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CLINICAL ARTICLE

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Determination of tibial somatosensory evoked potentials predicts detrusor sphincter dyssynergia in children with neurogenic bladder dysfunction

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Abstract

Introduction: Tibial somatosensory evoked potentials (SEP) are used to identify the neurological status and tethered cord (TC) in patients with spina bifida (SB). Its significance in contributing to the interpretation of urodynamics to determine bladder status is unknown. This study aimed to determine the correlation between SEP and urodynamics in children with SB.

Material and Methods: SEP and urodynamic results, for differential diagnosis of TC, were evaluated. SEP scores were correlated with urodynamic findings. SEP results were scored from 1 to 6, with 1, denoting a favorable score and 6, an unfavorable score. Age, gender, detrusor, and sphincter activities in urodynamics were noted. Results were analyzed using the χ^2 test and logistic regression analysis. Receiver operating characteristic (ROC) curve was formed to get a valid threshold for the SEP score to predict the urodynamic condition.

Results: There were 44 SB patients for whom SEP was done for differential diagnosis of TC. Fifteen patients who did not meet the inclusion criteria were excluded from the study. SB aperta was present in 17 patients and occulta in 12, respectively. The patients had a mean age of 6.6 ± 3.2 years. There were 13 boys and 16 girls. A strong correlation was found between high SEP scores and detrusor sphincter dyssynergia ($p < 0.001$). A SEP score over 3.5 was found to be 93% sensitive and 73% specific to predict this correlation. There was no relationship between detrusor activity and SEP scores ($p = 0.18$).

Discussion: Tibial SEP is an important noninvasive adjunct tool for the diagnosis of TC in patients with SB. Urodynamic studies are the gold standard in the evaluation of bladder status in neurogenic bladder dysfunction due to SB. Detrusor sphincter dyssynergia may be regarded as a sign of severe spinal cord injury in these patients.

Conclusion: Our findings suggest that in children with neurogenic bladder, high SEP scores may predict the presence of detrusor sphincter dyssynergia but not the status of detrusor function while providing pathophysiological evidence for neural injury.

KEYWORDS

cystometry, detrusor sphincter dyssynergia, spina bifida, tibial somatosensory evoked potentials, urodynamics

1 | INTRODUCTION

Spina bifida is a developmental anomaly of the spinal cord and vertebrae, characterized by posterior vertebral fusion defect. As this anomaly may involve the nerve roots or the spinal cord, neurological consequences are the main clinical concern in the follow-up of these patients.[1]

Spina bifida is also the most common cause of neurogenic bladder dysfunction in children.[2] All components of the lower urinary tract, namely detrusor, internal and external sphincters, act in coordination for proper storage and evacuation of urine.[3] When spinal cord injury happens, this coordination may be jeopardized. Urodynamic studies are still the gold standard to detect the neurourological condition for the evaluation and follow-up of these patients.[4] The primary purpose of urodynamic studies in patients with spina bifida is to define patients with high-risk bladders for upper urinary tract deterioration. They also help to define any changing neurourological status in primary or secondary tethered cord syndrome (TCS) before any permanent neurological injury.[5,6] This identification is critical because, if left untreated, neurogenic bladder may cause death with renal failure in as high as 20% of babies with spina bifida in their first year of life.[7]

Somatosensory evoked potentials (SEP) are the recordings of electrical activation in neural structures along sensory pathways to electrical stimulation of peripheral nerves. The neurological injury can be located and diagnosed with SEP.[6] Tibial SEP reflects the neural integrity of the peripheral nerve (S1), dorsal spinal column, and medial lemniscal system. This investigation is inexpensive, noninvasive, and technically easy to perform. Tibial SEP has been accepted to be a useful clinical tool in the early diagnosis and follow-up of spina bifida patients with TCS.[7–9] To the best of our knowledge, there has been no report in the literature regarding the clinical significance of combined tibial SEP and urodynamics in predicting the neurourological abnormality and follow-up in children with neurogenic bladder. Thus this present study aimed to investigate the relation between tibial SEP results and urodynamics to use those tests together to predict the location of neural injury along with the nervous system and to follow-up on any new neural damage in the future.

