

The Central Nervous System and its Role in Bowel and Bladder Control

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Abstract Bowel and bladder issues have been noted to be coexistent in children, and treatment of bladder symptoms without concomitant targeting of bowel issues generally leads to failure. This article explores the potential roots for this persistent connection between bowel and bladder and the role that the central nervous system plays in affecting both. An ever-increasing pool of knowledge drawn from multiple medical disciplines has provided us with a wealth of functional imaging information that is allowing us to map the areas of the brain better with regards to bowel and bladder function. We explore these new findings and attempt to connect the dots between the central nervous system bladder and bowel dysfunction.

Keywords Central nervous system · Bowel · Bladder · Voiding dysfunction · Overactive bladder · Pediatrics · Urinary tract infection · 5-HT4 · Schizophrenia

Introduction

History has much to teach us, and as the saying goes, it has a tendency to repeat itself. In parallel, we can look back at Ptolemy's geocentric theory that proclaimed that the Earth was the center of the universe. Similarly, if we look at the urologic literature, we see that urologists still see the bladder as the center and soul of voiding problems [1]. Urologists appear to be no different than pre-Copernican thinkers, holding fast to a Ptolemaic-like view of anatomy

and physiology, which I have termed as a vesicocentric model. This is evident from the numerous papers implicating one neurotransmitter or peptide as the source of overactive bladder (OAB). It is this mindset that has prevented us from moving in a direction that could lead to a solution for OAB instead of simply treating the symptoms that these patients have.

If we examine the lexicon of the pediatric urologist, it is filled with words and statements that are repeated routinely but are mistruths (eg, your child's bladder is autonomous; it is reflexive; in time it will mature; bladder size is too small). How is it possible for there to be a de novo isolated detrusor problem just after toilet training and for it to not be present beforehand? This does not make sense, and neither do some of the old adages that have been passed along from one generation of urologists to another.

Experience has told us that numerous treatments and ideas that we have held as inalienable do not make sense when they are scrutinized more closely. If we look at these tenets more closely, we see that they only can make sense in some situations, not in others. In medicine, the teaching is that one disease should be able to explain all of the patient's symptoms. One should look for that one disease process and not try to ascribe multiple diagnoses to these patients. In the children that we see with functional voiding issues, bowel problems, and, in many cases, behavioral problems, it would be best to ascribe all these issues to one problem and not to parse it out to three different diagnoses as we have been doing. Recent advances in imaging of the brain, better neuropsychiatric studies, and an improved understanding of gut physiology and neurobiology have begun to open the door so that these apparently disparate diseases can be placed under one disease process. This review explains how these three separate areas of the body and seemingly unrelated issues interact with one another.

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Bowel–Bladder Interaction

Rectal Distension

It has been a well-entrenched tenet of the management of functional voiding issues that bowel problems need to be addressed to be able to manage patients' lower urinary tract symptoms (LUTS). This combination of bowel and bladder problem was first described as dysfunctional elimination syndrome by Koff et al. [2] in 1998. Loening-Baucke's [3] work showed that the elimination or correction of constipation led to the concomitant resolution of incontinence and recurrent urinary tract infection (UTI) in the patients she treated. As time has progressed, there has been increasing evidence linking bowel problems with LUTS in children; the mechanisms are well reviewed in the article by Franco [4]. There has been work done that shows that rectal diameter in excess of 4 cm is associated with voiding dysfunction.

In work by Miyazato et al. [5], the researchers found that rectal distension leads to decreased amplitude and a shortened duration of bladder contraction, and it can almost abolish bladder activity. These effects can be reversed by the injection of strychnine and bicuculline intrathecally. This restores the amplitudes of bladder contractions to control levels. It is postulated that an inhibitory rectovesical reflex exists in the lumbosacral cord of rats. It is very possible that a similar reflex may be present in children because the association between hoarding of urine and rectal distension is so prevalent in children with dysfunctional elimination [6]. Distension in the rectal wall generates impulses that are transmitted distally through its walls via the myenteric plexus, activating the rectal sphincteric relaxation reflex, and causing smooth muscle relaxation in the internal anal sphincter. The degree of relaxation is in proportion to the fecal volume and the speed at which the rectum is distended. An increase in intra-abdominal pressure lowers the pelvic floor, thereby increasing intrarectal pressure. Relaxation of the external sphincter allows the fecal bolus to be expelled. In many children who have intermittent fecal soiling or fecal marks on the underwear, involuntary relaxation of the internal sphincter allows stool to present at the anus, thereby soiling the underwear. When they sense the stool at the anal verge, they clamp down on the external sphincter and the stool is pushed back in. Problems that would lead to autonomic dysfunction potentially would lead to issues with the internal anal sphincter and potentially lead to problems with sustained pelvic floor hypertonicity, which may persist during voiding. This may contribute to the detrusor hyperplasia commonly seen in children with constipation. In agreement with this concept, it has been very clear that when patients present for biofeedback training, they have a

