Introduction

Overactive bladder (OAB) is a clinical syndrome characterized by troublesome symptoms namely urgency, often with urinary incontinence, frequency and nocturia.[1] Although the condition is not life threatening, it induces a great negative impact on patients' quality of life and produces a plethora of healthcare concerns, with consequent, marked costs for the health systems. Estimations show OAB involves more than 50 million Americans and Europeans, which is 15% of the combined population.[2] Despite the composite structure of treatment, which includes bladder training, with or without pelvic floor biofeedback, different pharmacological agents, and minimally invasive surgical options as third line option (sacral neuromodulation, intravesical botulinum A toxin and posterior tibial nerve neuromodulation), about seventy-five percent of OAB cases aren't managed. All the actual treatments seem to be imperfect. As it is imperfect our knowledge about the pathophysiology of the condition, which increasingly appears to be multifactorial in many cases.[2]

Despite these difficulties, science does not stop and research in the molecular, clinical, and technological fields continues, outlining a horizon full of new possibilities. On a physio pathological point of view the good new appears to be patient phenotyping according to the presence of different cofactors playing an important role on the development and course of the disease, and possibly, on the response to treatment. Patients' phenotyping will have necessarily to induce the physicians to change their attitude towards affected patients, using a broader view, outside the boundaries of the bladder and urethra. And apart from the well-known and currently applied treatments, there are more therapies coming out. With regards to pharmacological agents, new B3-AR agonists,[3] novel TRPV1 inhibitors and P2X3 antagonists,[4, 5] and cannabinoid receptor agonists[6] are currently under investigation in both pre-clinical and clinical studies. Among new technologies, several tibial nerve stimulators are in development, and different organ stimulation (*e.g.*, dorsal genital nerve and saphenous nerve stimulation) are being realizing;[7, 8] also, new delivery systems are under investigation to improve intravesical drug administration,[9] and radiofrequency devices therapy appears to be an exciting treatment possibility.[10]

What is necessary is not to be trapped in dissatisfaction or apathy towards such a difficult condition to treat, or in aversion to new therapeutic possibilities. Always keeping in mind to treat the patient with the disease and not just the disease, what constitutes taking care of the patient.

Antonella Giannantoni

References

1. Haylen BT, de Ridder D, Freeman RM, *et al.* An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29:4–20.
2. Stewart WF, Van Rooyen JB, Cundiff GW, *et al.* Prevalence and burden of over-active bladder in the United States. World J Urol 2003;20:327–36.
3. Yoshida M, Takeda M, Gotoh M, *et al.* Efficacy of novel β3-adrenoreceptor agonist vibegron on nocturia in patients with overactive bladder: A post-hoc analysis of a randomized, double-blind, placebo-controlled phase 3 study. Int J Urol 2019;26:369–75.
4. Brown W, Leff RL, Griffin A, *et al.* Safety, Pharmacokinetics, and Pharmacodynamics Study in Healthy Subjects of Oral NEO6860, a Modality Selective Transient Receptor Potential Vanilloid Subtype 1 Antagonist. J Pain 2017;18:726–38.
5. Davenport AJ, Neagoe I, Bräuer N, *et al.* Eliapixant is a selective P2X3 receptor antagonist for the treatment of disorders associated with hypersensitive nerve fibers. Sci Rep 2021;11:19877–95.
6. Maniscalco GT, Aponte R, Bruzzese D, *et al.* THC/CBD oromucosal spray in patients with multiple sclerosis overactive bladder: a pilot prospective study. Neurol Sci 2018;39:97–102.
7. van breda HMK, Farag FF, Martens FMJ, *et al.* Subject-controlled, on-demand, dorsal genital nerve stimulation to treat urgency urinary incontinence; a pilot. Front Neurosci 2016;10:24.
8. MacDiarmid SA, John MS, Yoo PB. A pilot feasibility study of treating overactive bladder patients with percutaneous saphenous nerve stimulation. Neurourol Urodyn 2018;37:1815–20.
9. Liu Q, Liao L. Nano-BTA. A New Strategy for Intravesical Delivery of Botulinum Toxin A. Int Neurourol J 2022;26:92–101.
10. Xu ZH, Zhang PF, Wang YF, *et al.* A Multi-Center, Randomized, Blind, Controlled Clinical Trial of the Safety and Efficacy of Micro Radio Frequency Therapy System for the Treatment of Overactive Bladder. Front Med (Lausanne) 2022;9:746064.