2 | MATERIALS AND METHODS

Medical records of spina bifida aperta and occulta patients between January 2015 and February 2016 were evaluated. Ethical approval was obtained from Institutional Review Board of Istanbul Medeniyet University for this retrospective descriptive study (IRB No: 2020/0618). We retrospectively extracted the tibial SEP of spina bifida patients recorded in our clinic. Twenty-nine patients out of 44, had recent urodynamics, and their SEP recordings were clear enough for scoring. Therefore, 15 patients were excluded from the study in total. Two of them (aged 2.5 and 2.6) had an artifact that was interfering lumber responses and preventing a clear scoring of SEP. Twelve patients did not have recent ±6 month urodynamics and one patient could not cooperate to test ($n = 5$ years of age). Recording SEP from very young kids was challenging due to the requirement of a stable relaxed position for a few minutes. Muscle contractions related to involuntary movements were observed to induce artifacts and interfere with lumbar responses. On the other hand, in our experience, the patients with low extremity motor dysfunctions had lower artifacts due to fewer movements. The urodynamic studies were done according to the standard protocol recommended by the International Children's Continence Society (ICCS).[10,11] All urodynamic studies were done with the same urodynamic device and patch electrodes for sphincter function recording. Age, gender, detrusor, and sphincteric activities during urodynamic investigations were noted. Sphincter activity was termed dyssynergic when detrusor contraction was coupled with involuntary external urethral contraction during cystometry, in accordance with ICCS terminology.[11]

2.1 | SEP recordings

All electrophysiological recordings were performed according to standard protocols for this test using a five-channel EMG-UP device (Viking® on Nicolet ®EDX; Natus Neurology Incorporated). Patients were informed about the whole procedure and asked to lie on a comfortable bed for recordings. Surface electrodes were used for all recordings. Electrodes for cortical response were placed over the vertex of the skull (Cz point) and contralateral C3 or C4 according to the 10/20 International electrode system. The 10/20 system is an internationally recognized standard method for the placement of electroencephalography electrodes. The lumbar response was recorded over midline lumbar level (L1) and peripheral nerve response was recorded over the popliteal fossa. Electrical stimulation was applied to the posterior tibial nerve through the medial malleolus. The stimulation type was set to a constant current with a duration of 200 µs. Stimulation frequency varied between 1 and 2 Hz throughout the procedure. The intensity of the stimulus was above the motor threshold of the patient. Artifact free, 200 responses were averaged and repeated at least two times to show a reproducible response. Evaluations were done according to the age of the children and compared according to published pediatric norms by a neurophysiologist.[12] While the lumbar response (N22) was evaluated as present or absent, the cortical response (P37) was evaluated as normal, delayed, or absent (Table 1). We did not use amplitudes for scoring due to their high variability.

SEP scoring system was simplified from Yamada Shokei 2010.[13] SEP results were scored from 1 to 6 in terms of lumbar and cortical responses as 1, denoting a favorable score, and 6 as an unfavorable score, semi-quantitatively (Figure 1, Table 1). The scores of the recordings were determined according to the presence or absence of lumbar responses and normal, delay, or absence of cortical responses.

TABLE 1 Somatosensory evoked potentials rating scale.

	Tibial SEP—Severity Rating Scale	
Score	**N22 (lumbar response)**	**P37 (cortical response)**
1	Present	Normal
2	Present	Delayed
3	Absent	Normal
4	Absent	Delayed
5	Present	Absent
6	Absent	Absent

Abbreviation: SEP, somatosensory evoked potentials.

Source: Simplified from Yamada et al.[13]

2.2 | Statistical analysis

The statistical analyses were done with the computer program SPSS 22.0 (Statistical Package for Social Sciences, SPSS Inc.). Numeric values were given as mean ± standard deviation (SD). The numerical and categorical data were compared using the Pearson χ^2 test and univariate regression analysis. Receiver operating characteristic (ROC) curve was formed to give a significant threshold SEP score to predict the neurourological abnormality. A p value below 0.05 was considered to be statistically significant.

3 | RESULTS

During the study period, the SEP study was done on a total of 44 SB patients for the differential diagnosis of TCS. Fifteen patients were excluded who did not meet the inclusion criteria. There were 10 boys and 5 girls at a mean age of 7.42 years. The diagnosis was spina bifida aperta in 10 patients and spina bifida occulta, in 5 patients, in the excluded cohort. 29 patients were included in the study fulfilling the inclusion criteria. Spina bifida aperta was defined in 17 patients with myelomeningocele and occulta in 12 patients (six patients with lipomyelomeningocele, three isolated tethered cord, and two with fatty filum terminale), respectively. The patients had an age range between 2.4 and 11.6 years (mean age 6.6 ± 3.2 years). There were 13 boys and 16 girls. Among 17 patients who were operated for spina bifida aperta in the newborn period, seven of them were reoperated for TCS. All of them were already on follow-up for TCS after their first-year vertebral magnetic resonance imaging consistent with this diagnosis. In all patients with myelomeningocele there were alterations in urodynamic findings in comparison with their previous studies. In patients with spina bifida occulta, all the patients had the symptoms of early fatigue and leg pain and, therefore, they were examined for TCS. SEP was done only for patients considered for detethering surgery. According to patient data, there were more unfavorable high SEP scores when detrusor sphincter dyssynergia (DSD) was observed in the urodynamic study (Table 2). Seven patients with normal urodynamic findings and two patients who had only detrusor overactivity were observed to have normal SEP recordings. The distribution of patients according to their sphincter activity and SEP results was significant

