W13: Underactive Bladder—Clinical Implications, Mechanistic Concepts and Therapeutic Options

Workshop Chair: Anthony Kanai, United States
28 August 2018 13:30 - 15:00

Start	End	Topic	Speakers
13:30	13:50	Diagnosis and Clinical Implications of UAB	Marcus Drake
13:50	14:10	Comorbidities and Models of UAB	Lori Birder
14:10	14:30	New Therapeutic Options for UAB	Anthony Kanai
14:30	14:50	Mechanistic Concepts of UAB	Christopher Fry
14:50	15:00	Discussion	All Speakers

Aims of Workshop

Please note that where authorized by the speakers, PowerPoint slides presented at the workshop will be made available after the meeting via the ICS website www.ics.org/2018/programme. Please do not film or photograph the slides during the workshop as this is distracting for the speakers.

Aims of Workshop

This workshop will present up to date information on the clinical description and diagnosis of underactive bladder (UAB), associated co-morbidities, its pathophysiology and new drug targets. Topics will include: the pathological implications of aging; bladder ischemia, inflammation and fibrosis; their impact on decreased detrusor force generation and/or contractility; and the involvement of free radical formation and mitophagy. The therapeutic relevance of free-radical scavengers, as well as anti-inflammatory and antifibrotic agents will be discussed.

Learning Objectives

1) Provide up-to-date information on the clinical implications of UAB as a cause of impaired bladder emptying in the elderly population and in young women afflicted with Fowler's syndrome. This workshop will enhance our understanding of the basic science of aging and will provide knowledge to develop strategies that will increase the 'health-span' of the aging adult.

2) Identify comorbidities associated with UAB, discuss relevant animal models and show findings on the therapeutic benefits of free radical scavengers, anti-inflammatory and antifibrotic agents for the underactive bladder.

3) Characterise cellular pathways and mechanisms of action that may be responsible for UAB and whether they involve altered detrusor force generation and/or bladder sensation.

Learning Outcomes

After the course, attendees will have the latest clinical and scientific information on UAB, its pathophysiology, and relevant models to test new therapeutic agents. The information could be applied to attendees' research programs or patient management strategies.

Target Audience

Scientists, urologists and other healthcare workers interested in the diagnosis, pathophysiology and treatment of UAB.

Advanced/Basic

Advanced

Conditions for Learning

None, this is not a hands on course.

Suggested Learning before Workshop Attendance

1) Detrusor underactivity and the underactive bladder: a new clinical entity? A review of current terminology, definitions, epidemiology, aetiology, and diagnosis, Osman et al., Eur Urol., 65:389-98, 2014. PMID: 24184024.

2) Detrusor underactivity: Clinical features and pathogenesis of an underdiagnosed geriatric condition. Taylor JA and Kuchel GA. J Am Geriatr Soc., 54:1920-32, 2016. PMID: 17198500.

3) Review of underactive bladder. Chang YH et al., J Formos Med Assoc., [Epub ahead of print] 2017. PMID: 28969876.

Suggested Reading

1) Relaxin treatment reverses age related bladder fibrosis. Zabbarova et al., Neurourology & Urodynamics, 35: S176-S177, 2016.

2) Relaxin: Treatments for underactive bladder. Kanai et al., Integrative Physiology of the Urinary Tract – New Therapeutic Approaches and Concepts. Incontinence, 6th Edition, Volume 1, Chapter 2, Cell Biology, pp. 190-195, 2017. Paul Abrams, Linda Cardozo, Adrian Wagg and Alan Wein, Editors. ISBN: 978-0-9569607-3-3.

3) Voiding dysfunction due to detrusor underactivity: an overview. Drake et al., Nature Reviews Urology, 11:454-464, 2014. PMID: 25002201.

4) The potential role of unregulated autonomous bladder micromotions in urinary storage and voiding dysfunction; overactive bladder and detrusor underactivity. Drake et al., British Journal of Urology International, 119:22-29, 2016. PMID: 27444952.

5) Pathophysiology and animal modelling of underactive bladder. Tyagi et al., International Urology and Nephrology, 46:S11-S21, 2014. PMID:25238890.

6) Translational research and functional changes in voiding function in older adults. Kullmann et al., Clinics in Geriatric Medicine, 31:535-548, 2015. PMID: 26476114.

7) The passive and active contractile properties of the neurogenic, underactive bladder. Young et al., British Journal of Urology International, 111:355-361, 2013. PMID: 22712666.

8) Detrusor underactivity: Pathophysiological considerations, models and proposals for future research. Van Koeveringe et al., Neurourology & Urodynamics, 33: 591-596, 2014. PMID: 24839258.

