PATHOPHYSIOLOGY, MECHANISM AND MANAGEMENT OF OVERACTIVE BLADDER
SYNDROME-A REVIEW

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ABSTRACT

An overactive bladder (OAB) is a syndrome which causes an impulsive desire to pass the urine. This desire or urge may become difficult to control and eventually may lead to unintentional passage of urine. The marked increase in a number of patients who suffered with OAB feels very awkward and tiring to handle and may lead to psychological disturbance. For this reason, the identification of symptoms and appropriate diagnosis is very important. It is necessary to understand the pathophysiology, available treatment and recent updates to direct the researchers for further investigation. This review article focuses on comprehensive information of normal bladder physiology, neural control, regulation of micturition, pathophysiology, and prevalence of overactive bladder. This article gives an information regarding diagnosis, different approaches for treatments and future perspective of OAB syndrome.

INTRODUCTION

Since the last two decades, people suffering from OAB syndrome/symptom has increased enormously worldwide and is anticipated that it will cross 546 million populations by 2018. The annual worldwide healthcare cost for OAB is enhanced from €1.4 trillion to €3.2 trillion by 2018. Though the percentage of both male and female patients is most similar it is slightly more in women population [1]. In the initial phase of OAB syndrome, individual may not understand the indication of urine urgency which may occur due to the large volume of liquid intake, any physical exertion, stress-induced or any other defect occurred in the body functioning. At the initial stage, it is very difficult for both patient and physician to identify the symptoms of OAB [2]. Thus, making a note on the diary with date and time with respect to fluid intake, voiding and urine leakage will help to identify the symptoms of OAB. For physicians, it is necessary to evaluate the basic and clinical impact and get a detailed patient history to diagnose OAB. In clinical practice, the syndrome of OAB can be defined as a condition which is characterized by urinary urgency, with or without urge incontinence, usually with urinary frequency and nocturia [3]. Debbie Kinsey and colleagues revealed that the patients suffered from OAB are psychologically very disturbed and lived a lower quality of life than normal people [4]. This review article provides an insight of the neural control, bladder physiology, regulation of micturition in a normal individual and also disrupt the mechanism of micturition in OAB patients along with the risk factors, prevalence, assessment, management and future perspective of OAB. For this review article, an extensive literature survey was carried out on search engines including Pubmed, Science Direct, Google scholar by referring keywords as subsections mentioned in this article and collect the information available tentatively from year 1980.

Neural control, bladder physiology and regulation of micturition

The continuous efforts are taken in order to understand the complex and highly distributed functioning of neural control of urinary bladder and urethra which results in the process of micturition. The role of neural ascendancy on the bladder and urethra are to facilitate urine discharge when the mechanical, emotional and social circumstances are appropriate. The synchronized activities of urinary bladder for urine collection and discharge are managed by the central and peripheral nervous systems which are mediated through multiple neurotransmitter systems [5]. The various parts of the body involved in this coordination are the brain, smooth and striated muscles of the urinary bladder, bladder neck, urethra and urethral sphincter [6, 7]. In brief, during the time of storage of urine in the bladder, the detrusor muscle undergoes distess or unend while the external urethral sphincter gets contracted and the information related to bladder filling is continuously sent to the central nervous system (CNS). Inversely, during micturition, the bladder contracts and the external urethral sphincter come into relaxation mode, and results in to the discharge of urine [8]. The detailed mechanism of neural control and regulation of micturition are shown in fig. 1. At the top of spinal cord, there is a main control center in the Pons (the part of the brain-stem that links medulla oblongata and the thalamus) where it unswervingly stimulates the bladder neurons. This center restrains the urethral sphincter, which synchronizes bladder contraction and sphincter relaxation and eventually the bladder gets void. The nervous system at several levels regulates the bladder and urethral sphincters particularly the sacral segments and the Pons. The lower urinary tract (LUT) is innervated by hypogastric, pudendal and pelvic nerves of sympathetic, somatic and parasympathetic nervous systems respectively. These nerves have both afferent as well as efferent axons. The nervous systems involved in efferent and afferent actions lead to urine accumulation and further urine release from the bladder.