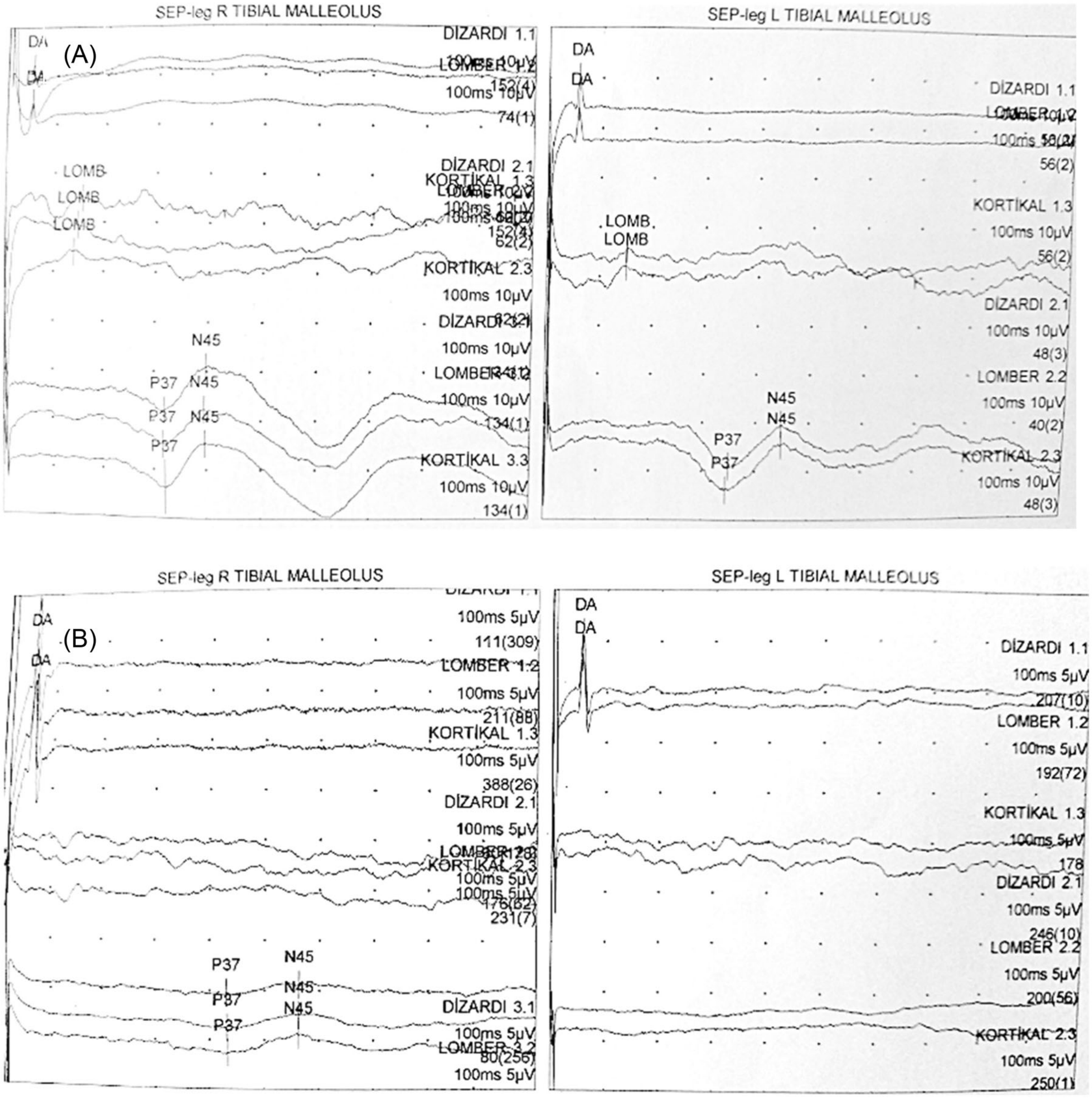

FIGURE 1 (A) Normal responses (upper-line popliteal, mid-line lumbar, lower-line cortical responses) elicited from the right and left tibial nerve. (B) Pathological responses; lumbar and cortical responses are absent in the left tibial nerve, an unclear lumbar response, and a very low amplitude cortical response in the right tibial nerve.