Diagnosis and Clinical Implications of UAB

Marcus Drake

UAB has recently been given a consensus definition by an ICS terminology working group; "Underactive bladder syndrome (UAB) is characterised by a slow urinary stream, hesitancy and straining to void, with or without a feeling of incomplete bladder emptying sometimes with storage symptoms". Thus, it is a symptom syndrome, which can be applied based on the patient's history. The clinical presentation is very varied and is particularly a feature for older people and those with neurological disease, where the principle problem is probably impaired bladder contraction due to loss of muscle mass or its innervation. A small but important group is young women with Fowler's syndrome (painless urinary retention, perhaps caused by sphincter dysfunction). When assessing affected people, healthcare professionals need to consider the possible underlying mechanisms, so consideration of possible neurological or psychological disease, muscle disorders, and drugs (medical or recreational) is needed. The bother associated with voiding and post voiding symptoms should be explored, and also the extent to which affected patients experience storage symptoms (which may actually be the principle reason for presentation). A patient reported outcome for UAB is currently under development by the ICIQ, based on qualitative research of the typical presentations.

Flow rate testing tends to show a slow take-off, low maximum flow rate, prolonged time course and interrupted voiding. The severity of any post void residual must be measured and could be an important factor in deciding whether to start intermittent self-catheterisation. The PVR might give rise to a predisposition to urinary tract infections.

Urodynamic testing is needed in many cases to explain the mechanism for the slow stream, and to exclude bladder outlet obstruction. During the voiding phase, there can be a long interval between "permission to void" and the start of bladder contraction, and an even longer interval before urine flow. The detrusor trace tends to show a wandering up-and-down pattern, and it is common to see the patient using abdominal straining/ Valsalva to enhance the expulsion. Detrusor underactivity (DUA) is a contraction of reduced strength and/ or duration, resulting in prolonged bladder emptying and/or a failure to achieve complete bladder emptying within a normal time span. The bladder contractility index is a useful approach to determining if there is DUA, based on detrusor pressure and maximum flow rate. Bladder contractility index (BCI) can only be used in men (those who still have their prostate). For women (and also men), a new urodynamic approach is under development.

Ultimately, therapeutic options are currently limited and generally have poor outcomes, relying on bladder stimulators, self-catheterisation and neuromodulation. Surgical intervention in men tends not to achieve a substantial improvement and carries important risk of adverse effects.

Comorbidities and Models of UAB

Lori Birder

UAB is currently a urodynamic-based diagnosis and does not take into account either bladder afferents or the central nervous system's role in its etiology. A broad definition of animal models for UAB can be subdivided into peripheral (those resulting in direct damage to the bladder, innervation or blood supply) versus central (following injury to the spinal cord, brainstem or higher centers). Current animal models for UAB include diabetic bladder dysfunction (DBD), ischemia, neurological and transgenic as well as aging models. Current animal models for aging include yeast, C. elegans, Drosophila, naked mole rats, primates and rodents. Aged mouse or rat models have been shown to reproduce some of the UAB features such as age-dependent loss of bladder volume sensitivity. Various models will be discussed including findings using the Fisher 344 strain of rat, which has been used to study the effects of aging on numerous organ systems including cardiovascular, neurological and lower urinary tract (LUT). While there is no consensus as to the preferred species or strain of animal to evaluate the impact of aging on bladder structure and function, the relatively short lifetime of the rat, the abundance of previous research using aged rat models, and the considerable knowledge about LUT function in this species makes it an attractive model to explore the mechanisms underlying bladder dysfunction in the aging human.

Animal models are useful but typically focus on studying a single etiological factor and may not be representative of the complex interactions and pathophysiology of UAB. Our preliminary data using an aging (3-30 mo) rat model has revealed an association with a number of complex changes involving increased oxidative stress. These changes, coupled with the decreased production of mediators contribute to altered bladder dysfunction as well as a number of co-morbid symptoms. During aging, external and internal stressors perturb normal cellular homeostasis, causing progressive cellular and tissue decline. Our research has also shown that aging correlates with altered expression of various mediators as well as changes within the extracellular matrix (ECM) and decreased lysosomal functions that can impact a number of organ systems. Lysosomes perform critical housekeeping

functions such as degradation of proteins and lipids and other cellular debris. A decline in this function may actually be one of the driving forces in the aging process. Thus, changes including the release of mediators and fiber architecture with age can adversely affect the mechano-biology and hence sensation and bladder function. This can result in either symptoms of bladder overactivity and failure to store urine leading to incontinence or underactivity in the elderly.

New Therapeutic Options for UAB

Anthony Kanai

The development of UAB is multifactorial with neurogenic (*e.g.*, spinal cord injury, diabetes mellitus) and myogenic (*e.g.*, detrusor hypertrophy and decompensation as a result of benign prostatic hyperplasia) components contributing to the condition. There is a higher prevalence of UAB in the elderly where up to 45% of men and women over the age of 70 years can exhibit urodynamically diagnosed detrusor underactivity. However, it is incorrect to classify UAB as primarily an aging disorder since a multifactorial aetiology is known including neurogenic, myogenic, and iatrogenic heterogeneity of symptomology.