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Pathophysiology of OAB and refractory conditions

Antonella Giannantoni

Overactive bladder: a "subjective disease"

According to the definition of the International Continence Society, Overactive Bladder (OAB) is a symptom complex comprising urinary urgency, with or without urinary incontinence, often with increased daytime frequency and nocturia in the absence of infection or other obvious aetiology.[1] The symptom core of the syndrome is "urgency", which is the "complaint of a sudden compelling desire to pass urine which is difficult to defer".[1, 2] The defining element of OAB, which is urgency, gives the condition a subjective foundation which renders derivation of basic science insights challenging and makes development of animal models impossible. The term OAB has now become widely used not only in urology among the involved specialists, but in the more general medical field, as due also to its high prevalence, varying largely from 1% to 38% according to the most recent reviews on the topic, and increasing in both sexes with an increasing age.[3] Indeed, OAB prevalence rates in the contemporary literature differs so largely probably because of different definitions used, variations in clinical data collection and analysis, types of performed clinical studies (retrospective vs prospective, community population vs clinics, different age population included). In addition, it is also possible that cultural, ethnic, and racial differences may play a role in adequately addressing the disease.[4]

OAB shows a great impact on quality of life, which is higher than that observed in hypertension and diabetes.[5] Furthermore, the economic impact of OAB is relevant for the health services: in 2020, the projected cost of managing patients with OAB in the US was 82.6 million.[6]

Physiopathology of OAB: new evidence and the target of phenotyping

From a physiopathological point of view, OAB remains the most fascinating, mysterious, not yet completely clarified syndrome existing among urological diseases. Although the inclusion of the term "bladder" in the definition suggests an underlying mechanism related to a bladder dysfunction, we currently have elements that many factors beyond the bladder contribute to the genesis and development of the disease.[7] Nevertheless, as in many cases the physiopathology of OAB remains unknown, the adjective most frequently used in its characterization is "idiopathic". In the last 10-15 decades, many observations have emerged from clinical and basic research studies, which have led to the formulation of some etiopathogenetic hypotheses underlying OAB.[8]

These hypotheses, which will be examined below, have led to the conviction that different subtypes of OAB exist, and that it may be possible to perform patient's phenotyping based on both the origin and the specific, clinical characteristics of the individuals affected. Indeed, a recently published review on the pathophysiology of OAB, has described the following observed phenotypes, with corresponding etiopathogenetic hypothesis:[8]

1. phenotyping according to the presence of detrusor overactivity (DO) on urodynamic evaluation, which includes the myogenic hypothesis, the urotheliogenic hypothesis, the urethrogenic hypothesis and the neurogenic hypothesis;
2. phenotyping according to the presence of comorbidities (pathophysiological cofactors), including metabolic syndrome, affective disorders, sex hormones deficiency, imbalance of urinary microbiota, functional gastrointestinal disorders, autonomic nervous system dysfunction.

Phenotyping according to the presence of detrusor overactivity

Detrusor overactivity represents a urodynamically based diagnosis of involuntary detrusor contractions during the filling phase of the micturition cycle,[1] which may

be responsible for the emergence of the clinical picture of OAB. Although DO and OAB have used interchangeably in the past, it is now clear that only about 50% of patients with symptoms of OAB present with a diagnosis of DO on urodynamic investigations.[9] Thus, other mechanisms have been hypothesized which may rely on a dysfunction of the bladder afferent signaling, potentially driving the symptom of urgency in the absence of DO.