tendency to be unable to adequately relax the pelvic floor if they are full of stool. We also noted that bowel regimens that only soften the stool did not work as well as those that utilized cathartics, thereby emptying the colon further and reducing rectal distension.

Bowel and Bladder Contractions

It is not rare for children to be incontinent of urine shortly after lunch in school, and it is common for parents to recount that their child will get up shortly after sitting down for a meal and have to run to the bathroom to urinate. These are signs that there is a common link between the bladder and the bowel. This concept is substantiated by work by Warne et al. [7], who found that, on 24-hour continuous urodynamic studies, colonic contractions preceded bladder contractions, linking the bladder and bowel together. A more recent publication by Cho and Oh [8] reveals that rectal contractions measured on urodynamics are associated with cerebrovascular accidents, spinal cord lesions, and reduced bladder compliance. Jia et al. [9] showed that there is a defect in the parasympathetic nucleus in patients with imperforate anus, therefore implicating the urodynamic abnormalities commonly found in patients who have an imperforate anus. This also implicates the parasympathetic nucleus in the modulation of micturition. We know that the parasympathetic nucleus is innervated by α -adrenergic pathways descending from the locus coeruleus. We also know that the parasympathetic nucleus fibers emanating from the rectum are aligned adjacent to bladder fibers. There is evidence that crosstalk occurs between the two. Pezzone et al. [10] have shown, in colitis models, that placing acetic acid in the rectum of rats can trigger bladder hyperactivity, and vice versa. We have seen this occur in patients who have had an acute flare-up of colitis and develop urinary urgency and frequency that is not controllable until the colitis comes under control.

Once these children are treated for their bowel issues with the appropriate therapy and the therapy is discontinued, we found that most children had a tendency to relapse within 6 to 12 months. This would indicate that there was some type of intrinsic defect in the colon that led to reaccumulation of stool. The idea that there is a persistent peristalsis problem in the gut is further substantiated by a recent publication by Franco et al. [11] that shows that the use of a 5-hydroxytryptamine receptor 4 (5-HT₄) agonist led not only to improved bowel movements, but also to an improvement in the ability to empty the bladder. In this case, it is not clear whether this was due to changes solely in the bowel or if it was due to alterations in 5-HT₄ levels in the central nervous system (CNS). Tegaserod is known to cross the blood–brain barrier, and

possibly could have been exerting its effect either at Onuf's nucleus or even farther up centrally in the brain.

A functional gastrointestinal disease with correlates to functional voiding issues is irritable bowel syndrome (IBS). Recent work [12•] has begun to highlight the role of CNS imaging in helping to determine the causes of this problem. It is apparent that patients with IBS have alterations in the brain. As it will become apparent later in the article, the alterations are in areas that are similar to those seen in brain imaging of patients with urgency. Cortical thinning also has been identified in these patients with IBS, and again, the thinning is in areas that are similar to those who have voiding problems as well as psychiatric problems. It appears from the available data that, in the patients with IBS, the issue revolves around modulation of pain. Synonymous to this would be the concept of the patient with severe urgency whose sudden and strong urge to urinate is perceived as an overwhelmingly strong sensation that produces discomfort or pain. The site that is implicated in both problems is the prefrontal cortex. In this IBS study, there also is an association with the hypothalamus, in which we again see parallels in the patients with OAB.