In the first stage, the sympathetic innervation is initiated between detrusor and the urethral sphincter. The connection between brain and LUT is at the T10-L2 level of the spinal cord via sympathetic outflow. This innervation provides a noradrenergic inhibitory action at bladder body and excitatory effect at bladder base and proximal urethral sphincter inputs via release of noradrenaline on β3-adrenergic receptors and α1-adrenergic receptors respectively. This results in activation of hypogastric nerve, which persuades the loss of tension of bladder body by β3-adrenergic receptors and narrow bladder opening and urethra through α1-adrenergic receptors. This sympathetic activation contributes for urine storage in the bladder and maintains storage for prolonged time [5, 8-12]. β-adrenergic receptors are also found in urothelium [13, 14]. During the urine storage phase, the volume...
of apical umbrella cells enhances the stretching of the bladder muscle. At the same time some mediators release and excite the sensory fibers [15]. In the second stage, the striated urethral sphincter (SUS) is innervated by somatic motor neurons which are located in Onuf’s nucleus [6, 16]. Pudendal nerves appear from S2-S4 levels that excite the distal SUS. Activation of sacral somatic nervous system results in tightening of SUS. In the third stage, pelvic nerves which are the part of the parasympathetic nervous system are responsible for release of excitatory transmitter acetylcholine binds to M3 muscarinic receptor which provokes the contraction of bladder and relaxation of urethra. This contributes to urinary bladder emptying [9, 17]. In additional mechanism, adenosine triphosphate (ATP) binds to P2X 
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Sensations of bladder fullness due to increase in volume and wall tension, are transmitted to the spinal cord by the hypogastric and pelvic nerves [6, 20], while the pudendal and hypogastric nerves, specifically the sensory input are passed through the bladder neck and urethra. Moreover, the pelvic afferent nerve consists of two fibers myelinated Aδ axons and unmyelinated C fibers. The myelinated Aδ axons are sensitive to un receptive expansion and dynamic tightening [20] and hence transmit the information of the bladder filling whereas the unmyelinated C fibers react actively to noxious stimuli for cooling [21] or chemical irritation [22]. In a physiological condition such as spinal cord injury (SCI), these unmyelinated C fibers are not sensitive to bladder filling. In periadventricular grey matter (PAG), middle pons and frontal lobe area, it was observed that the improvement in the brain activity relates to the bladder volume [23]. The coordination of efferent and afferent actions revealed that after filling the urinary bladder, the afferent signals from the receptors in the wall of the bladder and the urothelium are promulgated towards higher point of PAG [23, 24] through the sacral spinal cord [25]. A switching action is activated when these afferent indications attain an adequately high intensity and subsequently increase the afferent signals which move down via the spinal cord and stimulate the sacral sections. This leads to the detrusor contraction and also endorses urethral sphincter relaxation which ultimately initiates micturition. Afferent nerves will carry on conflagration and empty the bladder till it gets completely vacant [5]

OAB

The normal function of LUT is characterized by the capacity to stay incontinence during urine accumulation and emptying bladder as per the individual convenience after receiving the sensation of bladder fullness. Such function is controlled by neural and micturition regulation mechanism. Inhibition in these organized functions lead to irregular urine accumulation and discharge. The disturbances in the afferent nerve regulation of bladder function will affect the urine storage and emptying system coordination [26]. The indications of OAB are urgency, frequency, nocturia and urge urinary incontinence [2, 3]. There are three different causes of OAB such as neurogenic, non-neurogenic and idiopathic. In neurogenic etiology, most of CNS conditions such as stroke, Parkinson's disease, traumatic brain injury, multiple sclerosis (MS), SCI, etc. have been associated. In non-neurogenic etiology, bladder outlet obstruction, bladder infection, chronic cystitis, bladder cancer, bladder stone, etc. are associated with OAB with respect to age [3]. Smooth muscles of urinary bladder are known as detrusor muscles and comprised of body or dome and base. β-adrenergic and cholinergic receptors are predominantly present at the dome, while α-adrenergic receptors are located at the base and the proximal urethra [17, 27]. The parasympathetic motoneurons are responsible for release of excitatory neurotransmitter acetylcholine, and interact with the muscarinic receptors. This results to tightening of bladder muscle and relax urethra which leads to the bladder emptying [9]. Amongst the 5 muscarinic receptors, subtypes M2 and M3 are the principle receptors sited on the bladder, whereas M3 receptors are overriding for the tightening of the detrusor muscle [17, 28]. During bladder enlargement there is an overstated effect of released acetylcholine from the urothelium. Subsequently, response to CNS generates the feeling of urgency, premature triggering and also promotes the symptoms of OAB [29]. It is also observed that a component in muscle or tissue rather than the nerve impulses feel the sensation for involuntary rise in the bladder pressure [30]. In the OAB syndrome, urinary bladder won’t be full but detrusor overactivity and external urethral sphincter will promote the release of urine by creating a sensation of urgency [31, 33]. The detailed mechanism is illustrated in fig. 1.