The myogenic hypothesis underlying OAB, would be based on the observation of denervation-related supersensitivity phenomena.[10, 11] Accordingly, partial denervation of the detrusor, as due to chronic ischemia and oxidative stress, may alter the properties of the smooth muscle cells leading to increased excitability. Alongside this mechanism the hypothesis of an abnormal electrical coupling of smooth muscle cells into the bladder wall, leading to the emergence of unvoluntary detrusor contractions, was added later.[7] More recently, a large amount of scientific work has been carried out mainly on the sensory function of the organ, and therefore on the afferent bladder nervous transmission, giving a great boost to investigations on the role of the urothelium, as a real sensory organ capable of communicating with the underlying smooth muscle cells and nerve fibers through several neurotransmitters and receptors.[12]

According to urothelial origin of OAB there may be changes in urothelial receptors function and neurotransmitters release (ATP, NO, Ach, norepinephrine, prostaglandins, Nerve Growth Factor) as well as in the sensitivity and coupling of the suburothelial interstitial cell network, leading to an enhancement of the afferent signaling with resultant, unvoluntary detrusor contractions inducing the feeling of urgency of micturition.[13]

The origin of OAB can be also explained as coming from a urethral dysfunction, which configures the urethrogenic hypothesis of OAB. This is particularly clear when considering patients affected by mixed urinary incontinence in whom the entry of urine into the proximal urethra can represent the element driving urethral afferents stimulation with a consequent activation of the micturition reflex (urethral-vesical reflex).[14, 15] Another mechanism of urethra driven urgency relies on urethral pressure changes during bladder filling, a phenomenon termed "urethral instability", which may be caused by a dysfunction of pudendal nerves or central nervous system control.[16]

Alteration of the central nervous control on the micturition reflex, has been advocated since many years ago to explain the origin of OAB with and without DO in patients with diffuse lesions of the cerebral white matter (supraspinal origin of OAB). The underlying physiopathological mechanisms can be synthesized in a reduced supraspinal inhibitory control on micturition reflex and/or a reduced capability to elaborate afferent information at a central level.[17] As confirmed by several functional brain imaging studies recently performed, different areas in the brain and brainstem seem to be involved in such mechanisms, *e.g.* frontal and prefrontal cortex, insula, anterior cingulate gyrus/supplementary motor area.[17, 18]

Other pathological conditions that gradually turned out to have a great association with the overactive bladder syndrome are represented specifically by the metabolic syndrome and alterations of the psychological status, as anxiety and depression. In metabolic syndrome, different pathological factors may represent translational links for OAB: obesity, diabetes, systemic inflammation, increased sympathetic activity, hypoperfusion of pelvic muscles and urethral dysfunction, all factors due to the emergence and development of an insulin resistance condition. Both males and females can be affected by metabolic syndrome.[19, 20]

In recent times, the importance of affective disorders such as depression and anxiety in the aetiology of OAB and urinary incontinence has been greatly emphasized. Despite this growing interest, the exact nature of the association between OAB, UI and depression remains unknown, although depletion in some neurotransmitters (*e.g.* serotonin) and alterations in the afferent signalling to the limbic area of the brain seem both deeply involved.[21] In addition, alterations in the corticotrophin releasing factor neural pathway seem to represent other important contributors for the development of both depression and OAB.[22]

The role of functional gastrointestinal disorders in the emergence of OAB has been supposed due the frequently observed coexistence of constipation or faecal incontinence with symptoms of OAB. The explanation of this relationship can rely on the partial, common innervation of bladder and colon-rectum which has raised the possibility that OAB and gastrointestinal diseases may share common pathological features.[23] In addition, in particular diseases such as irritable bowel syndrome (IBS), many patients can be also affected by OAB or bladder pain. IBS is a functional gastrointestinal disorder characterized by symptoms such as abdominal pain or discomfort and alteration of bowel habits, despite the absence of an organic disease,[24] what can be explained by the existence of central sensitization phenomena involving the brain-gut-bladder axis.

The hypothesis of an imbalance of urinary microbiota underpinning OAB is based on the increasing evidence of different urinary microbiome composition particularly in women affected by OAB as compared to asymptomatic healthy subjects.[25, 26] In addition, it has been observed that female urinary microbiome influence also the severity of OAB, as the diversity and richness of urinary microbiome is accompanied by more severe OAB symptoms.[27] These and other observations confirm the hypothesis that changes in urinary flora may play an important role in the development of OAB, urinary incontinence and several lower urinary tract symptoms.

