Overactive Bladder during Childhood: When and How It Should Be Treated

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INTRODUCTION

Patients with overactive bladder (OAB) were assumed to have detrusor overactivity, urge syndrome, hyperactive bladder, persistent infantile bladder, and detrusor hypertonia. Children with OAB may present with symptoms of daytime frequent urination, urgency, incontinence and nighttime enuresis. The definition of pediatric OAB by the International Children's Continence Society (ICCS) is in accordance to the consensus of the International Continence Society (ICS) [1]. The core symptom of OAB in children is urgency [1]. It may occur with symptoms of urge incontinence, frequent urination and nocturnal enuresis, though these symptoms are not necessary for the diagnosis of OAB. In fact, OAB has an impact on the children socially, emotionally, and behaviorally. In addition, it poses negative effects on the family. Traditionally, many pediatric urologists and practitioners thought that OAB comes from a primary bladder problem or delayed maturation of the nervous system. Usually, the symptoms disappear as the children grow up. However in the study by Fitzgerald et al [2], childhood OAB was correlated to adult OAB. In the study by Minassian et al [3], the women with urinary frequency, urgency, stress incontinence, and urge incontinence had higher prevalence of childhood voiding dysfunction. Recent study results also pointed out that OAB is a centrally located neurological dysfunction, and it is associated with many disorders, such as bowel/sexual dysfunction and the control of blood pressure [4]. Based on the above findings, untreated pediatric OAB may persist throughout adulthood.

EPIDEMIOLOGY

The prevalence of pediatric OAB is difficult to determine since most of the studies focused on the daytime and nighttime incontinence which were not specific for OAB. In Korean children, the rate of OAB decreased from 22.89% at the age of 5 years to 12.16% at the age of 13 years [5]. In a study for children aged 1.5 to 27 years in the United States, nocturnal and diurnal enuresis was reported in 18% and 10% of cases, respectively [6]. The overall rate of enuresis in 7-year-old children in Finland was 9.8% (nightwetting: 6.4%, daywetting: 1.8%, mixed day and night wetting: 1.6%) [7]. In addition, 50.7% of children with daytime wetting were noted to have urgency. In the study by Cher et al in Taiwan, the overall rate of nocturnal enuresis in primary school children was 5.52% [8]. The results were similar to those reported in western societies. Enuresis was significantly more common in boys than in girls (7.4% versus 4.31%). In addition, although the prevalence rate of enuresis decreased with age, it never reached 0%. The results of the study by Karjiwara et al also showed the same trend [9]. In the patients with daytime urinary incontinence, urgency alone was the most common characteristic in both sexes.

Received: July 30, 2009 Accepted: August 11, 2009
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PATHOPHYSIOLOGY

The pathophysiology of OAB is not well understood. Traditionally, OAB is thought to be the result of maturation delay. Recently, researchers have shown that OAB may have an association with sexual dysfunction [10-12]. Also, the researchers also suggested that OAB may come from the centrally located neurological dysfunction [13]. The normal urination function needs the coordination of the brain, pons, spinal cord, peripheral autonomic sensory and somatic nervous systems, and the anatomical components of the lower urinary tract. Various efferent and afferent neural pathways and neurotransmitters are involved in urinary storage and emptying. Any disturbance of them will contribute to OAB symptoms. The following comments summarize the neurotransmitters associated with bladder function [4]. The serotonin (5-HT) enhances the sympathetic reflex pathway and inhibits the parasympathetic reflex pathway, so they facilitate urine storage. Dopaminergic pathways have the facilitating and inhibitory effect on voiding. Dopamine D1 receptors suppress the bladder activity, but D2 receptors facilitate the activity. Acetylcholine is the neurotransmitter acting on the muscarinic receptors of detrusor, and it results in bladder contraction. The sensitivity increases during some pathological condition, and it leads to OAB. Adenosine triphosphate (ATP) is another neurotransmitter that acts on the purinergic receptors ($P2X_3$). ATP just contributes to a small portion bladder contraction at normal conditions. However, it becomes more prominent in OAB cases.