Factors responsible for risk of OAB

Problems associated with urinary tract infections may lead to permanent bladder symptoms, which are recoverable. Progressive age is a prominent factor which is more likely to contribute in OAB symptoms. Other reasons for OAB are neurological changes; the drag of gravity or weight may cause pelvic base organs to prolapse and susceptible to urinary tract infection because of the weaker immune system [34-36]. In women, a significant drop in estrogen level observed after menopause, which results in thinner and drier tissues of bladder, urethra, and pelvic muscle atrophy may be the cause that leads to urgency and
frequency of urination [37]. Some conditions like pregnancy and childbirth, disease of the nervous system, bladder cancer, pelvic surgery, enlargement of the prostate, urinary tract infection, overweight, medications like diuretics, sedatives, antidepressants, certain occupations like teaching, nursing, police officers, truck/bus driving, etc. may cause the risk of OAB.

Prevalence of OAB

Progressive age is a primary cause for the increase in the prevalence of OAB [36, 38, 39]. As per Milsom, OAB symptoms are more prevalent in European countries like France, Germany, Italy, Spain, Sweden and UK using a random and stratified approach [36]. In this study, the general population of men and women aged over and equal to 40 y were selected and younger women showed more OAB signs than men whereas the reverse condition was observed in the aged population. There was no significant difference in the overall prevalence reported in women and men of 16.9% and 16.0% respectively when compared the complete population of both. In specific area of a base number of people suffered from OAB in 2008 Irwin conducted a separate study which estimates globally and prevalence reported in women and men of 16.9% and 16.0% aged population. There was no significant difference in the overall Progressive age is a primary cause for the increase in the prevalence of OAB like National Overactive Bladder Evaluation study and The Epidemiology of Lower Urinary Tract symptoms [35].

Evaluation and diagnosis

The patient's history is of prime importance to elicit the symptoms of OAB. The physician considers the LUTS, any medical condition related to OAB, dietary habits, bladder storage and emptying associated with OAB, ongoing medication, current or past surgical problem, any radiation treatment for lower body cancer, physical examination (Body mass index, abdomen, genitalia, relevant pelvic examination, any radiation treatment for lower body cancer, physical examination, relevant pelvic examination, neurologic, mental status), urine analysis, urodynamic testing, post-void residual (PVR) measurement with an ultrasound bladder scanner, urine cytology, cystoscopy etc. There must be check on the of observable urinary tract disease. In normal healthy patients the range of frequency is four to eight voids per 24 h, thus additional voids may be significant to assess OAB. The information to be received from the patient through questionnaire should include number of voids in a day divided as daytime and nighttime, amount of urine over 24 h, utmost discharged urine amount, average and highest urine amount, and night-time urine amount. An evaluation of lack of voluntary control over urination in terms of seepage episodes and usage of can also be obtained. The overall history, monitoring, test outputs will help to a physician for the evaluation of OAB and accordingly set the treatment approaches [2, 35, 41-44].