A Childhood Problem Continues Into Adulthood

From the perspective of the pediatric urologist, the child who has OAB has a good chance of continuing to have problems with OAB in adulthood. This correlation was seen in two published reports. In the first study, Fitzgerald et al. [13] noted that OAB in childhood correlated with adult OAB symptoms. They found that frequent daytime voiding in childhood correlated with adult urgency. A correlation exists between childhood nocturia and adult nocturia. Childhood daytime incontinence and nocturnal enuresis were associated with a more than twofold increased association with adult urge incontinence. Also, a history of childhood UTIs correlated with a history of adult UTIs. In a study of 170 women, Minassian et al. [14] found a higher prevalence of childhood voiding dysfunction in women who had urinary frequency, urgency, stress incontinence, and urge incontinence. They also noted a greater likelihood of a higher body mass index in their symptomatic patients. A recent publication by Stone et al. [15] also tends to highlight the fact that voiding issues in children should not be similarly discounted. In this study, it was found that up to a third of children who had voiding issues by age 9 years continue to have voiding issues by age 18 years. These children had been tested with urodynamics and magnetic resonance imaging (MRI) studies of their spine, indicating that there were no anatomic abnormalities; therefore, the only site of dysfunction could have been either the bladder or the brain.

Hyde et al. [16] found that adult patients with schizophrenia (SCZ) have an increased rate of childhood enuresis (21%) compared with their healthy siblings (11%) or with normal control patients (7%). This is the first, and thus far largest, study of childhood enuresis in adult patients with SCZ to date, and is the only study of adults with a history of enuresis examined with both neuropsychological testing and structural brain imaging. They also found that probands had significantly higher rates of enuresis than their nonpsychotic siblings (21.3% vs 11.2%) and control patients (21.3% vs 7.3%). Male probands also had significantly higher rates of enuresis than male siblings (23.2% vs 10.3%) or male control patients (23.2% vs 11.5%). Female probands had significantly higher rates of enuresis than female control patients (14% vs 4.6%) but not female siblings (14% vs 12%). No significant differences in rates of enuresis were found between siblings and control patients in the overall sample or male subset, but were found in female siblings versus female control patients (12% vs 4.6%). Siblings of probands with enuresis had significantly higher rates of enuresis than siblings of probands without enuresis (19.1% vs 7%). In analyses of cognitive data, it was found that probands with enuresis performed significantly worse than probands without enuresis on two measures, both involving speed-dependent verbal retrieval (letter and category fluency). A nearly identical pattern of findings emerged in control patients. Controls patients with enuresis performed significantly worse than control patients without enuresis on letter fluency and showed a trend toward worse performance on category fluency in comparison to control patients without enuresis. No other significant findings were found between the two control groups on neuropsychological measures. Thus, in both subject groups, enuresis was significantly and selectively associated with relatively poorer verbal fluency performance alone. No significant differences were found between siblings with or without enuresis on any neuropsychological measures.

Hyde et al. [16] found that enuresis potentially is heritable: the familial risk of enuresis was 2.6 times greater in siblings of enuretic probands than in siblings of non-enuretic probands. Moreover, they found that at least healthy female siblings of patients with SCZ have a significantly increased frequency of enuresis, suggesting that enuresis may be related to genetic risk factors for SCZ. This work is not the first to implicate the heritable nature of enuresis. In a large Finnish cohort ($n=3206$), if fathers were enuretic after age 4 years, the risk of offspring being enuretic was 7.1 times greater [17]. Comparing monozygotic ($n=1298$ pairs) to dizygotic ($n=2419$ pairs) twin pairs, the concordance rate for childhood enuresis (at age 4 years) was significantly higher in monozygotic twins. This was true in male pairs as well as female pairs [6]. A

recent study found that 23% of probands with childhood enuresis had a positive family history of childhood enuresis [18, 19]. Linkage analyses in families with a high density of enuretic children have implicated a variety of chromosomal locations including 4p16.1, 12q, 13q, and 22q11 [18].

