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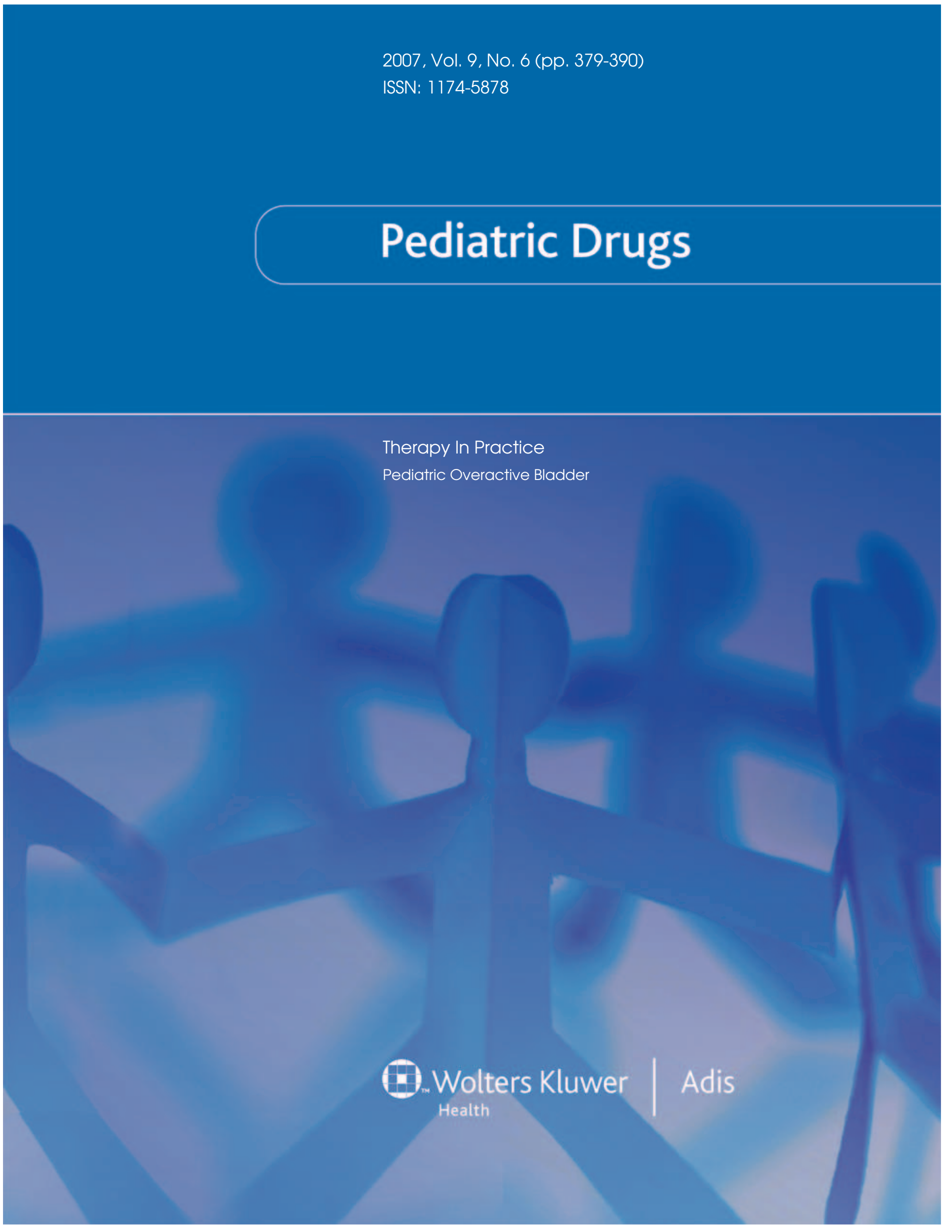

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Pediatric Overactive Bladder Syndrome

Pathophysiology and Management

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Contents

Abstract

Detrusor overactivity, also known as the overactive bladder syndrome (OAB), urge syndrome, hyperactive bladder syndrome, persistent infantile bladder, and detrusor hypertonia, is the most common voiding dysfunction in children. Until recently, the concepts that had been used to dictate the management of this problem in children were based on the foundation that this was a primary bladder problem and or a delay in maturation in the nervous system of children. The expectation that children would outgrow their problems led many pediatric urologists and other practitioners to tell the parents of these children ‘that they would not be wetting themselves on their wedding day.’ However, it has become apparent from recent studies in adult patients with voiding dysfunctions that they had symptoms present as children. Recent findings of associations between lower urinary tract symptoms and sexual dysfunction and between voiding dysfunctions and neuropsychiatric problems have opened up a new frontier into the possible mechanisms of OAB in children that would explain these problems, link them together, and explain the continued problems that adult patients face. These findings point to OAB as a symptom of a more centrally located dysfunction that affects multiple systems.

The objective of this review was to evaluate the neuroanatomy and neurophysiology of voiding and neuropharmacologic effects. We considered not only the available research and clinical data within the urologic field but also outside the field so that these data could be combined to generate a unified theory that could possibly explain many of the associated symptoms that are commonly found in pediatric OAB. Treatment modalities that are currently available for managing OAB were also explored.

Currently available data indicate that pediatric OAB and many pediatric voiding dysfunctions may be part of a more generalized problem that affects multiple systems: notably bowels, bladder, sexual and ejaculatory function, control of blood pressure, and even mood and behavior. We explain the relationship that the bowel has with pediatric OAB and also the link that other neuropsychiatric problems have with OAB. This article describes

which drug may be best suited to treat OAB in children and what treatment modalities are available when first-line drugs fail.

In conclusion, the movement away from a vesicocentric way of thinking to a more corticocentric mode of thinking along with new imaging modalities that can examine the brain as it works will be of great value in determining future treatments of OAB. Medications generated from these evidence-based studies will hopefully treat the underlying disease process and not just the symptoms.