The diagnosis of UAB can be problematic as it is only possible with urodynamics which can detect high post-void residual volumes (in the absence of significant outlet obstruction), urethral overactivity, detrusor hypoexcitability or insufficient contractility. Some experts believe that UAB is a consequence of untreated or treatment-refractory OAB. Besides aging, inflammation, ischemia, and neuropathy can cause significant alterations to the properties of bladder smooth muscle and innervation and these could also be the basis for the development of UAB. Previous studies on aged patients and mouse models of UAB have determined that detrusor contractility and afferent signaling are impaired, presumably due to changes in neurotransmitter release from the urothelium and/or the sensitivity and coupling of the suburothelium interstitial cell network. Therefore, animal models characterised by impaired efferent/afferent signaling due to either neurologic injury or genetic mutation could be valuable models for understanding the pathophysiology of UAB secondary to aging or neurodegeneration in the CNS or periphery.

Aging also correlates with increased deposition of fibrotic tissues throughout the body including the urinary bladder which can be a contributing factor to UAB symptoms. Moreover, comorbid pathologies involving chronic fibrosis may also contribute to UAB symptomology. This talk will present and discuss data on new therapeutic approaches including mitochondrial-targeted free radical scavengers, anti-inflammatory agents, antifibrotic soluble guanylate cyclase (sGC) activators and other antifibrotic agents that also increase detrusor force generation.

Mitochondrial-targeted free radical scavengers. XJB-5-131 decreases reactive oxygen species (*e.g.*, superoxide, O_2^-) which can react with nitric oxide (NO•) to form peroxynitrite (ONO_2^-) which can inhibit mitochondrial respiration and mitophagy leading to apoptosis.

Anti-inflammatory agents. LM11A-31/-24 scavengers inhibit neurodegenerative signaling *via* $p75^{NTRs}$ on urothelial cells (UCs) and afferent nerves, while promoting nerve regeneration pathways through $TrkA/B^{NTRs}$ to prevent urothelial apoptosis and inflammation.

Antifibrotic agents that also increase detrusor force generation. Human relaxin-2 (hRLX2) is a hormone that is a member of the insulin super family. It has two chains and acts through relaxin receptor (RXFP1) which has been identified in mouse and human bladders. It acts through β-chain intermediates to reverse fibrosis and increase bladder compliance, and α-chain intermediates to increase the expression of Cav1.2 and detrusor smooth muscle contractility.

sGC activators and stimulators that are antifibrotic: Activators and stimulators of sGC increase PKG activity leading to inhibition of N-type Ca^{2+} channels in afferent nerves to dampen NDO and inhibit TGFβ-1 and pSmad2 signaling in myofibroblasts to reverse bladder fibrosis.

Mechanistic Concepts of UAB

Christopher Fry

UAB is one that exhibits a contraction of reduced strength or duration so that there is a prolonged emptying or a failure of complete emptying in a normal time. This implies a pathology associated with the bladder itself. There are a number of possibilities that are not mutually exclusive: i) geometrical considerations of bladder shape; ii) a detrusor myopathy, manifested as reduced contractility; iii) functional motor denervation of existing detrusor smooth muscle; iv) replacement of detrusor muscle with non-contractile or less contractile tissue. Each of these possibilities will be considered in turn to aid our search for therapeutic approaches to ameliorate or reverse the consequences of a UAB.

Geometrical considerations. The underlying relationship between the pressure-generating variable, wall tension, and intravesical pressure itself is dependent on the capacity and shape of the bladder itself. Such geometrical effects will always be an underlying confounding variable and the magnitude of this in a patient population will be demonstrated.

Detrusor myopathy. Altered detrusor contractility reflects a change to the intrinsic excitation-contraction coupling process in smooth muscle. Evidence for any change in this process in contributing to poorly functioning animal and human bladders will be discussed. Evidence will be drawn from both *in vivo* urodynamic results from patients and *in vitro* isolated multicellular and single cell experiments measuring contractile function and regulation of intracellular [Ca^{2+}]. Allied to this hypothesis is whether there is also a change to detrusor electrical excitability – a decrease may imply a reduced ability to initiate and conduct electrical signals across the cellular syncytia in the bladder wall.

Functional denervation of detrusor smooth muscle. Voiding contractions are elicited by coordinated activation of postganglionic parasympathetic nerves that use acetylcholine (ACh) and ATP as excitatory transmitters (ACh exclusively in normal human bladder; ATP as an additional transmitter in human overactive bladder and that from most animals). UAB may result from a reduced functional nerve density or reduced effectiveness of transmitters (*e.g.*, through lower efficacy/potency or increased breakdown rate). Evidence for this as a contributor to bladder underactivity will be presented.

Replacement of detrusor muscle. A reduction of bladder wall tension development can also result from fewer detrusor myocytes in a given volume of tissue, due to increased deposition of ECM or a change of cellular type. In particular, an increased quantity of ECM is associated with greater generation of collagen and a change of its subtype; cellular changes include raised numbers of interstitial cells and increased differentiation to a myofibroblast phenotype. Such a change to gross tissue structure has been observed in many bladder pathologies and evidence will be presented if this is a significant contributor to a UAB phenotype.

It must be emphasised that none of these hypotheses is necessarily exclusive of another, so consideration needs to be given as to which play significant roles in the development of a UAB.