Glutamate is also the neurotransmitter that regulates the storage and voiding of bladder, and it comes from the ventral horn of the sacral spinal cord (Onufrowicz's nucleus). During the storage phase, the glutamate is released from the Onufrowicz's nucleus, and it activates the pudendal nerve, and then the rhabdosphincter contracts. Beyond glutamate, NA and 5-HT have the modulatory role in the Onufrowicz's nucleus. They enhance the rhabdosphincter contraction.

Unmyelinated C-fiber also has a role in OAB. It has several receptors interacting with various neurotransmitters, such as vanilloid receptor which is activated by capsaicin, purinergic receptor which is activated by ATP, and neurokinin receptor which is activated by substance P, neurokinin A, and nerve growth factor (NGF) receptor.

The interaction of different neurotransmitters and neural pathways is very complex. Any imbalance between them may lead to OAB. The exact pathophysiology of OAB still needs to be investigated.

TIMING OF TREATMENT

Healthy children usually attain daytime and nighttime continence at the ages of 3 and 6 years, respectively. In a study of Japanese primary school children, the daytime voiding frequency was 6.1±2.0 times per day [9]. Children with voiding frequency more than 8 times or urgency at small bladder capacity and/or incontinence day can be defined as having pediatric OAB. In our opinions, children with refractory symptoms of OAB unresponsive to conservative behavioral modification therapy need further investigation. In addition, if the urinary incontinence occurs beyond the ages of 3 or 6 years, the children should be investigated for underlying pathophysiology.

EVALUATION AND DIAGNOSIS

The evaluation of pediatric enuresis/OAB begin with thorough history taking, physical examination, and laboratory investigation to exclude the possibility of underlying pathologic and metabolic disorders [14].

History taking

History taking is the first step for diagnosis. We have to know the clinical presentation of the cases, developmental conditions, and underlying urological, medical, or neurological disorders. The clinical manifestations of pediatric OAB are similar to adult OAB. The classic features include urgency, frequency, urge incontinence, and nocturia/nocturnal enuresis. Some children may exhibit various coping strategies to prevent urinary leakage, such as squatting behavior or Vincent curtsy sign. From the patient's medical history, we must know whether it is nighttime, daytime, or both wetting, initiation of wetting (primary or secondary), voiding character, urinary tract infection (UTI) history, gastrointestinal tract condition (chronic constipation and fecal soiling), underlying neurological and psychological problems, family history for enuresis/incontinence, and current medication. Since the study by Loening-Baucke in 1997, constipation was considered to be associated with urinary incontinence [15]. When the children have recurrent UTI, further investigations for genitourinary tract abnormalities, such as vesicoureteral reflux, are necessary. Constipation has strong relationship with OAB. When the patient has chronic constipation, the treatment should include a laxative agent. A voiding diary is another tool to help us realize the voiding situation of the patient. Via these tools, we can realize the fluid intake, total voiding volume, average/largest/smallest voiding volume, timing and frequency of voiding, and distribution of daytime/nighttime voiding volume. We also can use the questionnaire to determine dysfunctional voiding symptom scores (DVSS) to quantify the severity of the disorder. It consists of 10 questions, and scoring the answer from 0 to 3 for each question. We define that the patient has an abnormal voiding pattern when the total score ≤6 in girls and ≤9 in boys [16].

Physical examination

The focus of the physical examination is the assessment of the abdomen, perineal area, and a complete uroneurological examination. If there is skin discoloration, bony abnormalities, dimpling, hair patches, or lipoma over the lumbosacral area, spinal dysraphism should be considered. If the patients have anomalies of the lower limbs, asymmetry of the buttocks, legs, or feet, or abnormal gait, then an underlying neurological disorder should be excluded, and further diagnostic modalities should be arranged.

Laboratory investigation

The laboratory studies can be classified into essential and conditioning tests.

1. Essential tests:

The essential tests include urinalysis, and ultrasonography for the urinary tract. Via the urinalysis, we can rule out the underlying UTI, glucosuria, or diabetes insipidus. The urinary tract ultrasonography includes renal ultrasonography, prevoiding and postvoiding bladder ultrasonography. The results reveal information about anatomical anomalies and emptying functions of the urinary bladder, such as hydronephrosis, post-void residual urine (PVR), and bladder wall thickness. An abnormally thickened bladder wall is a warning sign [17, 18].