(Pearson χ^2 test, $p < 0.001$). A strong correlation was found in univariate logistic regression analysis between high SEP score and DSD ($p = 0.004$) (odds ratio = 2.1, 95% confidence interval for Exp(B) between 1.27 and 3.49). A SEP score over 3.5 was found to be 93% sensitive and 73% specific to predict this correlation (area under the curve [AUC] = 0.824, $p = 0.003$). There was no correlation between detrusor activity during urodynamic study and SEP scores (Table 2) ($p = 0.18$). Ten of the patients had decreased lower extremity motor function and nine of these patients had DSD. SEP score was six (very severe) in nine patients and four in one patient with decreased lower limb function. Twelve of the patients were on clean intermittent catheterization at baseline. Eight patients were under anticholinergic medication. In three patients, detrusor was overactive, in four patients, detrusor was underactive, and in only one it was normal.

4 | DISCUSSION

Urodynamic studies continue to be the gold standard for assessing neurogenic lower urinary tract dysfunction in children.[4,14] In general, detrusor overactivity, decreased bladder compliance, increased leak point pressure, and DSD are regarded as major risk factors for upper urinary tract deterioration in the neurogenic bladder.[7,15]

TABLE 2 Number of patients with urodynamic results and SEP scores.

Urodynamic findings (*n*:29)	SEP Scores (*n*:29) Score 1 (*n*:9)	Score 3 (*n*:3)	Score 4 (*n*:3)	Score 6 (*n*:14)
Normal (*n*:12)	7	1[a]		4[a]
Underactive detrusor + DSD (*n*:8)			2	6
Overactive detrusor + DSD (*n*:5)		1		4
Overactive detrusor only (*n*:3)	2[a]	1		
DSD only (*n*:1)			1	

Note: There were no patients in Scores 2 and 5.

Abbreviations: DSD, detrusor sphincter dyssynergia; SEP, somatosensory evoked potentials.

[a]In 5 of 12 patients with normal urodynamics, SEP responses were not normal. In 2 of 9 patients with normal SEP response, urodynamics were impaired.

Electrophysiological recordings, in addition to urodynamic studies, are of interest in spina bifida patients and contribute significantly to the evaluation of pediatric spinal cord injury.[9,16] SEP are the most focused and studied technique in the literature. SEP is the recording of time-locked responses to external electrical stimulation of peripheral nerves, which can be recorded at various neural levels such as the spinal cord or cortex.[17] Duckworth et al. showed that SEP findings were well correlated with clinical findings in patients with spina bifida in their study. SEP was shown to be an indicator of the integrity of neural pathways between the point of electrical stimuli (S1 dermatome) and cerebral cortex (somatosensory cortex), and the absence of electrical signal transmission was considered a neural injury. Thus, they concluded that SEP provides the objectivity required in the pinprick test to assess the neurological status of spina bifida.[18] However, there is no information in the literature regarding the correlation of SEP with urodynamic findings in patients with neurogenic bladder due to spina bifida. This correlation was addressed in a patient group with diabetic cystopathy. Diabetic patients with abnormal tibial SEP also had more abnormal findings in their urodynamic studies, albeit the type of urodynamic abnormality was not mentioned in this study.[19] Tibial SEP was found to be more significant in the recovery of bladder and urethral sphincter function in patients with acute tetraplegic spinal cord injury.[20] SEP was interpreted to provide valuable information about the neurophysiological status of the patient, level of conus medullaris, degree of spinal cord displacement, and level of neurological injury.[17,21] The somatosensory pathway detected by tibial SEP originates mainly from the S1 peripheral nerve, projects to the spinal cord posterior column and medial lemniscal system, and terminates in the somatosensory cortex. The neural structures related to bladder functions that are evaluated by urodynamics include

