HAYDARPAŞA NUMUNE MEDICAL JOURNAL

DOI: 10.14744/hnhj.2020.54771
Haydarpasa Numune Med J 2022;62(1):24–30

hnhtipdergisi.com

ORIGINAL ARTICLE

Electrophysiologic Evaluation of the Autonomic Nervous System Functions in Children with Nocturnal Enuresis

Elem Yorulmaz[1], Gülümser Aydın[2], Tutku Soyer[3]

[1]Department of Physical Medicine and Rehabilitation, University of Health Sciences, Hamidiye Faculty of Medicine, Haydarpaşa Numune Health Application and Research Center, Istanbul, Turkey
[2]Department of Physical Medicine and Rehabilitation, Ankara Yıldırım Beyazıt University, Ankara, Turkey
[3]Department of Pediatric Surgery, Hacettepe University, Ankara, Turkey

Abstract

Introduction: The autonomic nervous system (ANS) is likely to play a role in some of the etiologic factors of nocturnal enuresis (NE), such as nocturnal polyuria, disorder of arousal, or detrusor hyperactivity. The aim of this study was to evaluate ANS functions in children with NE.

Methods: Twenty-two children with NE and 20 healthy children were allocated for this study. In electrophysiologic evaluation, palmar and plantar sympathetic skin responses (SSR) and RR interval variation (RRIV) were carried out in both groups. The minimum and mean latencies of SSRs, maximum and mean amplitudes of SSRs, RRIV at rest and during deep breathing, the difference between resting and deep breathing RRIVs, ratio of deep breathing to resting RRIV, and maximum to minimum RR interval at rest and during deep breathing were calculated. For group comparisons; Mann–Whitney U test was used for abnormally distributed data, independent t-test was used for normally distributed data for continuous variables.

Results: The mean ages were 10.75±3.49 and 10.91±3.10 years for patients and controls, respectively. There was no significant difference between the groups in terms of age and sex ($p>0.05$). Palmar and plantar SSRs could be obtained in all subjects in NE and control groups. There was no significant difference between the groups in SSR or RRIV parameters ($p>0.05$).

Discussion and Conclusion: This result suggests that ANS system functions may be normal in enuretic group when not classified for the etiologies. However, the effect of the ANS may be more evident for one of the above-mentioned etiologic factors. Therefore, assessing ANS functions in patients classified according to the etiologies may be more useful to demonstrate the link between ANS dysfunction and NE.

Keywords: Autonomic nervous system; nocturnal enuresis; RR interval variation; sympathetic skin response.

International Continence Society defines enuresis as the complaint of intermittent incontinence that occurs during periods of sleep. If it occurs during the main sleep period, then it could be qualified by the adjective "nocturnal."[1] Sleep disorders, antidiuretic hormone deficiency, nocturnal detrusor hyperactivity, genetic predisposition, and psychological factors are some of the factors that are implicated in the pathogenesis of nocturnal enuresis (NE) [2]. The studies investigating the autonomic nervous system (ANS), which is known to be a regulator in most of these etiologic factors, are limited in the literature [3-10]. These studies have been planned considering that ANS dys-

Correspondence (İletişim): Elem Yorulmaz, M.D. Saglik Bilimleri Universitesi, Hamidiye Tip Fakultesi, Fiziksel Tip ve Rehabilitasyon Anabilim Dali, Haydarpasa Numune Saglik Uygulama ve Arastirma Merkezi, Istanbul, Turkey
Phone (Telefon): +90 536 470 22 46 **E-mail (E-posta):** eleminal@gmail.com
Submitted Date (Başvuru Tarihi): 15.12.2019 **Accepted Date (Kabul Tarihi):** 12.01.2020

function may be responsible for detrusor hyperactivity but results are contradictory. In this study, it is aimed to evaluate autonomic functions in NE with two tests that can be applied quickly and easily in a standard electroneuromyography laboratory.