Detrusor overactivity is the most common voiding dysfunction in children. The condition is also known as the overactive bladder syndrome (OAB), urge syndrome, hyperactive bladder syndrome, persistent infantile bladder, and detrusor hypertonia. Its onset can be slow and insidious, with a gradual increase in the strength of the urge to void that can occur over a long period of time. The condition can also develop quite suddenly over a very brief period of time with dramatic episodes of incontinence in children who were previously dry. OAB appears to have a peak incidence that occurs between 5 and 7 years of age. Ruarte and Quesada[1] found an incidence of 57.4% in a group of 383 incontinent children ranging in age from 3–14 years. This group consisted of 38.9% boys and 60.1% girls.

Enuresis is estimated to affect 5–7 million children in the US ≥6 years of age.[2,3] The impact of enuresis in children can be quite profound. It can affect their lives socially, emotionally and behaviorally and will also impact on the everyday life of his/her family.[4] Urinary incontinence is a very large problem with a total economic impact in the US of $US26.3 billion in 1995.[2,3] In the US, the overall cost for the management of urinary incontinence increased from 3.94 billion in 1984 to 19.5 billion in 2004.[5] These represent quite significant economic burdens to these societies. Furthermore, from our understanding of OAB, we know that if the condition continues over a long period of time, thickening of the bladder wall will occur, which will have an impact in adulthood. As patients become older, the consequences of OAB become more profound and require greater effort to correct.[2,3] Furthermore, the costs associated with the indirect consequences of urinary incontinence, such as skin breakdown, need for psychiatric care, and treatment of urinary tract infections (UTIs), may be far in excess of the costs that are associated directly with OAB.

From a pediatric urologist perspective, the child with OAB has a very good chance of becoming an adult who continues to have problems with OAB. This correlation has been seen in two published reports. In the first study, Fitzgerald et al.[6] revealed that OAB in childhood correlated with adult OAB symptoms. These investigators found that frequent daytime voiding in childhood correlated with adult urgency. A correlation also existed between childhood nocturia and adult nocturia. Childhood daytime incontinence and nocturnal enuresis were associated with a >2-fold increased association with adult urge incontinence. Furthermore, a history of childhood UTIs correlated with a history of adult UTIs. In another study involving 170 adult women, Minassian et al.[7] found that there was a higher prevalence of childhood voiding dysfunction in women who had urinary frequency, urgency, stress incontinence, and urge incontinence. These investigators also noted that there was a greater likelihood of symptomatic adults having a higher body mass index.

The implications of these findings underscore the importance of childhood OAB and its impact in adulthood. The trend over the years has been to tell parents that these problems are self-limiting and they will resolve in due time as the child matures. It appears that this may not be the case and some children as they mature are simply better at compensating for their problems and eventually drop off the radar screen (our offices), either because of frustration with our inability to treat their problems or because they have developed coping strategies that satisfy their needs for the interim. A better understanding of the potential causes of childhood OAB could prevent undue problems in adulthood and make many children, as well as their parents and teachers, much happier.

The objective of this article was to discuss the prevailing thoughts on OAB and present new perspectives on the pathophysiology of OAB. A thorough understanding of the neuroanatomy is essential to understand the complex interplay between the bladder, spinal cord, and brain. We address the different drug classes that are available as well as different treatment modalities that are non-pharmacologic.

1. Prevailing Thoughts on Pediatric Overactive Bladder Syndrome (OAB)

OAB is not completely understood and the general belief is that it most certainly is a multifactorial problem. In some instances, anatomic abnormalities can lead to OAB (these will not be discussed in this review), whereas in other cases, functional voiding problems may be the source of OAB. In other instances, neurologic lesions may lead to the development of OAB.

The prevailing theory in children is that OAB is due to a delay in the acquisition of cortical inhibition over uninhibited detrusor contractions in the course of achieving the mature voiding pattern of adulthood. The site of maturational delay is thought to lie in reticulospinal pathways of the spinal cord but could also be in the micturition inhibitory center within the cerebral cortex. We do know that cortical control is normally established between 3 and 5 years of age. Delay in fine-tuning of bladder sphincter coordination during voiding will cause uninhibited detrusor contractions to be met with voluntary external urethral sphincter contractions, the control of which is thought to be acquired at an earlier age.[8] An increase in intravesical pressure can manifest itself in an array of symptoms that include urgency, urge incontinence, and nocturnal enuresis. OAB triggers bladder overactivity usually in the early filling phase, causing the pelvic floor to respond by voluntary contraction. This voluntary contraction leads to classic holding maneuvers, such as leg crossing, penile grabbing and squatting. It is thought that active external sphincter contraction may possibly cause a temporary reflex relaxation in the detrusor and therefore afford momentary relief from the effects of uninhibited bladder contractions. Persistent isometric contractions of the detrusor against the tightened sphincter or incomplete relaxation of the sphincter lead the bladder muscle to hypertrophy and this increased hypertrophy leads to a gradual decrease in functional bladder capacity and increased instability of the bladder, thereby creating a vicious cycle in which OAB is worsened. The concomitant increased pelvic floor activity may be associated with increased autonomic stimulation of the perineal organs and musculature. This increased activity may be associated with sexual dysfunction in adults.[9-13]

There is now compelling evidence[14-21] that abnormal high-pressure voiding occurs *in utero* in the fetus and may be the cause of renal damage in reflux (water hammer effect). This abnormal voiding may persist in some cases. The probable lack of outright detrusor abnormalities in this situation would thereby lead us to believe that the problem is more likely to originate from a neurologic source. Mitchell[22] has contended that lack of correct bladder cycling in the exstrophic bladder is the primary reason why such bladders do not function properly even after they have been closed. A similar example exists in boys with posterior urethral valves; in this group, even long after the valves have been ablated and bladder muscle has thinned out, there is persistence of abnormal voiding patterns. These situations are analogous to the child with a tracheoesophageal fistula or a tracheostomy who is not fed early in life and consequently is generally unable to develop normal swallowing patterns, necessitating intensive retraining. In all of these cases, there appears to be a link between repetitive normal muscle activity and the development of normal voiding and swallowing mechanisms. This form of muscle memory is most likely imprinted in the brain during development and is crucial to the proper functioning of the voiding reflexes during development and postnatally.

