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Review article

Genitourinary and gastrointestinal co-morbidities in children: The role of neural circuits in regulation of visceral function

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Summary

Objective
Pediatric lower urinary tract dysfunction (LUTD) is a common problem in childhood. Lower urinary tract symptoms in children include overactive bladder, voiding postponement, stress incontinence, giggle incontinence, and dysfunctional voiding. Gastrointestinal co-morbidities, including constipation or fecal incontinence, are commonly associated with lower urinary tract (LUT) symptoms in children, often reaching 22–34%. This review summarized the potential mechanisms underlying functional lower urinary and gastrointestinal co-morbidities in children. It also covered the current understanding of clinical pathophysiology in the pediatric population, anatomy and embryological development of the pelvic organs, role of developing neural circuits in regulation of functional co-morbidities, and relevant translational animal models.

Materials and methods
This was a non-systematic review of the published literature, which summarized the available clinical and translational studies on functional urologic and gastrointestinal co-morbidities in children, as well as neural mechanisms underlying pelvic organ 'cross-talk' and 'cross-sensitization'.

Results
Co-morbidity of pediatric lower urinary and gastrointestinal dysfunctions could be explained by multiple factors, including a shared developmental origin, close anatomical proximity, and pelvic organ 'cross-talk'. Daily physiological activity and viscero-visceral reflexes between the lower gastrointestinal and urinary tracts are controlled by both autonomic and central nervous systems, suggesting the dominant modulatory role of the neural pathways. Recent studies have provided evidence that altered sensation in the bladder and dysfunctional voiding can be triggered by pathological changes in neighboring pelvic organs due to a phenomenon known as pelvic organ 'cross-sensitization'. Cross-sensitization between pelvic organs is thought to be mainly coordinated by convergent neurons that receive dual afferent inputs from discrete pelvic organs. Investigation of functional changes in nerve fibers and neurons sets certain limits in conducting appropriate research in humans, making the use of animal models necessary to uncover the underlying mechanisms and for the development of novel therapeutic approaches for long-term symptomatic treatment of LUTD in the pediatric population.

Conclusion
Pediatric LUTD is often complicated by gastrointestinal co-morbidities; however, the mechanisms linking bladder and bowel dysfunctions are not well understood. Clinical studies have suggested that therapeutic modulation of one system may improve the other system's function. To better manage children with LUTD, the interplay between the two systems, and how co-morbid GI and voiding dysfunctions can be more specifically targeted in pediatric clinics need to be understood.

Introduction

Pediatric lower urinary tract dysfunction (LUTD) is a common problem in childhood. It is characterized by a number of symptoms based on their relation to the voiding and storage phases of the micturition cycle. Lower urinary tract (LUT) dysfunctions in children associated with the storage symptoms include overactive bladder (changes in voiding frequency and urgency), stress and giggle incontinence, enuresis, and nocturia [1]. Voiding postponement (hesitancy, straining, holding maneuvers) and dysfunctional voiding (weak stream, intermittency) mainly characterize the changes in the voiding phase of the micturition cycle. The International Children's Continence Society (ICCS) defines dysfunctional voiding as dysfunctional habitual contraction of the urethral sphincter during voiding; it accounts for up to 40% of pediatric urology clinic visits [1]. Large clinical databases also report the prevalence of daytime urinary incontinence in children, up to 10–17%

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[2,3]. Lower urinary tract symptoms that are experienced in childhood tend to linger throughout life, and may manifest themselves in adulthood in many different ways, ranging from urgency and frequency of micturition to the development of chronic pelvic pain syndromes [4–6].

Gastrointestinal (GI) dysfunction, constipation and/or fecal incontinence are commonly associated with LUTD, reaching up to 22–34% in comparison with children without constipation [7]. In addition, children with constipation have abnormal voiding parameters, even if they do not describe symptoms [8]. Interestingly, children who initially present to a gastroenterology clinic with GI dysfunction and those presenting with LUTD to a Pediatric Urology clinic have similar bladder and bowel symptoms, with >50% of children with LUTD having bowel dysfunction [9,10]. Consequently, the ICCS have named this condition as Bladder and Bowel Dysfunction (BBD), previously known as dysfunctional elimination syndrome [11]. In addition, BBD has also been found in 43% of children with primary VUR [12]. Constipation associated with functional megacolon has been identified as a common etiologic factor that is related to recurrent UTI and VUR [13]. Clinical studies have also established that urgency and risk of UTI is proportionally increased in children with chronic functional constipation [14].