2. Conditioning test:

When some disorder is suggested, advanced studies should be arranged to confirm the diagnosis. Urine culture is performed when there is a suggestion of UTI. Voiding cystourethrography is arranged for the diagnosis of the vesicoureteral reflex. When the patient has severe constipation, and bowel dysfunction is suggested, we will take a plain abdominal film. If the urine specific gravity is extremely low, we can check the fractional excretion of the sodium, urine osmolarity, vasopressin level or arrange a thirst test to confirm the diagnosis of diabetes insipidus. When neuropathic or non-neuropathic bladder-sphincter dysfunction is suggested, we can arrange uroflowmetry and urodynamic studies for further investigation.

During the uroflowmetry study, the most important parameters are the voiding volume, flow pattern, and maximal flow rate (Qmax). According to ICCS's definition, the flow pattern can be classified into 5 types: the bell-shaped, interrupted, plateau curve, staccato, and tower-shaped [1]. Only the bell-shaped curve is considered to be the normal pattern. Each abnormal flow pattern may be a clue of some pathological condition. The interrupted curve implies detrusor underactivity or acontractile bladder. The plateau curve implies bladder outlet obstruction. The staccato pattern implies sphincter overactivity. The tower-shaped curve usually occurs in patients with detrusor overactivity. However, the flow curve pattern only serves as a guide toward possible underlying etiologies. The inter-observer and intra-observer variability in the interpretation of flow curve is great. Chang and Yang reported poor inter-observer agreement on identifying specific uroflow curve patterns, but good inter- and intra-observer agreement in identifying normal flow curve [19]. The result was in accordance with the results in the study by Gacci et al [20]. Based on the findings from our study, we suggest uroflowmetry is deemed a screening tool to define those who may need further invasive and sophisticated study.

Several researchers have used uroflowmetry to screen healthy children in different countries. The prevalence of the normal bell-shaped curve was 97.2% in Sweden, 90% in Spain, 63% in Hong-Kong, and 79% in Taiwan [21-24]. The prevalence of abnormal flow patterns in the Chinese children seem to be higher than in other races. The study by Yang showed that bladder over-distention resulted in more nonbell-shaped urolfowmetry curves and more increased PVR [25]. At extreme over-distention, the peak flow rate decreased as well. The bladder capacity also had effects on the uroflowmetry. The difference in the prevalence of nonbell-shaped flow curve between the difference races

may come from the results of bladder over-distension [24]. In addition, small functional bladder capacity would result in abnormal flow pattern [25]. From the results of these studies, we know that the bladder capacity has an important role on the interpretation of uroflowmetry. Our suggestion is that the voided volume should be between 50% to 100% of the estimated bladder capacity, and at least two sets of uroflowmetry curves and PVR should be performed to avoid false positive results.

For a patient with OAB that is refractory to treatment for 1 to 3 months or who have an abnormal flow pattern during uroflowmetry, further investigation, such as voiding cystourethrogram (VCUG), conventional urodynamic study, videourodynamic study, or urodynamic study plus electromyography (EMG), should be arranged to determine a diagnosis.

TREATMENT

Anticholinergics have been the mainstay of OAB treatment for a long time. Recently, new treatment strategies have become popular, including the bowel program, timed voiding regimen, and biofeedback [13].

Medication

The first-line drug for OAB is anticholinergics. The ideal anticholinergic agents must increase the functional and maximum bladder capacity, but have no negative effects on Qmax [26]. However in the study by Van Arendonk et al, anticholinergics were effective for only 20% of patients who were wetting on a daily basis [27]. In addition, it is unlikely to be effective for patients who have frequent wetting and urgency that do not respond readily to the bowel program, timed voiding, and biofeedback [13,27]. Alpha-blockers are also effective drugs for OAB, especially when biofeedback has failed. Primary bladder neck dysfunction or external sphincter dyssynnergia is the major problem for many of these patients, and α-blockers can improve voiding functions [28].