A finding that confirms a central process and a genetic mode of transmission for a voiding dysfunction is the Ochoa urofacial syndrome.[23] In many ways, the Ochoa syndrome is similar to the Hinman (non-neurogenic neurogenic bladder) syndrome.

The Ochoa syndrome was first described by Bernard Ochoa of Columbia in 1979. Its prevalence is quite low, with <200 cases having been reported. The syndrome is genetically determined and transmitted by a recessive pattern of inheritance. It is associated with an unusual inversion of facial expression when smiling is attempted; the face becomes contorted into a grimace that makes it appear as if the individual is sobbing and crying, thus making it possible to recognize afflicted patients early in life (as early as 2 years of age). There is a consistent relationship between the grimacing expression on the face and a dysfunctional voiding pattern. The micturition reflex is processed in the reticular formation of the brainstem in close anatomical proximity to the origin of the facial nerves. Lesions within the reticular formation are expected to produce functional lesions affecting coordination, rather than paretic lesions as when the nuclei are involved. The proximity of this lesion to the facial nerves explains why facial expression is associated with this abnormality. The Ochoa urofacial syndrome has been mapped in immunology laboratories at the University of Florida, Florida, USA, using homozygosity mapping and DNA, pooling strategies in families from Colombia. The gene was mapped on chromosome region 10q23–4 in 1997.[24] Subsequently, genetic homogeneity was demonstrated through homozygosity mapping in American patients of Irish heritage. These examples may underscore the role of the CNS in the control of micturition. The fact that reflux is known to have a hereditary pattern, and that many children with OAB have parents with similar symptoms, points, together with data presented in section 1.2 in this review, to the underlying cause of OAB being a heritable problem.

1.1 Pathophysiology of OAB

Symptoms of hyperreflexia may have many potential causes and contributing factors. Urination involves the use of higher cortical centers in the brain, pons, spinal cord, peripheral autonomic somatic, and sensory afferent receptors in the lower urinary tract and the anatomical components of the lower urinary tract itself. Any disorder of these structures may contribute to symptoms of OAB. The normal bladder functions like a compliant balloon filling gradually. As filling occurs in the compliant bladder, the pressure remains low and below that of typical urethral resistance. With normal urination, urethral resistance decreases and contraction of the detrusor empties the bladder. Detrusor overactivity is usually associated with involuntary contractions of the detrusor. Overactivity of the detrusor from neuropathic causes can result in

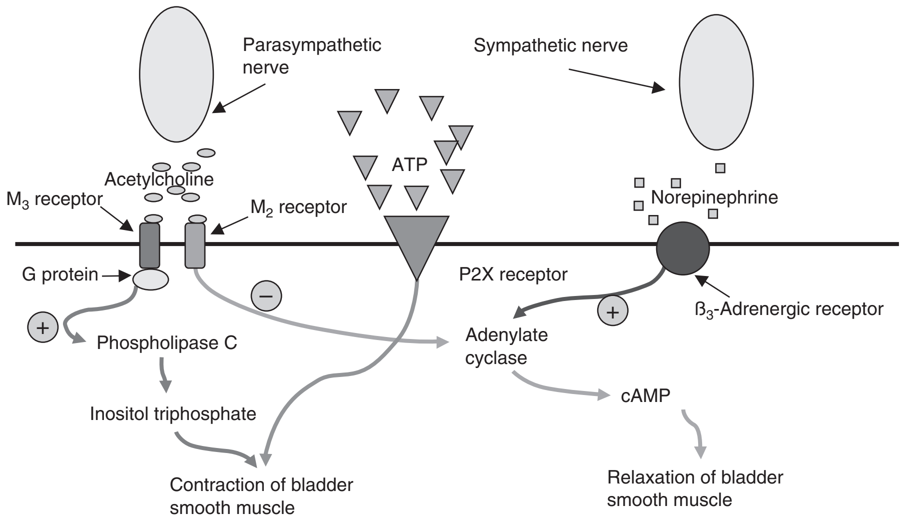

Fig. 1. Current concepts of autonomic efferent innervation contributing to bladder contraction and urine storage. In the normal human bladder, acetylcholine is the predominant neurotransmitter that causes bladder contraction. Acetylcholine interacts with muscarinic M_3 and M_2 receptors. The M_3 receptor activates phospholipase C by coupling with G proteins. This generates inositol triphosphate, which in turn causes release of calcium from the sarcoplasmic reticulum and contraction of bladder smooth muscle. M_2 receptors contribute to bladder contraction by inhibiting adenylate cyclase activity and decreasing intracellular levels of cyclic adenosine monophosphate (cAMP), which mediates bladder relaxation. In the normal human bladder, only a small proportion of bladder contraction is resistant to atropine. Resistance to atropine is most likely due to interaction of adenosine triphosphate (ATP) and P2X receptors (which belong to the purinergic receptor family). Stimulation of β_3-adrenoceptors may also lead to relaxation of the bladder. [This figure was published in *The Journal of Urology*, Vol. 178, Franco I,[26] Overactive bladder in children. Part 1: pathophysiology, 761-8, copyright Elsevier 2007, with permission.] **+** indicates activation; **−** indicates inhibition.

urgency or urge incontinence depending on the response of the sphincter.

OAB may also have a myogenic origin; indeed, the prevailing theory for many years has been that myogenic abnormalities are a primary cause of OAB. Treatment of these problems is based primarily on the use of acetylcholine receptor antagonists (anticholinergics) that target muscarinic receptors. However, it would seem simplistic to think that there would be a primary myogenic problem that affects the bladder without some form of myogenic processes that would be affecting other smooth muscles. It makes more sense to implicate a process that causes detrusor hyperplasia as a result of neurologic causes or outlet obstruction as the cause of these myogenic problems. If so, eventual correction of these problems should be the mainstay of treatment. This approach would eventually treat the underlying problem and eradicate the symptoms instead of just concentrating on the symptoms, as has been the case for many years.