Treatment for OAB

Lifestyle intervention, behavioral treatments, bladder training

After receiving the information from the patient through questionnaire and the regular monitoring activities through the bladder diary, the physician may initiate the treatment based on the intensity and the cause of OAB. The lifestyle intervention includes altering fluid intake, smoking termination, avoid bladder irritants like organic and carbonated beverages, coffee, body weight reduction, adaptation bowel role to spasm, constipation and spasm during bowel movements and sleeping time [35, 41, 42]. In behavioral treatment, the patient has to be trained in improving the control to restrain or disrupt detrusor tightening. To manage the seepage of urine, a deliberated pelvic floor muscle tightening should be practiced which makes possible to get better stress within the urethra and hinder the detrusor tapering. In the elderly population after the physical examination training for two seconds as mentioned above with fifteen replication has to be scheduled and this should be followed thrice a day. The patient should progressively increase this practice by almost one second every week, till they attain ten second tightening and relaxations. Gradually the patient is trained to uphold the urination in such a way that, whenever he/she feels the urgency, he/she tightens the pelvic floor muscles exclusively until the pressure is gone. The practice of walking towards the washroom at regular speed should be repeated whenever the sense of urgency arises. Trained professional shall instruct the patient for at least 3 mo to see the benefits of these instructions [41, 42, 44, 45]. In the bladder training program after reviewing the bladder diary of a patient, the physician has scheduled the longest comfortable interval between voiding the bladder in object to reduce its frequency. The patient is trained to empty the bladder after awakening, then at a pre-scheduled time of the day and finally before going to bed. In case if the sense of urgency occurs between prefix intervals, the patient is trained to tighten the pelvic floor muscles until the schedule voiding time have been reached. After 1-2 w, the patient is trained for gradually increasing time distance between the urination. During this training the patients are encouraged to sit down in urgency, take slow, deep breaths and concentrate on breathing instead of bladder sensation [42, 46]. For the above mentioned programs, the exercises must be completed daily with motivation to patience. If these measures fail to control the symptoms, then anticholinergic medications are added [33, 38, 43].

Anticholinergic or antimuscarinic drugs

As described in the first section of this review, the parasympathetic postganglionic nerves, releases neurotransmitter acetylcholine, this binds to the muscarinic receptor M3 on the detrusor muscle which results to the contraction of the bladder [9, 18]. In OAB patient, during the bladder filling the anticholinergic drugs competitively inhibit acetylcholine binding to M3 receptor as shown in fig. 1 and avoid instictive tightening of the bladder. Secondly, anticholinergic drugs inhibit potentially urothelial sensory receptors and decrease afferent nerve activity, i.e. sensory inputs from the bladder [41, 42, 47-51]. These drugs enhance the capacity of the bladder at the first automatic contraction response [2, 47, 52]. Since the anticholinergic drugs act competitively, the immense discharge of acetylcholine during urination will curtail the active motility consequence and detrusor muscle squeezes [42]. The selective anticholinergic drugs have more affinity for the M3 receptor and therefore may reduce the side effects associated with these drugs [35].

Commonly used anticholinergic drugs are oxybutynin, darifenacin, solifenacin, tolterodine, fesoterodine, trospium, propanteline, propiverine [1, 32, 35, 41, 42, 53]. Flavoxate [2] and propantheline [54, 55] are considered as the antispasmodic drug with anticholinergic activity. Flavoxate acts by involving intracellular cAMP accumulation and calcium obstructive action. It restrains the bladder tightening persuaded by different agonists or by electrical stimulation and decrease the occurrence of the bladder emptying. It enhances the bladder space capability and decreases urination pressure [56]. Propiverine inhibits the calcium invasion and modulates calcium of intracellular in urinary bladder smooth muscle cells causing musculotropic spasmolysis.

Due to anticholinergic action it also inhibits the efferent correlation of the nervous pelvicus [57]. Constipation and dry mouth are two most common adverse effects of the anticholinergics. Amongst the aged individuals serious side effects of antimuscarinics are cognitive deficits and confusion along with CNS effects such as insomnia, dizziness, sedation [2, 35, 41, 42]. After initiation of the therapy, careful management is required considering side effects, dose, dosage form, and pharmacokinetic-pharmacodynamic of individual drug [42].
β3-adrenergic agonist drug

