage or voiding symptoms. Therefore an adequate detection, processing and perception of signals from the lower urinary tract is crucial for its function.

The bladder brain axis in terms of mechanisms of disease and symptoms of pelvic dysfunction
Stefan De Wachter, MD, PhD

Normal storage and voiding is dependent on close communication between the lower urinary tract (bladder and urethra) and the brain. To operate smoothly, the LUT is connected to the central nervous system by three peripheral pathways, each ending at specific sites and spinal levels. There they connect with the central pathways, which basically are organized as on-off switching circuits, under final voluntary control of the higher brain centres. This neurologic system is by its complex nature very vulnerable and dysfunction in any of the pathways involved and any level, may give rise to symptoms of pelvic dysfunction, such as for example urgency, urinary incontinence, urinary retention, bladder pain, but may also contribute to other symptoms such as constipation, faecal incontinence or pelvic pain.

In this workshop the specific anatomy and physiology of the bladder – brain axis will be discussed, together with the possible interactions at the different levels. This will be done in the light of the clinical disorders. An overview will be given of different pelvic symptoms and dysfunctions in relation to specific disorders at the peripheral or central level site in the bladder brain axis.

At the end of this presentation, the audience should have a clear picture on
- The normal anatomy and physiology of the bladder brain axis
- Pathophysiologica changes in the bladder brain axis at peripheral and central levels
- How changes at a peripheral or a central level give rise to certain symptoms of pelvic dysfunction

Urothelial-cell signaling- a system with adjustable gain
Lori A. Birder, PhD
The pathophysiology of the overactive bladder syndrome (OAB), urodynamically associated with detrusor overactivity (DO), is multifactorial and may include neurogenic, myogenic, or idiopathic factors. The recognition of the functional contribution of the urothelium, the spontaneous myocyte activity during bladder filling, and the multiplicity of nerve transmitters involved in bladder muscle activation has sparked interest in both peripheral and central modulation of OAB/DO pathophysiology. Research on OAB has focused on detrusor dysfunction, usually without considering urethral muscle function as a potential contributor to OAB or DO. It has been speculated that the primary defect in DO may be found in the urethra.

Reflexes within the bladder, between outlet and detrusor smooth muscle and between bladder and pelvic striated muscle play an integral role in the neural control of the lower urinary tract.

In the smooth and striated muscle components of the female urethra, a number of nerves containing a variety of transmitters mediating contraction or relaxation can be demonstrated. Relaxation of the urethra may be achieved in different ways. Since noradrenaline is generally considered to be a main factor maintaining urethral smooth muscle tone, this implies that a decrease in noradrenergic activity can relax the urethra. Likewise, release of relaxant transmitters may relax the urethra by reducing existing contraction. Nitric oxide (NO) seems to be an important mediator of urethral smooth muscle relaxation, but a role of other transmitters cannot be excluded. Little is known of the possible role of transmitters released from the urethral epithelium/lamina propria and participating in signaling pathways conveying afferent activity eventually resulting in urgency and/or detrusor activity. However, there is some evidence that the mucosal pathway within the proximal urethra, which involves a cascade of epithelial inhibitory and stimulatory transmitters/mediators, may play a role in continence and sensation. The urethral epithelium is likely to be part of a signaling system involving projections of the neuroendocrine cells, interstitial cells and sensory nerve endings.

**Changes in urethral afferent signaling and smooth muscle control as contributor to LUTS**

Matthew O. Fraser, PhD

**Urethral afferent signaling:** The purpose of the lower urinary tract (LUT) is two-fold: to collect and store urine, and then to periodically release urine when environmentally appropriate. True mammals normally possess a compartmentalized urogenital system, with the complete separation from the gastrointestinal tract and various degrees of separation from the reproductive tract, depending on the biological sex of the individual. One of the hallmarks of mammalian evolution is the development of a urinary bladder-urethral complex, rather than the bladder emptying directly into a cloaca. Although the bladder is the primary
organ of urine storage and generates the pressure to evacuate urine, the urethra, a relatively recent evolutionary development, actively participates both in storage and release functions. The actions of these structures are coordinated through reflexes involving the spinal cord and brainstem, with inhibitory forces exerted from higher cortical centers.

Barrington (1931) described 7 such reflexes, 4 of which are particularly important to the current lecture are here rephrased:

**Reflex 2**: A urethra-spinobulbarspinal-bladder reflex – this is a long loop reflex, originating from pudendal afferents in response to intraluminal fluid flow, seen as a positive feedback mechanism that promotes efficient voiding.

**Reflex 3**: A proximal urethra-spinal-bladder reflex – this is a short loop reflex, originating from hypogastric nerve afferents, in which proximal urethral distension causes a non-voiding bladder contraction.

**Reflex 4**: A urethra-spinal-urethra reflex – this is a short loop reflex, originating from pudendal afferents in response to intraluminal fluid flow and causes relaxation of the rhabdosphincter.

**Reflex 7**: A urethra-spinal-bladder reflex – this is a short loop reflex, originating in parasympathetic afferents, may also contribute normally as a positive feedback mechanism to promote efficient voiding.

We will cover the roles of these urethral reflexes in normal and pathological LUT function.

**Smooth muscle control**: Sherrington (1892) observed that bladder contractile activity continued in Rhesus monkey bladders in situ following denervation. Over the years since that time, it has become apparent that bladder smooth muscle has intrinsic contractile activity using in vitro, ex vivo and in situ preparations. Sometimes this activity is coordinated, other times it is not. Various hypotheses have been forwarded regarding the nature of this activity, and these will be described. The normal control of this activity, its function and its role in LUTS will also be discussed.

**How can changes in sensory function contribute to the etiology of LUTS, primarily and secondary to pelvic surgery.**

Gommert A. van Koeveringe, MD, PhD

Urethral surgery, for example a “simple” mid urethral sling, a uretholysis, urethral diverticulum repair or a tape removal, can give rise to sensory dysfunction of the urethra. Consequently, this may lead to bladder activity disorders (overactive bladder or underactive bladder).

Also other pelvic surgery may compromise innervation and so lead to storage or voiding dysfunction. At older age or through metabolic disorders, mainly the sensory nerves get damaged and this sensory denervation leads to LUT symptoms. In addition when using a gel
with a local anesthetic to introduce catheters for a urodynamic investigation, the test may be compromised through a loss of urethral and in part bladder sensation. These are all everyday examples of compromised sensation as contributors to LUT symptoms. Moreover many current therapies for overactive bladder modulate or influence the sensory system. Antimuscarinics are more likely to affect the sensory system compared to the motor system. Sacral Neuromodulation is likely to exert its effect through stimulating afferent reflex limbs to the brain areas responsible for sensation in the lower urinary tract.