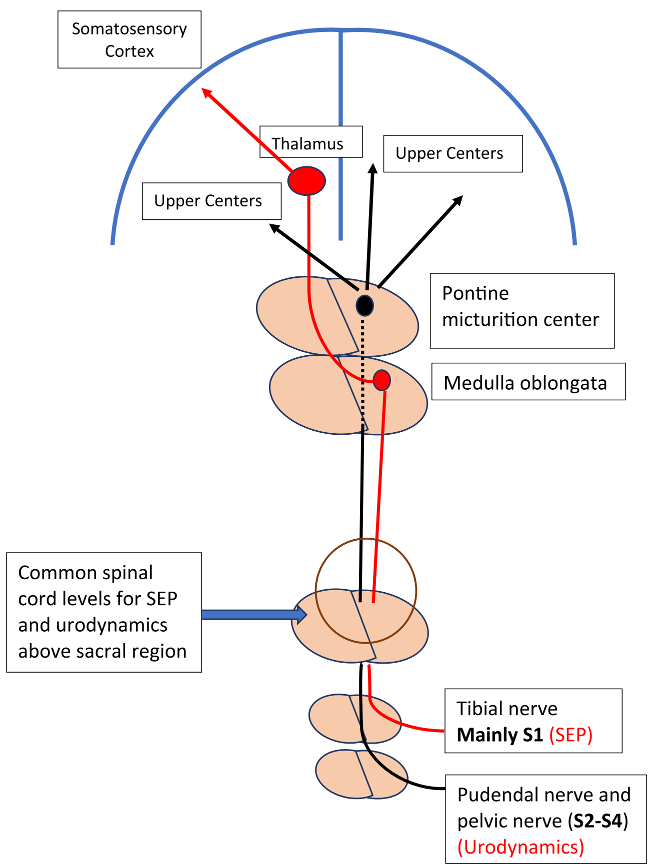

FIGURE 2 Comparative diagram for the neural pathways and common spinal cord levels for tibial SEP and urodynamics. SEP, somatosensory evoked potentials.

S2–S4 peripheral nerves, the spinal cord between the sacral level and pons, and suprapontine centers. There is an overlap of tibial SEP and urodynamics neural pathways at suprasacral infrapontine spinal cord level (Figure 2). Even if tibial SEP is normal, a urodynamic study can reveal information about lower sacral roots (below S1) and cauda equina. Tibial SEP can detect any dysfunction of upper sensory centers without any abnormality in urodynamics, as well.

During micturition, neural signals from the pontine micturition center induce synergistic detrusor contraction and sphincteric relaxation. The impairment in descending and ascending pathways in the spinal cord which are crucial for coordination between sacral Onuf's nucleus and the central pontine micturition center, is associated to the development of DSD.[22–24] An injury to the spinal cord disrupts neural communications between the sacral and pontine centers, which could indicate a lack of or delayed neural signal transmission in the tibial SEP response. Thus, a bilateral absence of lumbar SEP responses may be a strong indicator of DSD in urodynamics. This explanation was supported by the findings of the current study. When there was DSD in urodynamics, we detected higher absence or delay in SEP responses. Furthermore, none of the patients with DSD had normal tibial SEP responses, while patients with normal SEP scores had no DSD. To predict this correlation, a SEP score of over 3.5 was found to be 93% sensitive and 73% specific.

Higher neural centers such as prefrontal cortex and periaqueductal gray matter, have aprimarily inhibitory effect on the detrusor. Thus, a spinal cord lesion may result in detrusor overactivity by disrupting this inhibitory effect,[25] but this was not the observation in our study. An overactive bladder was found in two of nine patients with normal SEP responses, indicating a possible impairment that did not affect the somatosensory pathway. It was found that alterations in the urothelial, interstitial cell, and smooth muscle cell functions, may also induce neurogenic detrusor overactivity, which is impossible to be detected with SEP.[26] Those pathophysiological mechanisms may have role in the development of detrusor overactivity in those two patients which could be the explanation of this finding.

