Over Overactive Bladder (OAB)

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Overactive bladder or OAB is a symptom syndromes described by the International Continent Society (ICS) since 2002. Before that many synonyms such as hyperactive bladder, detruser hyperreflexia, and bladder instability were used interchangeable and causes confusion among physician writers and readers.

OAB symptoms comprise of lower urinary tract symptoms mainly urgency (a sudden strong desire to urinate symptom) with or without urgency incontinence (a sudden strong desire to urinate symptom with urine leakage), frequency of urination (urinate more than 8 times per daytime), nocturia (awaken to urinate more than 2 time per night)[1]. OAB can be diagnosed in a condition of ruling out other pathological diseases that cause lower urinary tract symptoms. Many life threatening pathological conditions such as lower urinary tract infection, obstructions and tumors of the lower urinary tract can produce these symptoms mimic OAB symptoms therefore careful workup and investigations should be done before diagnose OAB.

Incidence

Studies from 6 European countries revealed 16.6% of the population aged > 40 years has symptoms of OAB which increases with age[2]. As well as in USA approximately 33 million (16.5%) aged >18 years in the year 2002 had OAB symptom[3,4]. In Asia with a questionnaire-based survey done in 5502 females from 11 countries demonstrated the overall prevalence of OAB was 53.1%. The most common presenting symptom was urgency 65.4%[5].

Although OAB is not a life threatening condition but it leads to many health problem consequences with poorer quality of life than control group[6]. It increased the risk of hospitalized or nursing home 30% in women and 50% in men. Falls and fractures from sudden rising to toilet due to urgency and avoid wetting are the major causes. In one study claimed that OAB increased the risk 50% of femoral neck fractures in postmenopausal women[7]. Many OAB patients abandoned there social activity, travels, sports and isolated themselves which lead to depression in 50% of patients[8].

Pathophysiology of OAB

Bladder has two main functions first as urine storage and second as a pumping machine to expel urine. During urine filling phase the bladder is quiet without contraction, expanding with increasing sensation of fullness from first desire, normal desire, strong desire to urinate and urgency. Normal adult bladder capacity can hold up 350 to 500 cc of urine and urinate any time they want even in a small amount. Therefore adult urination is totally a voluntary control from the higher cortical brain.

But in OAB patients the bladder is out of control it sudden contract during filling phase (involuntary contraction) increase bladder pressure, sudden sense of urgency without or with urine leakage (urgency incontinence). This results in frequency of urination and nocturia. Disruption of normal neural pathway either afferent or efferent such as stroke or spinal cord injury can induce detrusor overactivity, called neurogenic cause. Abnormal detrusor muscle ultrastucture[9] and function itself can caused spontaneous contract and induce detrusor overactive[9,10].

To diagnose OAB

"Bladder is an unreliable witness" this quotation is known for experts in urological field. Symptoms of urgency with or without urgency incontinence, with frequency of urination and nocturia is caused by many medical or pathological conditions not specific for OAB. Therefore medical practitioners must rule out other conditions that can mimic OAB symptoms. Because OAB has marked effects on the patients' quality of life as well as their families, the therapist need to be prepared to consider the patient's psychosocial circumstances.

Lower urinary tract conditions:

1. Urinary tract infection (UTI) such as recurrent cystitis, Tuberculosis (TB) of urinary system
2. Bladder outlet obstruction such as BPH, stricture urethrae or meatus
3. Calculi in urinary system
4. Bladder tumour
5. Chronic bladder pain syndrome (Interstitial cystitis)
6. Estrogen deficiency, atrophic vaginitis

The author would like to emphasize that TB of urinary system is still commonly found in Thais population especially during AIDS era and missed diagnosis can occur. Bladder cancers, carcinoma in situ that also cause lower urinary tract symptoms instead of gross hematuria symptom that is well known.

Neurologic conditions:

1. Brain disease: cerebro vascular diseases, dementia,

Parkinson's disease, multiple sclerosis
2. Spinal cord disease: multiple sclerosis, disk herniate, spinal cord injury, meningomyelocele and tethered cord syndrome
3. Diabetic neuropathy

Some neurological condition such as Parkinson's disease after good medical control OAB symptoms can be relief as well.

Systemic conditions:
1. Volume over load, congestive heart failure
2. Diabetes mellitus cause osmotic diuresis
3. Sleep disorder
4. Abnormal arginine vasopressin release

Functional and behavioral conditions:
1. Polydipsia, excess caffeine or alcohol in take
2. Constipation
3. Impaired mobility
4. Psychological conditions

Excessive water drinking from misleading health advertisement (like drinking 8 glasses of water after awake) caused many normal patients to visit physician for frequency of urination, nocturia and was missed diagnose OAB.

