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Predictors of treatment failure with parasacral transcutaneous electrical nerve stimulation in children and adolescents with bladder and bowel dysfunction

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Summary

Introduction
Parasacral Transcutaneous Electrical Nerve Stimulation (parasacral TENS) has emerged as a promising treatment for children with Bladder and Bowel Dysfunction (BBD), being an efficient method without direct adverse effects. Little is known about clinical characteristics associated with poorer treatment outcomes in this specific patient group.

Objective
To evaluate potential clinical predictors of parasacral TENS treatment failure in children and adolescents with BBD.

Methods
This was a retrospective cohort study of children and adolescents aged 4—17 years diagnosed with BBD. All patients underwent three sessions of parasacral TENS for 20 min per week for a total of twenty sessions. Lower urinary tract symptoms (LUTS) were assessed by structured questionnaire, DVSS, and visual analog scale (VAS). Functional constipation (FC) was evaluated using the Rome IV criteria. Potential predictive clinical factors evaluated included age, daytime incontinence, nocturia, history of urinary tract infection (UTI), enuresis, pre-treatment DVSS scores, frequency, Rome IV sum, and fecal incontinence.

Results
Fifty-two patients were included in the study. The mean age (± standard deviation) was 7.8 ± 2.7 years, with a majority being female, 59.6 %. After treatment with parasacral TENS, complete LUTS response was achieved in 21 patients (40.4 %). A partial response occurred in 28 patients (53.8 %). In 3 patients (5.7 %), there was no response to treatment. As for FC, complete resolution was achieved in 35 (67.3 %) of the children, with 17 (32.7 %) remaining constipated. Among all participants, 16 (30.7 %) achieved complete resolution of both constipation and urinary symptoms. Of all the factors evaluated, history of UTI was identified as a clinical predictor of treatment failure for constipation in children with BBD undergoing parasacral TENS ($p = 0.038$; OR = 3.51; CI (1.04—11.84)).

Discussion
We suggest that children and adolescents with history of UTI are related to more severe FC, complicating treatment, requiring a multimodal and a more aggressive approach.

Conclusion
This study demonstrated that history of UTI is a clinical predictor of treatment failure for constipation in children and adolescents with BBD undergoing parasacral TENS.

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Introduction

Bladder and Bowel Dysfunction (BBD) is defined by the International Children's Continence Society (ICCS) as a disorder characterized by the association between Lower Urinary Tract Symptoms (LUTS) and functional constipation (FC) [1]. According to a Brazilian population study, the overall prevalence of this dysfunction in children is estimated to be 11.6 % [2]. Delays in the diagnosis and treatment of BBD can lead to clinical complications, such as recurrent urinary tract infections (UTIs) and vesicoureteral reflux, potentially resulting in damage and subsequent loss of renal function [3]. Furthermore, children with BBD exhibit a higher occurrence of emotional and behavioral problems, both due to the presence of urinary symptoms and the associated bowel dysfunction [4—6].

The initial treatment for BBD involves standard urotherapy [7,8], despite questions about its efficacy for enuresis due to the absence of high-quality studies [9]. Antimuscarinic have historically been used to treat children with LUTS, especially those diagnosed with overactive bladder. However, constipation, the principal side effect of this drug class, can worsen symptoms in children who already present with this condition before treatment [10,11].

In this context, Parasacral Transcutaneous Electrical Nerve Stimulation (parasacral TENS) has emerged as a treatment modality for LUTS, particularly for overactive bladder. In a randomized trial, Lordelo et al. demonstrated that 61.9 % of children with hyperactive bladder reported cure of their urinary symptoms [12]. In Another recently published randomized trial, Abreu et al. demonstrated that this modality of treatment was effective for treatment of BBD in children and adolescents, particularly for its effect on FC and enuresis [13]. In a systematic review and meta-analysis of randomized controlled trials, O'Sullivan et al. found that the chance of parasacral TENS success is 1.92 times that of children undergoing standard urotherapy alone, suggesting that parasacral TENS is beneficial in children with LUTS [14].

Although some authors consider that there is a lack of evidence on this topic, emphasizing the need for quality multicenter randomized controlled trials to prove the efficacy of parasacral TENS in children with LUTS [14,15], some studies have reinforced this modality as a promising treatment for BBD in children and adolescents [14,16—18]. Beyond its direct action on pelvic floor innervation, TENS is believed to affect micturition and constipation, through its neuromodulatory effect at the supraspinal level, where regions responsible for the control of defecation and micturition are located [19].

Few studies have investigated predictors for a poorer response to parasacral TENS treatment especially in children and adolescents with BBD. Hoffmann et al. identified that the only factor associated with a worse response to this modality of treatment in children with overactive bladder was the presence of nocturnal enuresis [20]. Santana et al., on the other hand, demonstrated that the time to reach maximum flow in uroflowmetry before treatment is associated with a worse response to parasacral TENS treatment in children and adolescents with BBD [21].

Considering that child with BBD present more severe conditions than those with only LUTS, impacting mental health and quality of life more significantly, it is reasonable to assume they may exhibit different factors influencing treatment outcomes. Thus, this study aims to identify factors associated with worse outcomes for urinary symptoms and constipation in children and adolescents with BBD undergoing parasacral TENS treatment.