Treatment for constipation and fecal retention

The correlation between bladder problems and constipation was established by Loening-Bauke in 1997 [15]. Of the children with constipation, 29% had daytime urinary incontinence, 34% had nighttime incontinence, and 11% had UTI. If constipation was well corrected, UTI did not recur, daytime urinary incontinence was corrected in 80% of patients, and nighttime urinary incontinence was corrected in 63% of cases. Constipation in children with OAB often presents with chronic abdominal discomfort, especially in the periumbilical area. Traditional use of a high fiber diet and increased fluid intake are recommended as the first line treatment. In addition, stool softener or cathartic is a common regimen. Beyond traditional regimens, tegaserod is another choice of bowel programs which is a 5-HT_4 agonist that causes increases in bowel motility [29,30]. In the experience of Franco [13], tegaserod was effective for refractory OAB children with constipation. There are two possible mechanisms for tegaserod. The first, it acts on the 5-HT receptor on the colon, promotes bowel peristalsis, and corrects constipation, which might correct OAB. The second, it might act on the receptor in the central nervous system, the Onufrowicz's nucleus that also regulates the bowel function. The effect of tegaserod on constipation and OAB still needs large scale clinical trials to prove.

Botulinum-A toxin injections

Botulinum-A toxin is a potent biological toxin. Traditionally, it was thought to temporarily block the presynaptic release of acetylcholine from the parasympathetic innervation. In the recent studies, several mechanisms have been mentioned. Beyond acetycholine, the Botulinum-A toxin also inhibits the release of ATP, substance P, and the axonal expression of capsaicin and purinergic receptors, such as the $P2X_3$ and TRPV1 receptors [31]. In addition, it also decreases the production of NGF in patients with neurogenic detrusor overactivity after the injection of Botulinum-A toxin [32]. All of the neurotransmitters and receptors have roles in the pathophysiology of an OAB. After the injection of the Botulinum-A toxin into the urinary bladder, the results include decreased muscular contractility, muscle atrophy, and chemical denervation. It could be used to decrease the detrusor overactivity, and the effect lasts for 3 to 6 months. Even for the cases of OAB with sphincter dyssynergia, Botulinum-A toxin injections also resulted in elimination of dyssynergic voiding pattern, detrusor hypertrophy and overactivity by chemical sphincterotomy. Botulinum-A toxin seems to be useful for pediatric OAB with or without sphincter dyssynergia [33-35]. The clinical experience of Botulinum-A toxin injection in patients with OAB showed it could increase the bladder capacity, decrease the intravesical pressure and the incontinence episodes [36]. What the problem is that the injection may cause a high rate of increased PVR requiring clean intermittent catheterization (CIC). The minimal effective dose of Botulinum-A toxin needs to be determined.

Biofeedback therapy

Biofeedback therapy has been used to resolve incontinence in children since the mid 1990s. The study by Palmer et al was useful for cases with OAB, especially with underlying bladder outlet obstruction (BOO) [37]. The key problem of this kind of therapy is the cooperation of children with health care providers. For children younger than 5 years, it is difficult to teach them to relax the pelvic floor muscle appropriately. Children with significant learning disabilities and behavioral problems are not candidates for biofeedback therapy.

Surgical treatment

BOO is an origin of OAB. In adults, benign prostate hypertrophy is the most common reason. For the children, the potential sites of obstruction are primary bladder neck dysfunction, dysfunctional voiding, posterior urethral valve, and anterior urethral valve. For primary bladder neck dysfunction or dysfunctional voiding, the medication or biofeedback therapy may improve the symptoms. If the response is poor or the diagnosis is in the posterior or anterior urethral valve, surgical relief of BOO may be bene-ficial [38].

CONCLUSIONS

Pediatric OAB often combines with voiding dysfunction, constipation, enuresis, UTI, and vesicoureteral reflux. The diagnosis depends on the results of detailed history taking, physical and neurological examination, laboratory studies, urinary tract ultrasonography, uroflowmetry, and urodynamic studies. The treatments are composed of therapy for UTI, relief of constipation, anticholinergics, behavioral therapy, biofeedback therapy, α-blockers, surgical treatment for anatomical bladder outlet obstruction, and Botulinum-A toxin injections for refractory OAB or idiopathic sphincter dyssynergia. The flow chart of