Side effect of medication: diuretic, narcotics drugs

Physical examination

High residual urine is known to increase urinary tract infection, stone as well as LUTS. Therefore all patients should undergo general physical examination focused on bladder palpation for full bladder as well as constipation especially in old age. Inspection of male genitalia and urethrae to rule out stricture urethrae, urethritis. Meatal stenosis, urethral prolapse or infected caruncle in female. Digital rectal examination for size, contour, consistency and pain at prostate gland must be evaluated. Pelvic examination in female for infection, atrophic vaginitis or pelvic inflammatory disease can cause lower urinary symptoms.

General neurological test, anal sphincter tone, bulbocavernosus reflex as well as peri anal sensations is check for neurological deficit.

Investigations

Clean catch urine examination must be obtained to rule out hematuria and infection not only in the first visit but also further visit when clinical in doubt. Cystoscopy should be done in cases with hematuria, recurrent UTI and refractory to medical treatment. In older men uroflowmetry can be done as a screening for voiding function. Then measurement of residual urine can be done by catheterization or bladder scan device measurement.

Complex urodynamics studies is recommended in cases failure of initial therapy, cases with hydronephrosis from detrusor overactivity or clearly influence treatment such as biofeedback, pelvic floor training. Combine video-urodynamics is a gold standard useful when anatomy and physiology of bladder and sphincter need evaluation.

Therapy

Non-drug active therapies are used as a first line in mild cases or combined with medication with a report of better outcome. The most commonly used are bladder training (BT), pelvic floor muscle training (PFMT), and electrostimulation.

BT generally refers to a combination of patient education, scheduled voiding, urge-suppression techniques, and PFMT[11]. It is a modality to gradual increase interval between voiding, using voiding chart as a guideline. With voiding chart the patient and physician will notice total fluid intake and output, maximum and minimum physiology bladder capacity, interval between each voiding and severity of urgency and urge incontinence symptoms as well as quality of life. Most patients with mild OAB understand their behaviors through voiding chart automatically and adjust themselves by decreasing fluid intake and increasing interval between each voiding before the next visit. These patients are easy to manage.

Pelvic floor muscle training has been advocated of improving pelvic floor control and reducing OAB, urge incontinence symptoms. It is more recommended in patients with stress incontinence.

Comparison between patients received anticholinergic drugs versus bladder training tended to favor the anticholinergic group. There is no difference in frequency and sense of urgency but more drug adverse event in the anticholinergic groups. No eligible trials between anticholinergic drugs versus pelvic floor muscle training or versus electrostimulation were identified. Studies show that combination of anticholinergic drugs and bladder training is superior to non drug therapies alone[12].

Anticholinergic or antimuscarinic drugs are the main pharmacotherapy for OAB nowadays[13, 14]. The rational for using this group of medication in OAB is to block the parasympathetic acetylcholine pathway and thus reduce the intensity of detrusor muscle contraction. Detrusor muscle comprises mainly of muscarinic type 3 and type 2 receptors. Type 3 muscarinic receptors are the main receptors responsible for detrusor muscle contraction after release of acetylcholine mediator from parasympathetic nerve terminals during voiding phase[15].

Unfortunately none of the anticholinergic drugs available to date is specific to muscarinic receptors in the pathological bladder, and as a result the drugs can cause side effects e.g. dry mouth or eyes, constipation or nausea, somnolence, and dizziness.

Many antimuscarinic drugs are available in Thailand. No ideal drug is superior to the others in reports of cure or improvement in OAB symptoms, leakage of urine and urgency. Studies showed that higher doses give better outcome but with higher adverse effect as well as withdrawal rates. With higher doses max cystometric capacity significantly increase and higher residual urine during urodynamics study is well known. Extended release drugs are well more tolerable with higher cure rate than immediate release[14].

Oxybutynin chloride has been used to manage detrusor overactivity for over 40 years.[16] It is the most well studied antimuscarinic drugs and remain gold standard treatment for detrusor overactivity.[16] The drug is applicable for adults and pediatric patients 6 years and older. It has both musculotropic relaxant and local anaesthetic (Lidocaine like) activity. Oxybutinin is a marginal M_3 and M_1 selectivity and higher affinity for parotid gland receptors than detrusor muscle. This selectivity explains the relative higher incidence of adverse effect compared with other antimuscarinics. It has immediate and extended release formulas on market. This drug is rapidly absorbed and metabolized in the liver by the cytochrome P-450 CYP3A4 emzyme. It can cross the blood brain barrier and produce central nervous system adverse events between 1.2% to 4.3% that is not significant differ from others. The International Consultation on Urological Disease gives this drug a level "1" of evidence

and a grade "A" recommendation to treat OAB. Dose 2.5-5.0 mg thrice daily for immediate release and 5-30 mg daily for extended release[17].