Cortical Control of Micturition

Studies utilizing functional MRI, which measures local cerebral blood flow (which is considered an indirect measure of regional normal activity), have given rise to an increasing pool of knowledge regarding the sites that are active during bladder filling and micturition. Several centers have been quite active in using this technique to monitor the control of micturition. Studies using these techniques have shown increased overall brain activity provoked by bladder filling. In particular, activation and deactivation of the brain regions involved in the mapping of body sensations (right insula/somatosensory cortex), emotional processing (anterior cingulate gyrus [ACG]/limbic cortex and parts of the frontal cortex) and decision making (parts of frontal cortex) [20••] imply their potential role in the control of continence. It is clear that the insula is the area where the mapping of sensation occurs, and as bladder volume increases, activity in the insula in normal patients increases. In patients with urgency, there is greater activity in these sites. In normal patients, gradual bladder distension leads to an increase in the activity in the ACG. In the patient with urgency, the activity in the ACG is increased. In the normal patient, there should be a concomitant decrease in the ventral medial prefrontal cortex (vmPFC) with bladder filling. The vmPFC has been shown to be correlated with the urge to urinate. It appears that inhibition or decreased activity of this site is essential to allow for normal bladder filling. The vmPFC is of parasympathetic origin [21•], and parasympathetic activity is known to lead to micturition. Therefore, decreasing activity in the vmPFC would lead to a reduction in the need to void. On the other hand, increased activity in the ACG is known to be associated with sympathetic activity [21•]. It is well known that increased sympathetic activity will lead to tightening of the bladder neck, which would lead to holding of urine. We also know that the ACG is responsible for executive functioning as well as for the processing of pain and is involved in autonomic control.

Work by Dasgupta et al. [22, 23•] and Blok et al. [24] have shown that activation of spinal stimulation does not lead to an increase in activity in areas that commonly are associated with micturition reflexes. On the other hand, activity changes occur in the areas that are associated with genital arousal, bladder filling, and sensation in the onset of micturition. These findings again implicate ACG in the prefrontal cortex in the control of micturition.

In a recent publication by Tadic et al. [20••], they showed that urinary incontinence, frequency, and daytime urge incontinence were positively correlated with increased activity in the rostral and subgenual ACG, insula, inferior frontal gyrus, parahippocampus, dorsal ACG, posterior cingulate gyrus, cuneus, and parietotemporal lobe. Based on work by Rainville et al. [25], the authors feel that dorsal ACG activation may indicate unpleasantness rather than sensation intensity. With these findings, we see the correlation between IBS and urgency, where there appears to be a problem with encoding for pain in the individual. Once these responses are invoked, the amygdala may come to play a role as well. Eventually, amygdala activation can lead to bypassing of higher cortical centers and to immediate fight-or-flight responses with its inherent physiological implications from the release of neurotransmitters and hormones from the hypothalamus. Once aberrant amygdala responses have been established, these pathways will supersede cognitive centers and can lead to maladaptive voiding responses or behavior that can eventually lead to abnormal micturition reflexes.

Hypothalamic–Pituitary Axis

It is known that there are direct connections between the ACG and hypothalamus, and that these connections may have further implications in OAB. The role of the hypothalamus as part of the limbic system as an initiator of the hypothalamic–pituitary axis, a neuroendocrine pathway that is integral to stress response, releasing corticotrophin-releasing factor (CRF) and, eventually, cortisol into the circulatory system. CRF acts as a CNS neurotransmitter; neurons in the brain project to the locus coeruleus, which is rich in norepinephrine (NE), and dorsal raphe nucleus, which is rich in serotonin (5-HT). CRF receptors are found in the intermediolateral dorsal column, implicating it in motor control of micturition. It is also found in dorsal root ganglia and collocates with substance P and other neuropeptides. There are conflicting reports as to what the exact role of CRF is in the spinal cord because some studies have implicated it as an agonist and other have shown that there are antagonist actions in CRF in animal models. It appears that in the brain, areas critical to the central stress response overlap with control of bladder activity. CRF has been implicated in obesity and in metabolic syndrome. Both have been associated with OAB in children and adults. A commentary by Alonso-Alonso and Pascual-Leone [26] in the *Journal of the American Medical Association* implicates the right side of the brain, and in particular, the PFC, in the pathogenesis of obesity. This common link between obesity and OAB could be due to problems encountered in the prefrontal cortex.

Conclusions

It is apparent from the literature that there are strong ties between the bladder and bowel in the CNS, and that it should not be a far stretch to expect patients that have bowel problems to have bladder issues as well. Whether the problem is a neurotransmitter-related problem or a problem due to signals that are being mixed up like an old-fashioned party line, it is clear that the two are intertwined and that management of LUTS is dependent on the appropriate management of both of the problems.

Cortical imaging studies are leading us to recognize that the site of persistent OAB is the frontal lobe and that dysfunction in this area is a critical part of the problem. Without correction of the CNS problem, we may only be treating problems and not treating the underlying disease process.

Disclosures Dr. Israel Franco serves as a consultant for Sanofi, Novartis and Allergan, and has previously served as a consultant for Astellas Pharma and LABORIE.

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