A variety of efferent and afferent neural pathway reflexes involving central and peripheral neurotransmitters are involved in urinary storage and bladder emptying. As yet, their relationships are not completely understood. However, with the use of functional magnetic resonance imaging (MRI) and positron emission tomography (PET) scans, we are now starting to see and understand better the role that the central neurotransmitters may play. Serotonergic activity facilitates urine storage by enhancing the sympathetic reflex pathway that inhibits the parasympathetic voiding pathway. Dopaminergic pathways may exert both inhibitory and facilitory effects on voiding. Dopamine D_l receptors appear to play a role in suppressing bladder activity, whereas D_2 receptors appear to facilitate voiding. Other neurotransmitters such as α-aminobutyric acid and enkephalin inhibit voiding in animals.

Acetylcholine, which interacts with muscarinic receptors at the detrusor, is the predominant peripheral neurotransmitter responsible for bladder contraction (figure 1). Pathologic states can alter sensitivity to muscarinic stimulation: for example, bladder outflow obstruction appears to enhance responses to acetylcholine similar to denervation supersensitivity. Normally, only a small proportion of bladder contractions are resistant to atropine, probably as a result of the interaction of adenosine triphosphate (ATP) with purinergic receptors; however, ATP may play a more prominent role in bladder contractions in patients with OAB.[25] Anatomical correlates of detrusor overactivity have been described. For example, bladders of patients with detrusor overactivity appear to have abnormal gap junctions between smooth muscle cells, and such correlates require further study.

Increasing attention is also being paid to the lower sensory afferent nerves in normal voiding and OAB.[25] During bladder filling, afferent activity of the bladder and urethra reaches the spinal cord predominantly via the pelvic nerve. Sensory input during bladder filling results in an increase in the sympathetic tone. Release of norepinephrine from the hypogastric nerve stimulates β_3-adrenoceptors in the bladder, causing the smooth muscle to relax, as well as α-adrenoceptors in the bladder neck, causing the smooth muscle of the bladder neck and proximal urethra to contract. Acetylcholine released by somatic pudendal nerve and sacral nerve fibers elicits contraction of the striated urethral sphincter and pelvic floor.

Glutamate is thought to be the primary descending neurotransmitter for the storage reflex. Glutamate is released in the ventral horn of the sacral spinal cord (Onuf's nucleus). In Onuf's nucleus, axons projecting from the CNS synapse with the pudendal nerve. Release of glutamate activates the pudendal nerve and leads to contraction of the rhabdosphincter. It should be noted that Onuf's nucleus is densely populated with serotonin 5-HT and norepinephrine terminals and contains a high density of 5-HT and norepinephrine receptors. 5-HT and norepinephrine play a modulatory role in that they enhance the contraction of the rhabdosphincter but are not able to induce a contraction of the rhabdosphincter on their own.[27] Once micturition starts, glutamate is no longer released and pudendal nerve activity ceases.

Myelinated A-δ sensory fibers respond to passive distention and active contraction of the detrusor muscle. Unmyelinated C sensory fibers have a higher mechanical threshold and respond to a variety of neurotransmitters. C fibers are relatively inactive during normal voiding but may play a critical role in symptoms of OAB in patients with neurologic and other disorders. Several types of receptors have been identified in afferent nerves, including vanilloid receptors, which are activated by capsaicin and possibly by endogenous anadamide; purinergic receptors, which are activated by ATP; neurokinin receptors, which respond to substance P and neurokinin A; and receptors for nerve growth factor. Other substances, including nitric oxide, calcitonin gene-related protein, and brain-derived neurotrophic factor, may also play an important role in modulating the sensory afferents in the human detrusor.[25] Better understanding of the complex interplay between these various neurotransmitters may yield new and more specific targets for drug treatment for OAB.

A full discussion of the role of all the neurotransmitters involved in the urination process is beyond the scope of this review. An excellent review of these neurotransmitters and their functions is available in an article by Yoshimura and Chancellor.[28]

1.2 Neural Pathways

The micturition center in the spinal cord is primarily located in three sacral spinal cord segments S2–4, with S3 being the most important. The center is anatomically located at vertebral levels T2 through L1. The gray matter in the spinal cord is divided into a series of zones. The parasympathetic preganglionic motor neurons lie within an intermediolateral gray column. The cells extend in a vertical plane along the border between the white and gray matters and in a horizontal plane at the base of the dorsal horn at lamina 7 and lamina 5 in the dog. The former serves as the center for bladder control and the latter more medial gray matter of parasympathetic cells serves as the center for rectal control. Somatic nerve fibers originate from the nucleus of Onuf in the mid-ventral spinal gray matter. Innervations to most striated muscles of the pelvic floor, including those of the periurethral and anal sphincters, originate within the nucleus of Onuf. Activity travels up the spinal cord via the spinothalamic tracts. Exteroceptive signals carried up the spinothalamic tracts include sensations of pain, temperature and touch generated in the urothelium. Proprioceptive sensory impulses initiated in the bladder muscles and the periurethral striated muscle travel in the posterior columns. Proprioceptive axons enter the dorsal portion of the gray matter otherwise known as the periaqueductal gray area and turn to travel rostrally to synapse in the pontine mesencephalic reticular formation. Exteroceptive sensory impulses travel in the spinothalamic tracts and synapse in the thalamus and sensorimotor cortex.[29]

In humans, stimulation of the hypogastric plexus originating from spinal levels T10 through L2 results in relaxation of detrusor muscle and contraction of the intrinsic sphincter, thereby inhibiting micturition. Stimulation of passive sympathetic nerves originating from spinal level S2 through S4 has the opposite effect. In children, a common procedure that is performed to cause the urge to urinate to cease is squeezing of the glans penis.[30] Clitoral compression can cause similar effects in girls. These actions eliminate the effects of intravesical pressure on urodynamic processes during the filling phase. The pudendal nerve reflex has been proposed as the mechanism of bladder inhibition with these maneuvers. Squatting on the heels in girls and what appears to be masturbatory behavior in boys and girls could actually be a mechanism used by some children to suppress bladder contractions. Pudendal nerve stimulation stimulates the sympathetic system that suppresses bladder activity via the β-adrenergic system with spinal interneurons that release inhibitory neurotransmitters such as enkephalin, glycine and α-aminobutyric acid.