Materials and Methods

This study was carried out with the approval of the Local Ethics Committee. Twenty-one children with NE according to the International Continence Society with a mean age o f 10.75±3.49 years and 20 children who were admitted to the hospital with any complaints other than urological complaints with a mean age of 10.91±3.10 years were included in the study. Since the main objective of the study is to evaluate ANS, in terms of identifying the parameters that may affect the ANS routine biochemistry tests, urine analysis, urine culture, urinary ultrasonography, and electrocardiogram tests were applied.

Inclusion criteria for the NE group; (1) meeting the terminology of NE defined by International Continence Society, (2) age of 5–15 years range, (3) no history of dry period for 6 months or more, and (4) History, physical examination, and laboratory investigations revealed no other pathology that could explain the symptoms of enuresis nocturna.

Inclusion criteria for the control group; (1) being in similar age groups with patient group and (2) no symptom or history of NE.

Exclusion criteria: (1) Obesity (over 120% of normal values according to age), (2) systemic diseases (diabetes mellitus, hypo-, or hyper-thyroidism) and drug use which may be the cause of peripheral neuropathy or autonomic dysfunction (β-blockers, anticholinergics, phenytoin, and isoniazid), and (3) heart diseases.

Demographic data (age, gender, height, and weight) were recorded for all cases. The parents of all 42 children included in the patient and control groups were informed about the study by the physician and written approvals were obtained. A detailed history and routine nerve conduction studies were evaluated to rule out the presence of peripheral neuropathy, sympathetic skin responses (SSR), and RR interval variation (RRIV) tests were performed to evaluate autonomic functions. Four patients in control group were evaluated with history and physical examinations in terms of peripheral neuropathy because their family did not approve routine nerve conduction studies.

All electrophysiological studies were performed with Medelec Synergy electroneuromyography device (Oxford Medical Instruments, Old Working, United Kingdom). The room temperature was 23–26°C during the process. To investigate the presence of peripheral neuropathy, sural nerve sensorial conduction studies in both lower extremities, tibial and peroneal nerve motor conduction studies in one lower extremity, and median/ulnar nerve sensorial and motor conduction studies in one upper extremity were performed in all cases. The autonomic functions of the patients were evaluated by SSR and RRIV tests. Both tests were performed while lying in the supine position in the semi-dark room. During the recording, the superficial skin temperature in the recording area was kept between 32°C and 36°C.

SSR recordings were performed with superficial disc electrodes. The active electrode was placed into the palm and reference electrode was placed on the dorsum of the hand for the upper extremities: For lower extremities, active electrode was placed on the medial portion of the sole; reference electrode was placed on the dorsum of the foot. The grounding electrode was placed at the wrist and ankle level. The recording system was set to 0.1–1000 Hz for frequency range, 0.5–2 mV/division for the sensitivity, and 1–5 s/division for the sweeping speed. Stimulation applied to the non-dominant wrist on the median nerve and to the same side ankle on the posterior tibial nerve. Stimulation was performed with bipolar superficial electrodes, irregular, and 1-min intervals to avoid habitat with duration of 0.1 s and with an intensity of 10–30 mA. At least eight successful SSRs from both extremities were recorded simultaneously with each stimulus. Amplitudes and latencies of SSRs were evaluated in this study. The amplitude was measured from the negative peak to the positive peak. In each series, the average and highest amplitude values were recorded. The latency was calculated as the time from stimulus artifact onset to the beginning of the response. The mean and shortest latency values of SSR latencies in each series were determined [11].

RRIV recordings were recorded by superficial disc electrodes from the back of both hands after resting in the supine position for 10 min. Electromyography apparatus was used with filter settings at 20–100 Hz, a sensitivity of 0.5 mV/division, and a sweeping speed of 2 s/division. The positive peak of the QRS complex was adjusted to the left side of the oscilloscope, using the delay-line technique for recording during resting and deep breathing at 6/min frequency. Thus, two consecutive QRS complexes were made to fit the screen. At least 20 QRS complexes were triggered and following 20 were evaluated for RRIV. The formula a/b X 100 was used for the RRIV assessment. In this formula, "a" corresponds to the difference between the shortest and

longest R-R interval in a series of 20 and "b" corresponds to the time interval between the mean beginning of the fixed QRS and the mean value of the jittering QRS complex. RRIV at rest and deep breathing, the differences and the ratio of these two values were evaluated as well as the ratio of maximum RR distance to the minimum RR distance at rest and deep breathing [12].