Methods

This retrospective cohort study was conducted from a database collected prospectively at a center specializing in treating childhood micturition dysfunctions. The Institutional Ethics Committee approved the study under protocol number 72982317.3.0000.5544. Children and adolescents aged 4—17 years diagnosed with BBD, treated between 2010 and 2019, and undergoing parasacral TENS were included. Exclusion criteria were anatomical or neurological alterations of the genitourinary and gastrointestinal systems.

We used a structured questionnaire containing questions about the presence of LUTS using the concepts determined by the ICCS (urgency, daytime incontinence, nocturia, urinary frequency, containment maneuver and enuresis). Dysfunctional Voiding Scoring System (DVSS), modified and validated for Portuguese, was used to quantify symptom intensity. Functional Constipation was defined as the presence of at least two positive Rome IV criteria. Additionally, a structured questionnaire evaluated the potential predictive clinical factors before treatment: sex, age, presence of enuresis, nocturia, daytime incontinence, frequency, pre-treatment DVSS score, Rome IV score, and previous history of UTI.

Standard urotherapy was then directed for seven weeks before or during parasacral TENS treatment. Urotherapy consisted of the following guidelines: explaining bladder and bowel function and demystification; urination not exceeding 3 h; avoiding certain foods (coffee, tea, sodas, chocolate, and citrus fruits during treatment); urinating before sleeping; consuming a higher volume of liquids during the day (about 5/8 cups of 200 ml/day, depending on age), avoiding drinking liquids at least 2/3 h before sleeping in those with enuresis; not retaining urine when there was urgency; guidance on the adequate consumption of fiber-rich foods in those children/adolescents reporting low intake of these foods, and guidance on the proper toilet position. After standard urotherapy, patients who maintained LUTS and FC after urotherapy were included. 32 were subjected to treatment according to the recommendation of ICCS to treat constipation first, followed by daytime urinary incontinence and then enuresis, 20 participants did not take laxatives or other drugs before or concomitant parasacral TENS as part of a randomized study protocol. Electrotherapy was applied by attaching two surface electrodes in the parasacral region in 20 sessions lasting 20 min, three times/week, with a frequency of 10 Hz, pulse width of 700 μs, and intensity variable depending on patient tolerability. No medication affecting the bladder was used before or during treatment.

Patients were reassessed until 15 days after the end of electrotherapy treatment through the reapplication of

questionnaires to collect outcome variables. Additionally, the Visual Analog Scale (VAS) was completed by the children's caregivers and analyzed according to the ICCS criteria (no response, partial response and complete response) [1]. The failure of functional constipation treatment was assessed based on the Rome IV questionnaire. Poo diary, uroflowmetry or ultrasound were not performed during parasacral TENS treatment. Data analysis was conducted using the Statistical Package for the Social Sciences (IBM SPSS® Statistics), version 14.0 for Windows, Armonk, NY: IBM Corp. A significance level of 5 % was set for all tests. Categorical variables were subjected to the Chi-square test and are presented in absolute and relative frequencies. Quantitative variables were subjected to the Kolmogorov–Smirnov test to check for normality, with normal variables expressed as mean (standard deviation) and non-normal variables as median (interquartile range). The T-test was used for normally distributed quantitative variables, and for non normally distributed variables, the Mann–Whitney test was applied. Associated factors were submitted to a multiple logistic regression model to evaluate possible interferences from other variables, such as age and sex, with those remaining in the model having a p value < 0.10. Statistical significance was also verified through the measure of association (odds ratios [OR]).

Results

A total of 52 patients were studied, with an average age of 7.8 ± 2.7 years, most of whom (59.6 %) were female. The clinical and demographic characteristics of the studied population are shown in Table 1.

Regarding urinary symptoms, a complete response was achieved in 40.4 % of cases, while another 44.2 % had a partial response, and 15.4 % showed no response to treatment. There was no association between the variables studied as predictors of treatment response and a worse outcome of urinary symptoms. As for the outcome of defecatory symptoms, 67.3 % achieved complete resolution, while 32.7 % remained constipated after treatment. History of UTI have maintained in the multiple logistic regression model (p = 0.038) and was associated with FC treatment failure (p = 0.038; OR = 3.51; CI (1.04–11.84)) (Table 2). This study also evaluated the persistence of symptoms after treatment, as shown in Table 3. No relationship was found between complete resolution of urinary symptoms and constipation (p = 0.26).

Table 1 Clinical and demographic characteristics of patients with BBD treated with parasacral TENS.

	Total 52 n (%)
Sex	
Male	21 (40.4)
Female	31 (59.6)
Age mean (SD)	7.8 (2.7)
History of urinary tract infection	23 (44.2)
Daytime incontinence	35 (67.3)
Frequency	28 (53.8)
Enuresis	35 (67.3)
Nocturia	20 (38.5)
ROME IV M (IIQ)	3 (2–3.75)
Fecal incontinence	12 (25.6)

TENS = transcutaneous electrical nerve stimulation; N = number.