In this study, tibial SEP responses were abnormal in 5 of 12 patients with normal urodynamics. Urodynamics was impaired in two of nine patients with normal SEP responses, but no DSD was present. This dissociation between SEP and urodynamics supports the use of tibial SEP and urodynamics in combination in the follow-up of those patients. Otherwise, relying on a single method may result in the omission of new neurological dysfunctions. If a patient's urodynamics are severely impaired, relying solely on urodynamics for follow-up will be ineffective. Tibial SEP can be a useful tool in these patients to catch any changes in the integrity of neural structures and vice versa. Due to tethering and complications (such as hydrocephalus), SB can cause neural damage at various levels of the nervous system including peripheral nerves, spinal cord, and suprapontine levels. Therefore, a single method is insufficient to monitor and follow changes at all of these levels. Urodynamics has several parameters and our results suggest that the DSD parameter correlates with SEP scores. DSD is considered a sign of spinal cord impairment based on the neurophysiology of bladder functions. Detrusor hypoactivity and hyperactivity are associated to upper- and lower-level dysfunctions at the distinct neural structures of SEP and urodynamics pathways. As a result, our findings revealed that there was no correlation between detrusor activity and SEP, as we had predicted. Furthermore, there was no association between detrusor overactivity and SEP scores in our study. In TCS patients, DSD and detrusor overactivity are common urodynamic abnormalities. However, a recent investigation in patients with secondary TCS assessed the urodynamic measures longitudinally, and the findings were consistent with ours.[27] When urodynamics were compared between "before first" and "before second" retethering, DSD change was greater than detrusor overactivity occurrence. It was suggested that DSD occurrence was increasing with progression and its disappearance was associated with improvement. Authors came to the conclusion that DSD was an indication of secondary TCS as a result. Moreover, the etiology of detrusor veractivity is still unclear, and changes in urothelial, suburothelial, and smooth muscle cells may be involved.[2,28] Based on those studies, we suggested that detrusor overactivity might not be as reliable as DSD for follow ups of TCS especially when they have a previous neuronal pathology.

To summarize, finding any abnormality in the tibial SEP of an SB patient does not necessarily imply that the urodynamics is abnormal as well; urodynamics may be perfectly normal. However, if DSD is found in a patient's urodynamics, it indicates an abnormality in SEP, showing impairment in spinal cord integrity. This conclusion is supported by the correlation between SEP and DSD. All the relationships could theoretically be explained by neurophysiology, but our findings highlight the importance of combining tibial SEP and urodynamics in SB patients with suspected TCS.

The limitations of this present study were its retrospective design, relatively small patient population and a high number of excluded patients. The etiology of neurogenic bladder dysfunction was not uniform, as it was secondary to both spina bifida aperta and occulta. Despite all of the efforts to standardize urodynamic studies, there may be differences in interpretation between evaluators. Detrusor overactivity was detected with urodynamic studies, but we were unable to identify its other possible biochemical and physiological mechanisms. We also lack detailed investigations such as magnetic resonance tractography and functional magnetic resonance studies of the nervous system, which could provide the mapping of the neural injury. Future studies that clarify these details will help in the understanding of the neuropathophysiological course of spina bifida in children.

5 | CONCLUSION

There is a lack of data in the literature about the correlation of SEP findings with neurourological abnormality in children with neurogenic bladder. The exact correlation between the tibial SEP findings and the urodynamic results in these patients may be a strong indicator of spinal cord impairment. In ideal conditions, SEP studies should be combined with urodynamic studies to cover all neural levels in the diagnosis of TCS, from sacral nerves to the central nervous system. This is especially helpful in the follow-up of tethered cord when one of the test results—SEP or urodynamics—is completely deteriorated. If urodynamics is abnormal, we suggest adding SEP for follow-up of spinal integrity to increase sensitivity because DSD correlates with SEP, which indicates suprasacral infrapontine impairment. DSD may be considered a sign of spinal cord impairment, and the current study supports this interpretation by showing the relation between DSD and SEP in patients with spina bifida. To make stronger recommendations, larger cohort studies are required.

AUTHOR CONTRIBUTIONS

Concept and design of the manuscript: Ezgi Tuna Erdogan, Kerem Ozel, and Zeliha Matur. *Acquisition, analysis and/or interpretation of data*: Kerem Ozel, Orkhan Alizada, Huseyin Canaz, and Ibrahim Alatas. *Drafting or critically revising the manuscript for important intellectual content*: Ezgi Tuna Erdogan, Zeliha Matur, and Orkhan Alizada. *Final approval of the version to be published*: Kerem Ozel, Orkhan Alizada, and Ibrahim Alatas. *Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved*: Ezgi Tuna Erdogan, Kerem Ozel, Zeliha Matur, Orkhan Alizada, Huseyin Canaz, and Ibrahim Alatas.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

All data generated or analyzed during this study are included in this article. Further enquiries can be directed to the corresponding author.

ETHICS STATEMENT

The study was approved by the Institutional Review Boards of Istanbul Medeniyet University. The approval number (IRB) is: 2020/0618. Written informed consent was obtained from the parent or official guardian of each patient. The privacy rights of human subjects were always observed. Current retrospective descriptive study does not require a clinical trial registration.

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