There is a close relationship between OAB and bowel problems. It is possible that stretch receptors within the bladder wall can be stimulated by the extrinsic fecal mass thereby triggering detrusor contractions of various amplitudes and sustaining a vicious cycle of continued contractions. It is also possible that colonic contractions may trigger bladder contractions via shared neural pathways in the pelvis or spinal cord as evidenced by findings in patients with imperforate anus.[31] Recently, Pezzone et al.[32] and Ustinova et al.[33] reported that acute colitis triggers bladder hyperactivity in rats, providing experimental evidence for crosstalk between different pelvic viscera. This has also been observed in the author's experience; in patients with colitis, acute flare-ups of this condition are also generally associated with an increase in voiding symptoms. When the colitis is controlled, the voiding symptoms also cease. Patients can exhibit dyssynergic voiding as well as urgency/frequency in these situations. The author has also found that many cases of young boys presenting with chronic erections and girls complaining of chronic vaginal or perineal pain have been corrected with a good bowel program. These crosstalk mechanisms support findings noted in patients with imperforate anus, patients with colitis, and even in normal children who experience a sudden urge to void associated with gaseous distention or a colonic contraction that at times is imperceptible to them. This crosstalk mechanism underscores the importance of a bowel management program in the treatment of OAB.

The role of serotonin and norepinephrine in the nervous system is far ranging. Serotonin predominates in the enteric nervous system, whereas norepinephrine predominates in the sympathetic autonomic nervous system. Neurons expressing serotonin and norepinephrine are concentrated in a few distinct nuclei in the brainstem (i.e. medulla and pons) but these axons traverse large distances from the prefrontal cortex to the caudal spinal cord. These neurons are involved in the 'fight or flight' reflex by facilitating motor activity and inhibiting pain perception. They play a major role in the regulation of mood, pain perception, attention, temperature, gastrointestinal motility, sleep, sexual function, and the micturition process.[27] These neurotransmitter pathways appear to be gaining increasing recognition in terms of their importance in the management of voiding dysfunctions, particularly with respect to modulation of critical functions, in both children and adults. Schuessler[27] feels that stress incontinence appears to be a problem arising from poor modulation of reflexes that are 'all or none' responses. It is not surprising that agents that affect serotonin and norepinephrine homeostasis have widespread effects and are used for the treatment of conditions ranging from depression to lower urinary tract symptoms and erectile and ejaculatory dysfunction.

It was initially thought that sacral neuromodulation was effective mainly on pelvic floor muscles by inducing muscle hypertrophy. The change in histochemical properties was supposed to lead to improved pelvic floor efficiency. However, given that neuromodulation takes place below the threshold for direct motor responses, this theory is not convincing. It is currently well accepted that the effects of sacral root modulation occur at the spinal and supraspinal level by inhibition of spinal tract neurons involved in the micturition reflex and interneurons involved in spinal segmental reflexes in postganglionic neurons. Furthermore, there may be inhibition via primary afferent pathways and indirect suppression of guarding reflexes by 'turning off' bladder input to internal sphincter sympathetic or external urethral sphincter interneurons. In addition, some groups believe that urinary retention is all a result of changed pelvic floor behavior directly or as part of a returning brainstem 'on/off' switch mechanism.[34]

Functional MRI- and PET-scanning studies indicate that bladder fullness is associated with increased activity in the anterior midbrain.[35-38] In these studies, signals from this area were seen to travel to the substantia nigra. This is a source of ascending dopaminergic neurons to the striatum, which is reciprocally connected to the brainstem micturition centers. The anterior midbrain was also seen connecting to the pons and medulla (micturition center) with increased activity. A third site of increased activity was noted in the cortical centers, primarily in the anterior and posterior cingulate gyrus. The anterior gyrus is associated with executive activity, whereas the posterior gyrus is associated with evaluative activities. An example of a typical evaluative activity would be making the decision to empty the bladder even though it is not completely full. This cognitive functioning would prevent a sudden urge to have to go to the bathroom. Patients who have increased activity in the micturition centers and midbrain with urgency typically do not have increased activity in the cortical centers, primarily the cingulate gyrus. In a group of patients who had urge syndrome with spinal stimulators, once the stimulators were turned on an increase in activity in the cingulate gyrus areas was noted. The cingulate gyrus is associated with contextual representations, which is better known for behavior control. Inability to activate the cingulate gyrus and suppress autonomic activities leads to hyperreflexia.

Inactivity in the cingulate gyrus may be a good explanation for OAB seen in familial settings. This decreased activity in the cingulate gyrus and frontal lobes may also explain the high association of voiding dysfunction in patients with behavioral, learning, and psychiatric disorders. Disorders such Asperger syndrome, Tourette syndrome, bipolar disease, depression, obsessive-compulsive disorder, panic disorder, anxiety disorder, attention-deficit disorder (ADD), and attention-deficit hyperactivity disorder (ADHD) are all associated with decreased activity in the frontal lobes.[39] It is well known that there is an increased incidence of urinary incontinence in children who have ADD/ADHD.[40,41] It is also recognized that in children who have problems with incontinence the incidence of behavioral and psychiatric disorders is three times greater than in the general population.[42-44] An association exists between increased urinary incontinence and obesity.[45] There is also an increased incidence of stool incontinence and constipation in patients with obesity.[46] Recent studies also indicate that there is an increased incidence of obsessive-compulsive behavior in chronically obese male and female patients, as well as an increased incidence of depression in chronically obese males.[42] The association between obesity, incontinence and constipation may all be linked to a possible problem with disinhibition in the frontal lobe that could explain all three phenomena.