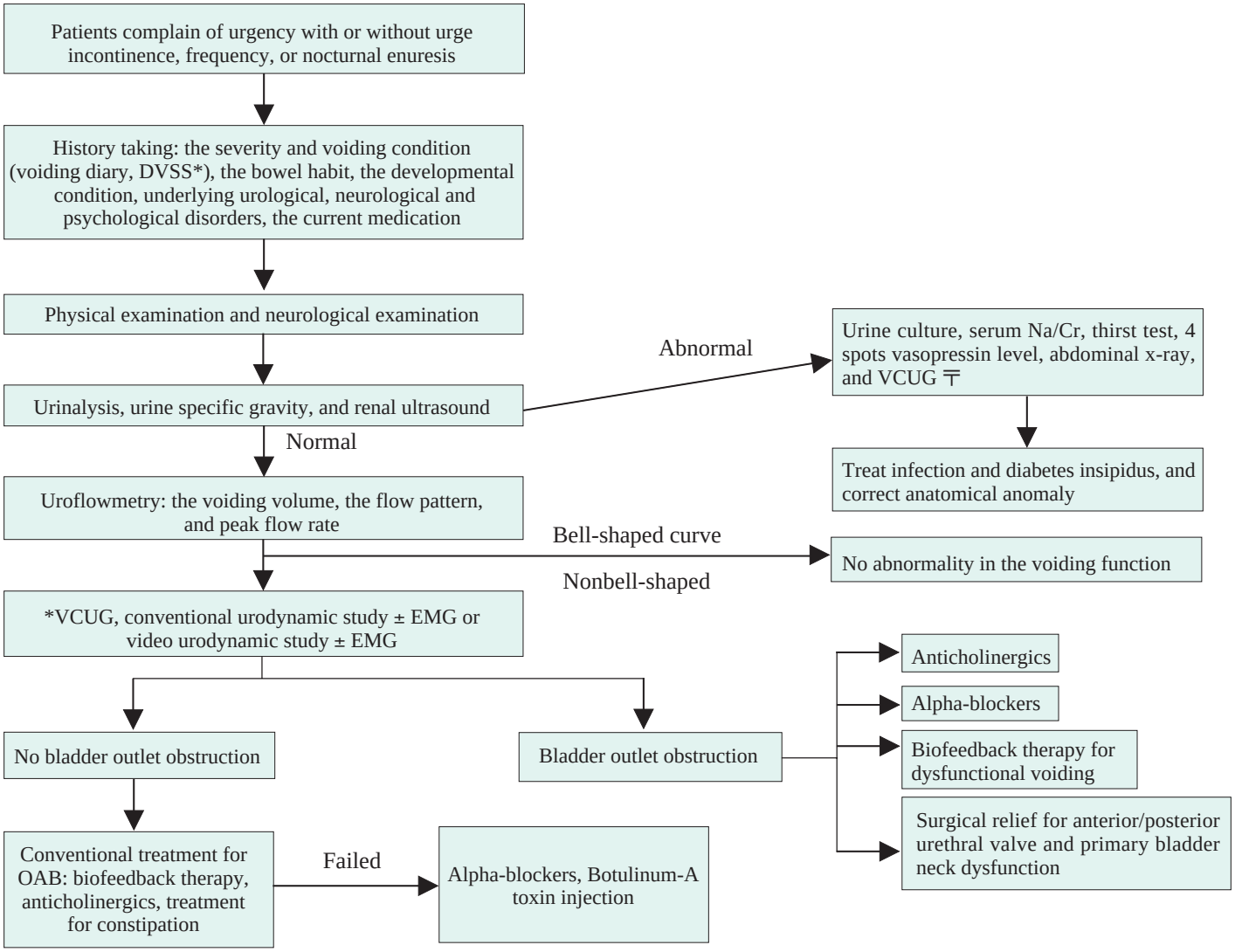

Fig. 1. The flowchart for the diagnosis and treatment for pediatric OAB. (VCUG, urodynamic study ± EMG, and videourodynamic study ± EMG were performed when the anatomical obstruction was suggested, or the responsiveness to conventional OAB treatment was poor)

evaluations, management and treatment strategies of pediatric OAB are summarized in Fig. 1. Pediatric OAB could be a lifelong problem. We have to correct the problem as early as possible to prevent problems during adulthood. Further studies are necessary to develop more effective treatment modalities.

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