Statistical Methods

SPSS 16.0 statistical package program was used for statistical analysis. The distributional assumption in groups was assessed by the Kolmogorov–Smirnov test. For group comparisons, Mann–Whitney U test was used for abnormally distributed data, independent t-test was used for normally distributed data for continuous variables. Descriptive data were expressed with mean±standard deviation (mean±SD) or median (minimum-maximum) where appropriate. $p<0.05$ was accepted as the limit of significance in all statistical analyses.

Results

The mean age was 10.75±3.49 years in NE group including 22 patients (12 boys and ten girls) and 10.91±3.10 years in control group with 20 children (14 boys and eight girls). There was no significant difference between the groups in terms of age and sex ($p>0.05$).

Palmar and plantar SSRs could be obtained in all subjects in NE and control groups (Figs. 1 and 2). There was no statistically significant difference between two groups in terms of palmar and plantar minimum and average SSR latencies or maximum and mean SSR amplitudes of all extremities ($p>0.05$). Palmar and plantar SSR latency and amplitude values and statistical comparisons are shown in Table 1.

RRIV traces were recorded at rest and with deep respiration in all individuals in enuresis and control groups (Figs. 3 and 4). RRIV mean values were 29.7±16.3% at rest and

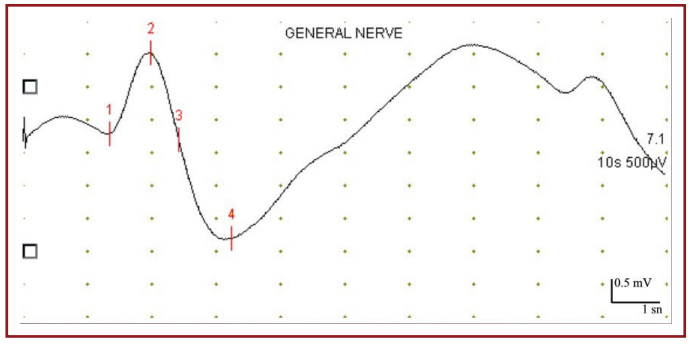

Figure 1. Right palmar sympathetic skin response trace sample in a patient with nocturnal enuresis.

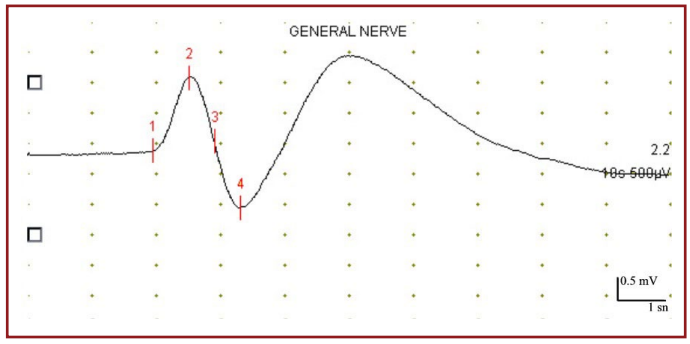

Figure 2. Right plantar sympathetic skin response trace sample in a patient with nocturnal enuresis.

49.6±23.1% with deep respiration in the control group; 31.9±17.3% at rest and 55.4±35.7% for deep breathing in the enuresis group. RRIV values obtained with deep respiration were significantly increased compared to RRIV values obtained at rest in both groups ($p<0.01$). There was no statistically significant difference in RRIV values obtained at rest and deep respiration, differences, and rates of RRIV values obtained at rest and with deep respiration, and the ratio of maximum RR distance and minimum RR interval obtained at rest and with deep respiration between two groups ($p>0.05$). RRIV data and statistical comparisons of both groups are given in Table 2.