2. Drug Therapy of OAB

Many classes of drugs have been studied or proposed for the treatment of symptoms of OAB in adults; however, only two anticholinergics have formally achieved approval for use in children. Several pitfalls limit the quality of clinical studies: these include heterogeneity of the patients and their symptoms and the fact that many patients can have more than one confounding problem. Clinical trials performed in children have generally utilized patients with neurogenic voiding problems and have not concentrated on non-neurogenic patients.

2.1 Anticholinergics

All anticholinergic drugs can have bothersome adverse effects. Dry mouth is the most common; however, constipation, gastroesophageal reflux, blurred vision, urinary retention, and cognitive adverse effects can also occur, although these symptoms are generally less bothersome in children. While there is a potential for adverse cognitive effects and delirium with use of anticholinergic drugs in children, these adverse effects are generally limited to overdosage situations. In adult trials, quantitative electroencephalographic data have suggested that oxybutynin has more CNS effects than trospium chloride or tolterodine.[47] Certainly, long-acting anticholinergic agents and newer, more selective agents should be tested for clinically important cognitive adverse effects.

Recent data suggest that anticholinergics may be functioning more on the sensory limb of the reflex arc in neurologically intact patients than on the motor side.[48]

Oxybutynin is a non-selective anticholinergic agent that relaxes bladder muscles and has local anesthetic activity. It is available in immediate and extended-release forms, as well as in a transdermal patch. Immediate-release oxybutynin appears to be efficacious for the treatment of neurogenic and non-neurogenic overactivity of the detrusor muscle with urge incontinence. The efficacy of immediate-release oxybutynin has been limited by anticholinergic adverse effects, such as dry mouth, of the parent drug and its active metabolite (*N*-desethyloxybutynin). Generic immediate-release oxybutynin is relatively inexpensive and may be useful for patients whose symptoms are best managed by a short-acting drug (e.g. symptoms that are bothersome only when the patient is away from home or at night). A once-daily controlled-release formulation of oxybutynin appears to have the same beneficial effects as immediate-release oxybutynin, with fewer adverse effects, a benefit that has been ascribed to more constant levels of the parent drug and, possibly, a lower rate of conversion to the active metabolite in the stomach and small intestine.[49] A transdermal oxybutynin patch is also available that is as efficacious as immediate-release oxybutynin but with half the incidence of dry mouth.[50,51] In one placebo-controlled trial, the patch caused local skin erythema in >50% of the patients (3% of cases were severe) and was associated with pruritus in up to 17%.[50] Oxybutynin has been instilled intravesicularly through a catheter with minimal adverse effects to treat severe overactivity of the detrusor muscle in patients with neurogenic bladders; however, its use is of limited value in children with non-neurogenic problems.

Tolterodine is an anticholinergic that is available in short-acting (twice-daily) and long-acting (once-daily) preparations. Adverse effects with this agent are similar to those reported for short-acting oxybutynin, with dry mouth occurring in 20–25% of patients, and the rates of discontinuation because of adverse effects are similar to those for placebo (5–6%).[25] Randomized, controlled trials indicate that propiverine and trospium chloride are effective for the treatment of urge incontinence and have fewer adverse effects than short-acting oxybutynin.[52-55] Tropsium chloride is currently available in the US; however, propiverine is not as yet. Although hyoscyamine, like short-acting oxybutynin, may be useful for some patients with intermittent symptoms or under specific circumstances, it can be associated with prominent adverse effects.[25] Propantheline bromide has proven efficacy for the treatment of urge incontinence, but the need for multiple daily administrations and the relatively high incidence of adverse effects are drawbacks.[25] At least two new anticholinergic drugs (darifenacin and solifenacin) with selective M_3 receptor antagonist actions and, theoretically, fewer systemic anticholinergic adverse effects than currently available agents, have yet to be studied in children; only limited anecdotal data regarding use of these drugs in children are available to date.

Further research is needed to determine the optimal use of anticholinergic drugs as monotherapy or combined with other agents such as α-adrenoceptor antagonists (see section 2.3) and behavioral therapy as treatment for OAB.

2.2 Antidepressants

The author has found imipramine, a tricyclic antidepressant with both anticholinergic and α-adrenergic effects and, possibly, a central effect on voiding reflexes, to be effective in controlling urge incontinence in some children who were refractory to anticholinergic therapy. However, imipramine can cause postural hypotension and cardiac-conduction abnormalities and thus must be used carefully. Amitriptyline, another tricyclic, has been used more frequently for the management of interstitial cystitis and OAB in adults but its use in children is limited.[56,57]

Selective serotonin reuptake inhibitors and serotonin noradrenaline reuptake inhibitors have been useful in older patients with OAB, especially when there is evidence of anxiety disorders of clinical significance. The author has found that management of the anxiety problems at the central level or in combination with anticholinergics is more effective than management with anticholinergics alone.

2.3 α-Adrenoceptor Antagonists

α-Adrenoceptor antagonists have been playing an increasing role in the management of OAB in the author's practice over time. Aside from the role that they play in the management of bladder neck dysfunction and urinary retention, these agents have been found to be useful for ameliorating the symptoms of urgency and urge incontinence in some children. In many cases terazosin is the author's first-line drug for urgency and frequency because of its non-selective properties and potential to cross the blood-brain barrier. More selective α-adrenoceptor antagonists, such as tamsulosin and alfuzosin, may be better suited for management of bladder neck dysfunction that can lead to detrusor hypertrophy and instability.