Discussion

This study demonstrated that children and adolescents with BBD who had a history of UTIs achieved worse outcomes in the treatment with parasacral TENS for FC (p = 0.038; OR = 3.51; CI (1.04–11.84).

Given that the most common mechanism for UTIs in children involves contamination by microbial agents from the intestinal flora [22], children with BBD are at an increased risk for developing UTIs, as highlighted in various studies [23–25]. Therefore, it is speculated that more severe functional constipation could exacerbate the pathogenesis of UTI history, with the following pathophysiological bases justifying this association [1]: The presence of large volumes of feces in the rectum compressing the posterior bladder wall could cause invagination, irritation of the trigone, and obstruction or distension of the urethra [2]. In the context of dyssynergic constipation, with minimal relaxation of the pelvic floor muscles, the contraction of perianal muscles intending to retain feces could contribute to the contraction of the external urethral sphincter, predisposing to urinary retention. Conversely, contraction of the external urethral sphincter might inhibit the defecation reflex [3]. Hyperstimulation of the autonomic system, and [4] the possibility that both issues are related to neurophysiological immaturity [26,27].

Considering the findings of this study, it is plausible that the pathogenesis of UTI can be related to a severe FC condition, explaining a poorer treatment response. This suggests that this group of children may benefit from a multimodal and more aggressive approach, combining laxatives with neuromodulation, to achieve a higher treatment success rate. Furthermore, a more aggressive treatment in children with UTI should prompt further research to be carried out.

The Rome IV score sum and the presence of fecal incontinence were investigated as predictors for worse treatment response, with no association found between them (p = 0.095; p = 0.44). Additionally, no association was observed between the Rome IV score sum and fecal incontinence with a history of UTI (p = 0.074; p = 0.272). However, it is known that a higher Rome IV and fecal incontinence are not validated in the literature as parameters for establishing the severity of functional constipation.

Hoffmann et al. showed that the presence of nocturnal enuresis was related to a worse outcome in children diagnosed with overactive bladder undergoing parasacral TENS (P = 0.004) [14]. However, this result was not observed in the current study (P = 0.30). Significant limitations of the study include the small sample size and the short-term follow-up. Studies with a larger sample size and with a follow-up of at least 2 years, according to ICCS [1], are needed.

Table 2 Univariate analysis of factors associated with constipation and LUTS parasacral TENS treatment in patients with BBD.

	Constipation			LUTS		
	Remained constipated n (%)	Complete response n (%)	P	Incomplete response n (%)	Complete response n (%)	P
History of UTI	6 (20.7)	23 (79.3)	**0.038**[a]	17 (58.6)	12 (41.4)	0.87[a]
Age						
>9 years old	9 (64.3)	5 (35.7)	0.77[a]	9 (64.3)	5 (35.7)	0.67[a]
<9 years old	26 (68.4)	12 (31.6)		22(57.9)	16(42.1)	
Daytime incontinence	13 (31.0)	29 (69.0)	0.58[a]	24 (57.1)	18 (42.9)	0.45[a]
Frequency	7 (25)	21 (75)	0.20[a]	18 (64.3)	10 (35.7)	0.45[a]
Enuresis	11 (32.4)	23 (67.6)	0.94[a]	22 (64.7)	13 (35.3)	0.30[a]
Nocturia	5 (25.0)	15 (75.0)	0.16[a]	9 (45.0)	11 (55.0)	0.89[a]
DVSS M (IIQ)	11 (7—17)	12.5 (10—7.5)	0.26[b]	11 (8—17)	13 (8.0—16.0)	0.93[b]
ROME IV M (IIQ)	3 (2—4.25)	3 (2—3)	0.09[b]	3 (2—4)	3 (2—3.5)	0.84[b]
Fecal incontinence	3 (25)	9 (75)	0.44[a]	6 (12.7)	6(12.7)	0.43[a]

TENS = transcutaneous electrical nerve stimulation; UTI = urinary tract infection; N = number.
[a] Chi-square test
[b] MannWhitney u testt

Table 3 Persistence of symptoms after parasacral TENS treatment in patients with BBD.

		Constipation complete response n (%)		Total n (%)	P value
		Yes	No		
LUTS complete response n (%)	Yes	16 (30.7)	5 (9.6)	21 (40.4)	p = 0.26[a]
	No	19 (36.6)	12 (23.1)	31 (59.6)	
Total n (%)				52 (100)	

N = number.
[a] Chi-square test.

The use of the Visual Analog Scale as a response criterion may also limit the study due to its subjective nature. Furthermore, the loss of information during the follow-up of the children, especially time to reach maximum flow in uroflowmetry, anthropometric data, and rectal diameter prevented the evaluation of these factors as potential predictors of worse treatment response.

Conclusion

We conclude that a history of UTI is a predictor of treatment failure for FC in BBD children and adolescents undergoing parasacral TENS.

Ethical considerations

This project was approved by the Ethics Comitee of the institution under CAAE 72982317.3.0000.5544.

Declaration of generative AI and AI assisted technologies in the writing process

Generative AI and AI-assisted technologies were NOT used in the preparation of this work.

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Conflict of interest

We have no conflict of interest.

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