Discussion

NE is a clinical and genetically heterogeneous disease observed in 5–10% of the 7-year-old population. It is assumed that its pathogenesis is multifactorial. The enuretic child wets his/her bed because either bladder (over-) filling fails to wake him/her up or uninhibited detrusor contractions fail to wake him/her up or both. According to this way of looking, enuresis is a result of nocturnal polyuria, nocturnal detrusor hyperactivity, and high arousal threshold [2,13].

Nocturnal excess urine production due to lack of nocturnal vasopressin has been shown in some of the children with enuresis. However, polyuria is not observed in all enuretics, and enuresis is not seen in all children with polyuria. Furthermore, the presence of polyuria cannot explain why children do not wake up [13]. Many enuretic children wet their bed either their bladder is full or they suffer from nocturnal detrusor hyperactivity. Although some of the studies with urodynamic and cystometric measurements have shown normal diurnal bladder function in children with enuresis,[14,15] many studies showed that uninhibited detrusor contractions develop during sleep [16-18]. Besides, the coexistence of NE with urgency or urge incontinence and smaller urine volumes of children with non-polyuric NE

Table 1. Latency and amplitude values of palmar and plantar sympathetic skin responses

	Control group n=20	NE Group n=22	p
Palmar SSR minimum latency-R (s)ǂ	1.15±0.95	1.20±0.12	0.112*
Palmar SSR minimum latency-L (s)ǂ	1.16±0.85	1.22±0.13	0.147*
Palmar SSR average latency-R (s)ǂ	1.32±0.11	1.36±0.11	0.232*
Palmar SSR average latency-L (s)ǂ	1.31±0.89	1.34±0.12	0.450*
Palmar SSR maximum amplitude-R (mV)ǂ	6.42±4.05	5.44±3.42	0.186*
Palmar SSR maximum amplitude-L (mV)±	4.95 (2.30–20.2)	4.70 (1.10–14.5)	0.900**
Palmar SSR average amplitude-R (mV)ǂ	3.50±1.70	3.43±2.29	0.320*
Palmar SSR average amplitude-L (mV)±	3.21 (0.80–10.1)	3.36 (0.86–11.6)	0.743**
Plantar SSR minimum latency-R (s)±	1.93 (1.40–2.10)	1.83 (1.42–2.48)	0.950**
Plantar SSR minimum latency-L (s)±	1.92 (1.42–2.04)	1.80 (1.42–2.80)	0.588**
Plantar SSR average latency-R (s)ǂ	2.06±0.13	2.07±0.35	0.762*
Plantar SSR average latency-L (s)±	2.07 (1.71–2.19)	2.07 (1.49–3.03)	1.000**
Plantar SSR maximum amplitude-R (mV)±	3.90 (1.50–22.5)	3.14 (0.80–11.5)	0.488**
Plantar SSR maximum amplitude-L (mV)±	3.40 (2.10–18.8)	2.90 (1.20–10.2)	0.217**
Plantar SSR average amplitude-R (mV)±	2.24 (0.91–12.9)	2.20 (0.45–6.81)	0.623**
Plantar SSR average amplitude-L (mV)±	2.39 (1.08–13.4)	1.94 (0.70–7.65)	0.217**

SD: Standart Deviation; Min-Max: Minimum-Maximum; R: Right; L: Left; NE: Noctunal Enuresis; *Independent t-test; **Mann Whitney U test; ±Median (Min-Max); ǂMean±SD;SSR: Sympathetic skin responses.

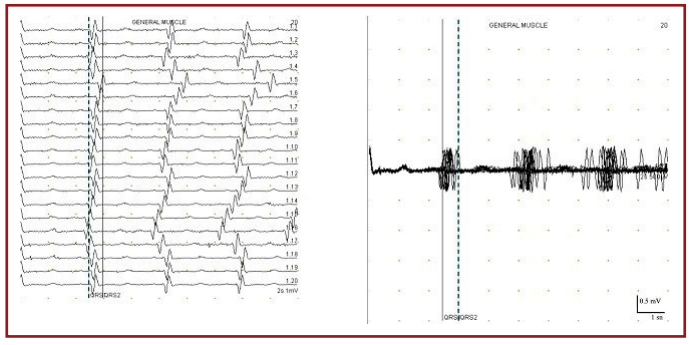

Figure 3. Resting RR interval variability trace samples in a patient with nocturnal enuresis.