Hypothesis of sex hormones deficiency

In females the link between oestrogens deprivation, OAB, urinary tract infections and vulvo-vaginal disturbances has been deeply investigated. These symptoms

together configure a complex syndrome named genitourinary syndrome of menopause.[28] The underlying mechanism of oestrogens deprivation inducing OAB could be represented by changes in bladder afferents excitability, increased release of Ach, increased detrusor contractility via Rho-kinase pathway activation.[29] In males the evidence is not so abundant, but it seems that androgens deprivation may be linked to the emergence of OAB.[30]

Hypothesis of autonomic nervous system dysfunction

Subclinical variability of the autonomous nervous system during bladder filling has been recently detected in patients affected by OAB. Several studies have been conducted by measuring the hearth rate during filling cystometry in subjects affected by idiopathic OAB, showing a predominant parasympathetic activity with an empty bladder and a preponderant sympathetic activity at the end of bladder filling.[31]

The existence of a sub-clinical dysfunction of the autonomous nervous system could explain at least in part the presence of idiopathic OAB in patients in whom DO is not detectable.

Refractory OAB: what it is and how to win the battle with it

Lifestyle interventions and behavioural therapies, often combined with anticholinergic medications represent the first step in OAB treatment.[32] Unsatisfactory treatment outcome often has been reported as frequently occurring in patients treated with this kind of therapy,[33] but the exact prevalence of refractory patients (non-responders) is still unclear. Missing definition of "refractory OAB" seems to represent one of the main problems when addressing and treating patients affected by the condition.[34] Several symptom-based definitions and patient-reported outcomes with inconsistent thresholds are used in the literature to establish whether patients respond or are refractory to conservative and/or antimuscarinic treatment.[33, 35] As examples, in a previous study by Kuo**,** refractory of OAB was defined as "failure of antimuscarinic treatment during the previous 3 months before undergoing botulinum toxin injection".[36] In another study of Brubaker *et al.*, idiopathic OAB was defined as "inadequate symptom control after at least 2 previous therapies which had to include anticholinergics and at least 1 behavioural therapy, physical therapy or biofeedback".[37] Nitti and Chapple defined refractory OAB as "insufficient efficacy of antimuscarinics or intolerability to these agents", again a definition which lacks patients' perspective.[38, 39] Also the available guidelines refer to patients refractory to antimuscarinic treatment but still avoid to define the criteria for such definition.[32]

On patient's point of view, different expectations have been described about OAB treatment, and different explanations have been reported as causes of treatment failure.[35] Indeed, proper evaluation of treatment outcomes appears to be of major importance; beyond objective parameters, symptom bother, and quality of life should be always considered, and patients 'satisfaction in relation to their expectation remains the most important outcome parameter.[40]

Difficulty in defining what is refractory OAB, and different prevalence rates of responders to treatment or of refractory cases, as reported in the published literature, have led over time to development and use of many pharmacological agents (*e.g.*, several antimuscarinic drugs, beta-3 agonists, botulinum toxin) and different, often combined strategies (increasing anticholinergic doses, combination of anticholinergic drugs with botulinum toxin and/or beta-3 agonists), with variable success rates in the control of OAB symptoms.[41]

Beyond problems in defining refractory OAB and patient and physician expectations of treatment, we now recognize that the frequently observed multiple pathophysiological mechanisms, even coexisting in the same patient, could explain the reasons for the often-ineffective treatments. We should remember that OAB is a subjective symptom and not a disease, difficult to explain on a pathophysiologic point of view and difficult to measure. When we are faced with a patient who presents symptoms of OAB we need to realize we have not made a diagnosis, but we are at the beginning of a path, perhaps long, which however is aimed first to phenotyping him/her and then trying to treat. It means that there is not one single type of OAB, but different OAB phenotypes which can be difficult to assess and can require different, personalized therapeutic approaches or, more likely, a multimodal therapeutic approach.

Reorganizing our ideas thanks to growing knowledge in the field, and reviewing the meaning of this condition, particularly in pathophysiological terms, appears the only way to obtain consistent therapeutic benefits in patients affected by OAB.

References

1. Abrams P. Cardozo L, Fall, *et al.* The standardisation of terminology of lower urinary tract function: report from the Standardisation Sub-committee of the International Continence Society. Neurourol Urodyn 2002;21:167–78.
2. Haylen BT, De Ridder D, Freeman RM, *et al.* An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Neurourol Urodyn 2010;29:4–20.
3. Milsom I, Abrams P, Cardozo L, *et al.* How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001;87:760–6.