Because non-selective α-adrenoceptor antagonists can cause postural hypotension, they require gradual titration of the dose and must be used carefully. In patients with a family history of fainting easily or postural hypotension, dose titration is essential even with the selective α-adrenoceptor antagonists. For the most part, children tolerate α-adrenoceptor blockade well and the author has used terazosin in children as young as 2 years of age with bladder neck dysfunction associated with high-grade vesicoureteral reflux. The role of α-adrenoceptor antagonists used alone, with anticholinergic drugs or with behavioral therapy requires further study.

2.4 Other Drugs

Although currently available β-adrenoceptor agonists have not been shown to be useful for OAB, more selective β_3-adrenoceptor agonists may have therapeutic value.

Drugs that act by means of ATP-sensitive potassium channel transporters to hyperpolarize smooth muscle and decrease spontaneous bladder contractions, may be useful for suppressing involuntary bladder contractions without interfering with normal voiding.[58] However, first-generation agents in this class have been shown to have effects on vascular smooth muscle and can cause hypotension.[58]

Drugs that act on sensory afferent pathways are also being developed and hold promise when used either alone or in combination with other drugs. Vanilloids such as capsaicin and resiniferatoxin activate nociceptive sensory nerve fibers through an ion channel, known as the vanilloid receptor subtype. This receptor is a non-selective cation channel that is activated by heat and protons, suggesting that it functions as a transducer of painful thermal stimuli and acidity *in vivo*. Vanilloid receptors are located predominantly on C-fiber bladder afferents and activating these receptors initially excites and subsequently desensitizes C-fibers.[28] Resiniferatoxin appears to be more potent and less irritating than capsaicin and may be more useful clinically. Other drugs that block receptors on sensory afferents, such as neurokinin receptor antagonists, might not cause urinary retention, which can occur with use of anticholinergic agents.

The role of phosphodiesterase inhibitors in OAB needs further exploration and only time will tell if these agents may also play a useful role.[59,60]

2.5 Botulinum A Toxin

Botulinum A toxin is the most potent biological toxin known. The toxin acts on the neuromuscular junction at the external sphincter to block vesicle transport of acetylcholine, in essence producing chemical denervation. Clinical effects begin within 5–7 days and are reversible because of terminal resprouting, which occurs within 6 months.[61] The clinical success of botulinum A toxin is supported by laboratory research that shows marked decreases in release of labeled norepinephrine and acetylcholine in botulinum A toxin-injected rat bladders and urethras. While the therapeutic effects of inhibiting acetylcholine release are obvious, blocking norepinephrine release may also provide clinical benefit by inhibiting sympathetic transmission in smooth muscle dyssynergia. This is why some patients with combined internal and external dyssynergia treated by the author have responded well to botulinum A toxin injections.

Botulinum A toxin injections of the detrusor have been performed for non-neurogenic OAB in symptomatic adults with some success. One of the drawbacks of this treatment is the need for retreatment, since the probable underlying cause is not in the bladder but elsewhere. Hoebeke et al.[62] published their experience in 15 children indicating that durable (>12 months) relief of symptoms could be achieved in >50% of the patients with a single injection. Only three patients did not respond, and patients that had partial responses appeared to respond to a second injection. These findings are encouraging and could help improve the treatment of OAB in children in whom the etiology is not sphincter dyssynergia.

On the other hand, use of botulinum A toxin injections for sphincter dyssynergia could possibly be very beneficial in elimination of the dyssynergic voiding pattern and could possibly help eliminate the detrusor hypertrophy that is commonly associated with detrusor overactivity. Botulinum A toxin injection produces a reversible chemical sphincterotomy, which obviates the need for a major surgical procedure with its attendant risks. Botulinum A toxin has been used to treat spinal cord injury patients with detrusor sphincter dyssynergia in adults and children with spina bifida. Its use to treat non-neurogenic detrusor sphincter dyssynergia has been described by Steinhardt et al.[63] in a neurologically healthy child in 1997 and by Diaz-Soldano et al.[64] in a series of 20 girls with 'lazy bladder' and external sphincter spasticity who were treated with botulinum A toxin on a prospective basis. Even though this study[64] appears to have been flawed for many reasons, it further strengthened the foundation for use of botulinum A toxin injections in neurologically healthy children. More recently, a series of 20 patients presented by Radojicic et al.[65] indicated that treatment of detrusor sphincter dyssynergia is clearly helped by the use of botulinum A toxin injections in neurologically healthy children.

The author can also report exceptionally good results in children who were administered botulinum A toxin to treat external sphincter dyssynergia of non-neurogenic origin.[66] In this study, 12 patients were injected with botulinum A toxin 300U in and around the external sphincter; all 12 patients responded well to the injections with no adverse effects. Only one patient had to be reinjected more than once. One patient who had required intermittent catheterization had been unable to empty her bladder, leaving a post-void residual volume of 250mL each time. Following botulinum A toxin therapy, this child is completely dry, has no accidents, and voids to completion at 1.5 years post-injection. Another child who responded well to botulinum A toxin had previously been offered augmentation cystoplasty to manage his intractable wetting and severe detrusor sphincter dyssynergia, with consequent chronic epididymitis.

In summary, the results of limited studies available to date suggest that botulinum A toxin represents a viable option for treating detrusor sphincter dyssynergia. In patients receiving this therapy, correction of detrusor sphincter dyssynergia has led to resolution of the associated OAB symptoms.

2.6 Biofeedback Therapy

Biofeedback therapy has been used in urology for many years. Use of Kegel exercises was initially introduced to help patients with stress urinary incontinence. Subsequently, in the mid-1990s, biofeedback was introduced to the management of children who had chronic wetting problems as well as an inability to empty the bladder completely. Biofeedback therapy was commenced at the author's institution in 1997 and the program has been extremely successful.[67] Many children who did not respond to initial treatment for constipation and who exhibited signs of external sphincter dyssynergia subsequently underwent biofeedback therapy. First, a uroflow study with concomitant abdominal and perineal electromyography (EMG) would be performed. This study would indicate that external sphincter dyssynergia was present by exhibiting increased activity in the perineal sphincter EMG probe. If no increase in activity in the perineal sphincter probe was observed and there was abdominal straining, the presence of internal sphincter dyssynergia would be suggested. If there was internal and external sphincter dyssynergia present, treatment would consist of the use of α-adrenoceptor antagonists as well as biofeedback.