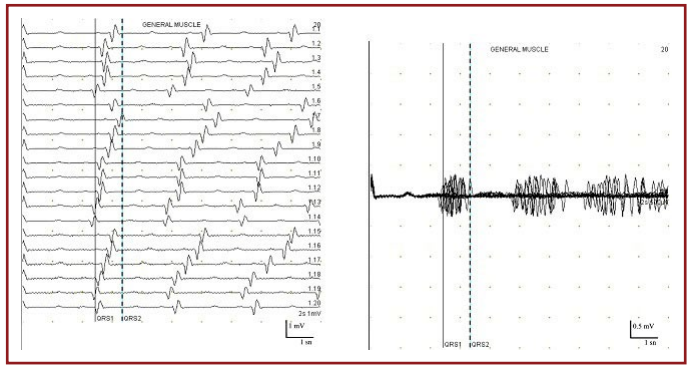

Figure 4. Deep breathing RR interval variability trace samples in a patient with nocturnal enuresis.

may be shown as indirect evidence for this hypothesis [13]. Bladder distention and detrusor contractions are strong arousal stimuli. Therefore, it was thought that enuretic children were deep sleepers but it was shown that there was no predominance of bed-wetting during non-rapid eye movement sleep and the children with enuresis spent a higher percentage of total sleep time in light sleep and had higher cortical arousal indices [19-22].

These data suggest that a common regulator responsible for the continuation of the physiological balance of urine production – bladder contraction and probable arousal with bladder distension or detrusor contraction, which is normally necessary to remain dry at night, may be impaired in NE. The fact ANS plays a role in the continuity of these three physiological equilibria[23-26] suggest that a disorder in ANS may result in NE. Therefore, in children with NE, it is possible to have an idea about the etiology and the treatment can be predicted. There are few studies in the literature evaluating autonomic functions in NE. Cardiac and ocular tests were usually used to assess autonomic functions in these studies and the results are contradictory [3-10].

Yakıncı et al.,[4] examined the autonomic functions of children with NE using clinical and electrocardiographic tests during the day. The parasympathetic nervous system hyperactivity was shown and the sympathetic nervous system functions were normal in children with NE in their study group.Two studies using 24-h holter electrocardiogram have contradictory results. One of them suggested a sympathovagal imbalance in the predominance of sym-

Table 2. Control and NE group RR interval variability data

	Control group n=20	NE group n=22	p
Resting RRIV (%)ǂ	29.7±16.3	31.9±17.3	0.669*
Deep ınspiration RRIV (%)±	42.7 (16.2–111.0)	41.7 (18.8–144.4)	0.840**
Resting RR Max RR/Min RR±	1.31 (1.16v2.35)	1.33 (1.10–2.05)	0.669**
Deep Inspiration RR Max RR/Min RR±	1.54 (1.18–3.50)	1.53 (1.21–6.19)	0.840**
Δ Deep Inspiration RRIV - Resting RRIV (%)±	19.3 (0.94–80.4)	21.5 (0.04–85.3)	0.940**
Deep breathing RRIV/Resting RRIV±	1.69 (0.34–4.73)	1.82 (0.48–4.09)	0.920**

SD: Standard Deviation; Min-Max: Minimum-Maximum; RRIV: RR Interval Variation; NE: Nocturnal enuresis. *İndependent t-test; **Mann Whitney U test; ±Median (Min-Max); ΔMean±SD.