During the urine storage phase in the bladder, the sympathetic nerve releases catecholamine (noradrenaline) which binds to the β3-adrenergic receptors on the detrusor muscle. It also provides inhibitory action resulted in a relaxation of the bladder [5, 8, 9]. The single and only approved drug mirabegron acts as a potent and selective β3-adrenoceptor agonist as demonstrated by in vitro laboratory experiments. In mammalian species, it relaxes the smooth muscle of the bladder through the increased cAMP concentrations in the tissue. In OAB rat models, mirabegron enhances the average emptiness volume per urination, reduces the frequency of non-voluntary tightening and increases the bladder capacity without disturbing discharge stress and enduring urine volume. Mirabegron illustrates decreased annulled incidence. Hence, mirabegron can be used in patients who stop the previous anticholinergic therapy [58-61]. Some of the common side effects of mirabegron are tachycardia, urinary tract infections, nausea, constipation, headache, diarrhea, dizziness and uncommon or irregular heartbeat, increased blood pressure, angioedema [62, 63].

Other agents

Desmopressin acetate

It is a synthetic analogue of antidiuretic hormone (ADH) vasopressin which is formed by the hypothalamus and preserved in the posterior pituitary gland [2, 64]. The primary role of ADH is to contract extracellular fluid volume in the body. Desmopressin acts on the kidneys by reducing the amount of urine produced at night and also responsible for re-absorption of water by kidney [65, 66]. Desmopressin acts by imitating the ADH role. Due to hyponatremia, the nasal dosage form is no more indicated for primary enuresis [2, 65, 67]. As such desmopressin is a safe medicine with less side effects such as a headache, stomach ache and occasional emotional disturbance [68].

Tricyclic antidepressants

Imipramine and amitriptyline have been used for OAB treatment due to their many therapeutic properties as well as an alpha-agonist action [2, 69, 70]. Their antidepressant activity is feebler than the others of the same category. There is a limitation of imipramine use amongst the old aged patients for OAB syndrome [70]. However, it has been mentioned that due to the central effect of the automatic emptiness, imipramine has been suggested to combine with the urge–stress incontinence especially in older women [34]. The side effects observed are vast including dry mouth, constipation, stomach pain, nausea, cardiac arrhythmias, urinary retention and drowsiness [35].

Invasive therapies

When patients are not responding to the medications and therapies, the physician may offer a highly specialized and expensive therapy such as Botulinum toxin A. In most of the cases, tolerability can be limited due to significant side effects, although in some cases it shows a significant clinical success. Following are the invasive therapies used to treat severe OAB condition.

Botulinum toxin A

This is a strong neurotoxin formed by Clostridium botulinum. It works by restraining the calcium intervened discharge of acetylcholine at the pre-synaptic neuromuscular intersection in peripheral nerve endings and facilitates in permanent flaccid muscle paralysis [71, 72]. This binding of the toxin to the peripheral and central nerve ending is well discriminated [73]. The molecule gets absorbed by attaching to the neuronal cell membrane with the heavy chain [72, 74]. Then a dually reaction disconnects the heavy and the light chain. The free light chain attached to the acetylcholine vesicles performs as a zinc-dependent endopeptidase which divides in numerous proteins required for the combination of neurotransmitter vesicles with the cell shell, and avoids acetylcholine ejection and conjugating the neuromuscular end-plate [72, 75]. The reconstituted solution is administered in the bladder through injection via flexible or rigid cystoscope which is kept away from trigone and base. A total of 15 to 20 injections may be required during management of the OAB. Summary of the Product Characteristics of BOTOX® 100 Units was describing the spot of injections in the urinary bladder [71, 76]. Possible side effects of Botulinum toxin A may include generalized diplopia, blurred vision, dysphasia and weakness.