Each biofeedback session lasts for approximately 45 minutes with a trained nurse performing the biofeedback therapy. Initial biofeedback therapy included simple relaxation and contraction exercises while the patient monitored oscilloscopic activity of the perineum. The technology has evolved such that the session now uses a computerized system with a game-like interactive setting, where the child attempts to move an icon of his/her choice, i.e. dolphin, car, or bird, within the predetermined ranges that have been set. This has facilitated the training process and lowered the age at which children can be treated. Preliminary data from use of this program at the author's institution indicate a reduction in the number of biofeedback sessions required for children to master pelvic floor relaxation.

Biofeedback therapy is limited by the ability of the child to cooperate with the healthcare provider running the session. Children <5 years of age are typically incapable of utilizing biofeedback therapy on a regular basis. Occasionally, some children aged <5 years can be taught to relax their pelvic floor muscles appropriately with biofeedback. Children with significant learning disabilities, behavior problems, and other neurologic problems are not candidates for biofeedback. Biofeedback therapy is useful in the management of OAB primarily by reducing outlet resistance during voiding, which leads to detrusor hypertrophy and therefore to detrusor instability.

2.7 Urethral Overdistention

Management of OAB and bladder instability using urethral dilation is a practice that has been ongoing for many years in adult urologic practices. Numerous women with urethral syndrome have had their urethras dilated monthly for years on end. Many of these women have classic symptoms of OAB, pelvic discomfort, and dysuria. This mechanism of overdilation probably works in a very similar fashion to the use of botulinum A toxin at the level of the external sphincter. This temporary sphincterotomy occurs either by overdistention and/or tearing of the sphincter muscles. Central neural processes may lead to resetting of receptors in the spinal cord and possibly in the brain, which may lead to decreased activity of the sphincter. This decrease in sphincter activity will result in improved bladder emptying secondary to reduced outlet resistance, which means the detrusor muscle in the bladder will not have to work as hard. This decrease in detrusor activity will in turn translate into a possible reduction in overactivity at the bladder level.

2.8 Spinal Cord Stimulation

Spinal cord stimulation is a technique that has been used with increasing regularity in adult patients with OAB. Selective stimulation of the sacral nerves and the pudendal nerves has led to significant improvements in OAB in patients who have had stimulators implanted. The role of spinal stimulation in children is yet to be well defined. Only one study by Humphreys et al.[68] has indicated some usefulness in children with voiding dysfunction.

2.9 Peripheral Nerve Stimulation

Electrical tibial nerve stimulation is based on the traditional Chinese practice of using acupuncture points over the common peroneal posterior tibial nerves to inhibit bladder activity.[34] Transcutaneous posterior tibial nerve stimulation has been evaluated in clinical trials with variable results. The technique involves use of a 34-gauge stainless steel needle, which is inserted approximately 5cm cephalad to the medial malleolus just posterior to the margin of the tibia. A stick-on electrode is placed on the medial surface of the calcaneus. Limited reports of its use in children have also indicated efficacy.

In one study of percutaneous electrical nerve stimulation by Hoebeke et al.,[69] 17 of 28 children with non-neuropathic bladder sphincter dysfunction who had been refractory to medical treatment had a resolution or improvement in their symptoms, 16 of 19 patients who had abnormal frequency showed marked improvement, and mean bladder capacity increased significantly overall. This study indicates a role for peripheral nerve stimulation as a means of improving OAB in children. The exact mechanism of action for this modality is unclear. What we can extrapolate from recent findings with sacral modulation is that electrical tibial nerve stimulation may function in a similar fashion to sacral modulation by having an effect on the brain.

3. Conclusion

It is becoming apparent that the vesicocentric theories that had been proposed in the past for OAB need to make way in favor of a more corticocentric way of thinking. At the present time, anticholinergics seem to be able to treat only the symptoms of this disorder, whereas α-adrenoceptor antagonists appear not only to treat symptoms but also to act on the root of the problem.

More research efforts need to be made in terms of assessing the CNS as the primary site of dysfunction and targeting treatment at appropriate sites in the CNS. Development or re-evaluation of present medications that target central sites is critical to the progression of treatment of OAB beyond the present state. Maintaining the status quo and continuing to believe that treatment of symptoms is the correct path does our profession and our patients a disservice. Correction of the underlying root cause of the problem should be our goal, and it is up to us as physicians to probe deeper into this problem and not accept the status quo view that in many instances may have been built on a foundation not supported by evidence-based medicine. Continued advances in functional neural imaging will continue to open up new frontiers in this field and hopefully provide the evidence that is necessary to form the foundation that will serve as the source of answers to these problems.

Medications that are developed utilizing the data garnered from this evidence-based medicine approach will hopefully treat the underlying disease process and not just the symptoms. It is increasingly apparent that norepinephrine and serotonin are critical in the modulation of voiding processes. Treatment with drugs that target these neurotransmitters needs to be explored further. The current stigma associated with the use of SSRIs and the present restrictions imposed by the exorbitant cost of new drugs may inhibit the present development of drugs that can have modulatory effects on voiding neural pathways. The continued use of stimulation modalities, whether peripheral or central, is a strategy that requires continued exploration in the future.

The complexity and difficulties encountered when conducting studies in children need to be overcome to allow greater advancement in this field. It is becoming apparent that childhood OAB is a lifelong problem and correction of the problem at a young age may prevent further problems in adulthood. Hopefully, device makers and drug manufacturers can recognize this and target treatments for children that can prevent more profound problems in adulthood.

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