pathetic activity in NE;[3] and in the other study, increased parasympathetic activity was shown [6]. In another study using the same method, it was shown that parasympathetic activity during sleep was higher in the enuresis and control group than during the daytime and it was more significant in the enuresis group. During the daytime, sympathetic activity in control group and parasympathetic activity in enuresis group were more dominant. These data suggested that children with enuresis have parasympathetic system hyperactivity during sleep and daytime and that the cyclical rhythm of ANS functions is impaired in children with NE. After treatment, improvement of the impairment in the cyclic rhythm of ANS functions in children with NE was also shown in this study [5]. In one of the two studies evaluating ocular autonomic functions, pupil diameter measurements were performed and pupil diameter was found to be wider in children with NE and this result was interpreted in favor of ANS dysregulation as parasympathetic hypoactivity [7]. In the other study in which the pupil cycle time was evaluated, it was suggested that pupil cycle time which was found to be prolonged in children with NE showed parasympathetic system hypoactivity and as a result, parasympathetic system dysfunction in this patient group [8]. In a study aimed to assess risk factors for excessive autonomic activation during sleep and its association with sleep problems, impaired behavior, and poor academic performance in primary school children; ANS functions were assessed with nocturnal home pulse oximetry and they suggested that children with excessive autonomic activation had a higher prevalence of enuresis [9]. In most recent study, children with NE were evaluated using continuous ambulatory blood pressure monitoring during sleep to assess heart rate and blood pressure. The decreased change in heart rate during sleep was shown and it was termed as autonomic disruption [10]. In the present study, autonomic functions in children with NE were evaluated in two standardized tests with high sensitivity (SSR and RRIV) in a standard electroneuromyography laboratory, and no significant difference was found between the enuresis and control groups. Contrary to expectations, these results suggest that there is no impairment of autonomic functions in children with NE. This conclusion is in contradiction with the results of the studies mentioned above. This may be due to differences in methods between studies and may also be due to limitations in studies.

In general, the reliability of the results obtained in the studies is highly correlated with the sensitivity and specificity of the selected tests. Among many tests used to assess ANS, SSR and RRIV are commonly used neurophysiological ones due to their easy application and reliable results [27,28]. In a study of patients with peripheral neuropathy, it was suggested that at least one of these two tests was found pathologic in all patients with clinical disautonomia. These results indicate that if both tests are used together, their diagnostic values are quite high and preferable for the diagnosis of autonomic dysfunction [29]. It is also reported in the literature that at least two autonomic tests should show abnormalities to confirm the presence of autonomic dysfunction [30]. However, in studies suggesting autonomic dysfunction in children with NE was only cardiac or ocular ANS tests were used [3-10].

Some limitations of this study may have an effect on the results. The most important one is the low number of cases in the groups. Furthermore, the tests used during the daytime were applied in this study and these application times of the tests were not standardized. Therefore, an autonomic dysfunction which is more prominent during sleep may not be detected. As a matter of fact, in some of the previous studies, all-day tests were used, [3,5,6] but there are studies assessing ANS momentarily in the daytime and also showed autonomic dysfunction [7,8].

Although various factors (Arginine-vasopressin deficiency, detrusor hyperactivity, and sleep disorders) may be re-

sponsible for the etiopathogenesis of enuresis, autonomic functions were not evaluated in any study in which patients were categorized by etiology or etiologic evaluation was not carried out in studies assessing autonomic functions [3-10]. The regulatory function of ANS may be more decisive in any of these physiological factors than in others.

The results of this study indicate that autonomic functions can be detected as normal in NE groups that are etiologically heterogeneous, suggesting that autonomic dysfunction alone may not be responsible for all the different etiopathogenesis of NE. There is a need for further studies in which cases are classified according to the etiology by objective tests and the effect of the treatment on ANS functions is evaluated. Thus, besides evaluating the relationship between enuresis and ANS function, assessing which etiologic factors are related to probable autonomic dysfunction may be ensured. With the results of these studies, ANS tests may be useful in the treatment approach and follow-up.

Acknowledgement: I would like to thank Cüneyt Ensari, M.D. and Timuçin Şipal, M.D. for patient referring.

Ethics Committee Approval: The study was approved by the Clinical Research Ethics Committee of Kırıkkale University according to the principles of the Declaration of Helsinki. (2008/024).

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: E.Y., G.A., T.S.; Design: E.Y., G.Y., T,S.; Data Collection or Processing: E.Y., G.A.; Analysis or Interpretation: E.Y., G.A., T.S.; Literature Search: E.Y.; Writing: E.Y., G.A., T.S.