Co-morbidity of pediatric lower urinary and GI dysfunctions could be explained by multiple factors, including a shared developmental origin, close anatomical proximity, and pelvic organ cross-talk via connected neural pathways [15].

This review clarified and summarized the potential mechanisms underlying pelvic organ co-morbidities in children, with regard to the relationship between lower urinary and colorectal dysfunctions. It covered the current understanding of clinical pathophysiology in the pediatric population, anatomy and embryological origins of the pelvic organs, role of neural circuits and developing neural pathways in regulation of functional co-morbidities, and available translational models with which to study the underlying mechanisms.

Treatment options for co-morbid lower urinary tract dysfunction and gastrointestinal symptoms in children

Treatment of children with BBD usually starts with a behavioral-modification program that consists of: timed voiding (5–7 times a day); improvement of pelvic floor relaxation by adjusted posture and breathing exercises; double voiding before bedtime; reduction in caffeine, colorants and carbonation from the diet; and treatment of constipation with increased fiber [16]. With behavioral modification alone, >55% of children had a significant symptom improvement, confirming the functional link between the bladder and bowel [16]. Behavioral therapy in children with bladder-sphincter dysfunction also decreased the prevalence of functional fecal incontinence by 21–30%; however, no direct correlation was found between improved functional fecal incontinence and bladder-sphincter dysfunction [17].

In children and adolescents who fail behavioral modification, there are a variety of therapeutic and physical therapies that address bladder and bowel physiology, the pelvic floor and the central nervous system [16,18], but the mechanisms by which BBD are linked are not well understood. To better manage these patients, this interplay between the two organ systems and how we can more specifically target co-morbid GI and LUT dysfunction in the clinic need to be fully understand.

Anatomical development of genitourinary and gastrointestinal systems

In early fetal development, a close relationship between pelvic organs is evident. Both the LUT and GI systems develop from a shared cloaca. During the seventh week of gestation, the urorectal septum grows caudally, dividing the cloaca into the urogenital sinus and anorectal canal [19]. An extensive supply of nerves and vasculature forms to support the growing tissues. Numerous developing neural subpopulations have been identified and show distinct patterns of distribution among LUT tissues [20]. Sensory and motor nerves produce distinctive neurotransmitters and signaling molecules, however, they are anatomically indistinguishable and no data currently exist on the spatiotemporal distinction between these populations. The paired pelvic ganglia that develop in the LUT close to the anterior pelvic urethra also contain a mixture of both sympathetic and parasympathetic neurons [21].

The complex anatomy of genitourinary and GI systems rapidly changes during embryogenesis. The close developmental link between urogenital (bladder, urethra, genitalia) and distal GI (colorectum, anal canal) tracts may explain the co-occurrence of genital anomalies (ambiguous genitalia, hypospadias, chordee and micropenis in males, cleft clitoris in females) with anorectal defects [22]. Normal development and innervation of the bladder, urethra and outlet also play a critical role in maintaining urinary continence after birth [23]. Therefore, even small perturbations in differentiation processes or timing in one tissue can translate into functional defects affecting the entire system, and, likely, cause long-term LUTD not only in children but also in adulthood.

Neural mechanisms controlling maturation of the micturition reflex

Development of LUTD in children closely correlates with their psychological and emotional state. Delayed development, difficult temperament, and maternal depression/anxiety were shown to be associated with daytime wetting and soiling [24]. In a large epidemiologic study of a cohort of 8213 children aged 7.5–9 years, children with daytime wetting had significantly increased rates of psychological problems, especially separation anxiety, attention deficit, oppositional behavior, and conduct problems [25]. As the nervous system in children continues to develop into adolescence, early life interventions can affect structure and connectivity of neural circuits, and also impact on