Neuromodulator implants

Sacral neuromodulation is an operative treatment for individuals with refractory OAB. Tanagho and Schmidt are the pioneers of this surgery in which an electrode is to be implanted in the S3-S4 sacral foramen to create persistent electric sacral nerves activation and reinstate normality for emptying behavior [77]. Basically, this surgery is divided into two stages, in the first phase the efficacy of implantation has been demonstrated and then second phase follows permanent implantation. A tinned quadripolar lead is inserted through the skin into the S3 foramen using bony landmarks and fluoroscopic guidance. The nerve core is stimulated electrically to judge the position. To evaluate the correct placement of quadripolar lead there are some responses to be observed in the toes, rectum, labia, penis and vagina. An external pulse maker is coupled to the quadripolar lead after positioning in S3 foramen which has the ability to alter the activation force, frequency and pulse width. Fifty percent or more in OAB condition is the criteria for device or it should be removed if no improvement is observed [78, 79]. Although the considerable use of sacral neuromodulator is observed in past decades, the exact mechanism remains feebly illuminated. Leng and Chancellor have stated that the automatic urination is caused due to the activation of the unmymelinated C fibers and alpha-myelinated afferent fibers in pelvic and pudendal nerve roots [80]. Electric stimulations produced by sacral neuromodulator stimulate the pacemaker of the bladder and are capable of restraining the neural reflexes [81]. According to the additional mechanism, the sacral neuromodulator impacts straight hindering efforts to the bladder, which repress OAB and develops urinary withholding [82]. There are number of complications due to neuromodulator implants which need surgical correction involves the relocation of the device due to pain. The most commonly observed side effects are pain at stimulator site, pain due to misplacement of lead, temporary electric shock [83]. It is used in pregnancy, but remains unclear and undetermined whether associated with teratogenic effect. Overall, this is a complicated treatment and adverse events are dependent on the type of complication [79].

Augmentation cystoplasty

An augmentation cystoplasty (AC) is a surgical operation for bladder enlargement (increasing the size of the bladder). Bladder augmentation was found to be useful, especially with underlying neurological disorders such as SCI, MS and myelodysplasia. Detubularised patch of the ileum is the most frequently used bowel segments for AC. While ileum is not suitable for augmentation, sigmoid colon is the most common alternative. Augmentation caecocystoplasty (the caecum) and augmentation gastrocystoplasty (the stomach) can also be used in this surgical procedure [84]. The results of both autoaugmentation and ureterocystoplasty are either poor [85] or revision of surgery is required [86]. The AC involves there is a high risk of complications such as prolonged postoperative ileus, transient urinary fistula, wound infection, bleeding which requires reoperation, metabolic complications, acid-base and electrolyte disturbances, haematuria-dysuria syndrome in gastrocystoplasty, peptic ulceration and/or perforation of the bladder, urinary stone formation after augmentation, potential increased risk of malignancy, bowel disturbance and urologic surgery after AC [84].

New drug delivery system (NDDS) for urinary bladder diseases

The conventional drug delivery system may lead to the fast absorption from gastrointestinal tract resulting to minimum efficacy with side effects of the drug. The long-acting targeted drug delivery system is used for treatment or management of OAB syndrome with fewer side-effects and better patient compliance. Table 1 illustrates the NDDS available or under development for the drug delivery to treat OAB syndrome.
CONCLUSION

The plethora of research illuminates in this review provides information of OAB and its different therapies like behavioural modification, drug therapy and the combination of both. For the evaluation and initiation of these therapies, a urologist should collect the history of the patient, information about lifestyle, urination of patient and perform a physical examination, different tests like urine analysis. If the symptoms are not managed by these treatments, then invasive therapies like botulinum toxin A injection, neuromodulator implants, augmentation cystoplasty may be exploited by a physician with complete control and balancing the efficacy and complications or side effects of invasive therapies. In future, researchers have to explore the drug therapies with limited side effects and high beneficial for the patients over an available class of drugs. Antimuscarinics are mostly used as first-line therapy, but showed many side effects due to less receptor selectivity. Hence, it is necessary to investigate more selective antimuscarinic agents. Invasive therapies are slowly getting popular in OAB patients despite of more complications than efficacy percentage. Investigators are needed to pay an attention for decreasing the complications and side effects of these therapies and simultaneously improving the relief ratio. Moreover, educational resources should be provided to the people for creating awareness, especially in women population to let them understand the issue and accordingly the healthcare services can be provided.

AUTHORS CONTRIBUTIONS

Both the authors namely Pankaj Mandpe and Bala Prabhakar were involved equally in literature survey, framing contents, writing draft paper and finalising the review paper.

CONFLICTS OF INTERESTS

Authors declared that there are no potential conflicts of interest.

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