Tolterodine was developed as an organ bladder selective antimucarinic drugs over salivary glands[18]. Therefore it proved to have less undesirable antimuscarinic side effect than oxybutynin but with similar efficacy. Tolterodine is non selective muscarinic receptors for M_1 to M_5. It is a tertiary amine with relatively low lipophilicity, well absorb and extensive metabolize by liver. Although tolterodine and oxybutynin are tertiary amines, tolterodine is 30 times less lipid-soluble than oxybutynin and crosses the blood brain barrier to a lesser degree. This may explain the low incidence of cognitive disturbance and central nervous system side effect over Oxybutynin. Extended release form is more popular than the immediate release form. The International Consultation on Urological Disease gives this drug a level "1" of evidence and a grade "A" recommendation to treat OAB. Dose 1-2 mg twice daily for immediate release and 4 mg daily for extended release[17].

Tropium chloride has been available in Europe as an antimuscarinic agent over 20 years. It is a non specific antimuscarinic agent similar affinity for the M_1 to M_5. It has three pharmacologic properties distinct from other antimuscarnic drugs[19]. First it is a positively charged quaternary ammonium compound; therefore it can not pass the blood brain barrier and caused low adverse CNSS effect as placebo in clinical trials. This is a predominant character over other antimuscarinic drugs that can be use safely especially in elders. Second it is not metabolized in liver like others antimuscarinic drugs therefore it will not interact with other medications. Third 60% of absorbed trospium is excreted as a pharmacologically active. Excretion of active compound in the urine may block muscarinic receptors at afferent nerve ending which is abundant in the submucosal layer. This topical afferent blockage may have influence on urgency and urge incontinence symptoms combine with its systemic effect. The International Consultation on Urological Disease gives this drug a level "1" of evidence and a grade "A" recommendation to treat OAB. Dose 20 mg twice daily[17].

Propiverine is an antimuscarinic drug with a calcium channel blocking properties. It has equal potency to treat OAB as others[20]. The International Consultation on Urological Disease gives this drug a level "1" of evidence and a grade "A" recommendation to treat OAB. Dose is 15 mg 2 to 4 times per day[17].

Solifenacin is an organ bladder antimuscarinc specific over salivary gland greater than tolterodine, oxybutynin and darifenacin respectively[21]. It is a new once daily antimuscarinic drug and metabolize in liver. Dose 5-10 mg daily[17].

Darifenacin is the first specific antimuscarinic to M_3 approved by Food and Drugs Administration (FDA) for OAB treatment in December 2005[22]. It is not available in Thailand nowadays. This M_3 selectivity could confer advantages in patients who have cardiovascular side effect, impaired cognition, complaint of dizziness, or sleep disturbance[17].

Most OAB patients in clinical practice response well with combination of behavioral therapy and antimuscarinic drugs treatment. But in refractory OAB patients or in patients unable to tolerate antimuscarinic side effects many of these treatments are armamentarium options.

Intravesical instillation with antimucarinic drugs such as Oxybutynin[16] may reduce systemic side effects with report of favorable outcome. It is suitable for patient who required self clean intermittent catheterization. Other instillation substances such as capsaicin and resininferotoxin are used in refractory OAB patients. These substances block vanilloid receptors at afferent C-nerve fiber in the bladder and inhibit abnormal irritative sensory reflex[23]. Resininferotoxin is more potent than capsaicin with no painful irritation adverse effect as capsaicin that requires analgesic locally bladder or even general anesthesia in some patients. The instillation effects last about 2 months or less.

In Siriraj Hospital we develop and extract capsaicin from Thai chilli to treat intractable OAB as well as patient intolerant to antimuscarinic side effects. It is very cheap contrast to its favorable outcome[24].

Intramural detrusor or suburothelium injection of Botulinum toxin injections is well known for treatment of hyperreflexic bladder in neuropathic bladder patients. Botulinum Toxin blocks the excretion of acetylcholine from parasympathetic nerves ending in neuropathic bladder patients. Now its use is also extended for refractory OAB patients and patients untolerate to antimuscarinic adverse effect. Its effect last for 6-9 months and repeat injection produce similar outcome as first dose until antibodies to Botulinum toxin is produced. The doses of injection are individual in each report between 100-300 units with or without trigone injection[25].

Sacral nerve modulation or sacral nerve stimulation (SNS) has proved its usefulness for urinary urge incontinence and idiopathic voiding dysfunction since early 1990's. The collective efficacy data demonstrate that approximately 70% of patients who undergo SNS testing for urgency, frequency, or urge incontinence achieve success compared with 4% in the control group[26]. With its new Tined leads development, the implantation percutaneously to sacral nerve 3 can be accomplished easily. This device is very expensive therefore only few patients can achieve. Surgical bladder augmentation or urinary diversion is not a common procedure for OAB patients nowadays.

CONCLUSION

OAB is a common disease in both sex and the incidence increases with age. Although not a life threatening disease (SNS) but patients lost quality of life and solitary life lead to depression. Therefore to diagnose OAB is strict on the definitions and rule out other pathological disease that mimic OAB symptoms. Physical examination is mandatory to rule out neurodeficit as well as anatomical disorder. Many armamentariums, as mentioned are effective to treat OAB symptoms nowadays.

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