Conflict of Interest: None declared.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Hashim H, Blanker MH, Drake MJ, Djurhuus JC, Meijlink J, Morris V, et al. International continence society (ICS) report on the terminology for nocturia and nocturnal lower urinary tract function. Neurourol Urodyn 2019;38:499–508.[CrossRef]
2. Nevéus T. Pathogenesis of enuresis: Towards a new understanding. Int J Urol 2017;24:174–82. [CrossRef]
3. Dundaröz MR, Denli M, Uzun M, Aydin HI, Sarici SU, Yokuşoğlu M, et al. Analysis of heart rate variability in children with primary nocturnal enuresis. Int Urol Nephrol 2001;32:393–7. [CrossRef]
4. Yakinci C, Müngen B, Durmaz Y, Balbay D, Karabiber H. Autonomic nervous system functions in children with nocturnal enuresis. Brain Dev 1997;19:485–7. [CrossRef]
5. Fujiwara J, Kimura S, Tsukayama H, Nakahara S, Haibara S, Fujita M, et al. Evaluation of the autonomic nervous system function in children with primary monosymptomatic nocturnal enuresis--power spectrum analysis of heart rate variability using 24-hour Holter electrocardiograms. Scand J Urol Nephrol 2001;35:350–6. [CrossRef]
6. Unalacak M, Aydin M, Ermis B, Ozeren A, Sogut A, Demirel F, et al. Assessment of cardiac autonomic regulation in children with monosymptomatic nocturnal enuresis by analysis of heart rate variability. Tohoku J Exp Med 2004;204:63–9. [CrossRef]
7. Yakinci C, Er H, Müngen B, Durmaz Y, Karabiber H. Pupil cycle time in children with nocturnal enuresis. Tr J Med Sci 1999;29:69–70.
8. Dundaroz R, Turkbay T, Erdem U, Congologlu A, Sakallioglu O, Tascilar E. Pupillometric assessment of autonomic nervous system in children with functional enuresis. Int Urol Nephrol 2009;41:231–5. [CrossRef]
9. Brockmann PE, Urschitz MS, Noehren A, Sokollik C, Schlaud M, Poets CF. Risk factors and consequences of excessive autonomic activation during sleep in children. Sleep Breath 2011;15:409–16. [CrossRef]
10. Bascom A, McMaster MA, Alexander RT, MacLean JE. Nocturnal enuresis in children is associated with differences in autonomic control. Sleep 2019;42:zsy239. [CrossRef]
11. Shahani BT, Halperin JJ, Boulu P, Cohen J. Sympathetic skin response--a method of assessing unmyelinated axon dysfunction in peripheral neuropathies. J Neurol Neurosurg Psychiatry 1984;47:536–42. [CrossRef]
12. Shahani BT, Day TJ, Cros D, Khalil N, Kneebone CS. RR interval variation and the sympathetic skin response in the assessment of autonomic function in peripheral neuropathy. Arch Neurol 1990;47:659–64. [CrossRef]
13. Nevéus T. Nocturnal enuresis-theoretic background and practical guidelines. Pediatr Nephrol 2011;26:1207–14. [CrossRef]
14. Hindmarsh JR, Byrne PO. Is the enuretic female bladder without instability normal? Urol Res 1981;9:133–5. [CrossRef]
15. Whiteside CG, Arnold EP. Persistent primary enuresis: A urodynamic assessment. Br Med J 1975;1:364–7. [CrossRef]
16. Yeung CK. Nocturnal enuresis (bedwetting). Curr Opin Urol 2003;13:337–43. [CrossRef]
17. Schewe J, Brands FH, Pannek J. Voiding dysfunction in children: Role of urodynamic studies. Urol Int 2002;69:297–301. [CrossRef]
18. Medel R, Ruarte AC, Castera R, Podesta ML. Primary enuresis: A urodynamic evaluation. Br J Urol 1998;81:50–2. [CrossRef]
19. Yeung CK, Diao M, Sreedhar B. Cortical arousal in children with severe enuresis. N Engl J Med 2008;358:2414–5. [CrossRef]
20. Reimão R, Pachelli LC, Carneiro R, Faiwichow G. Primary sleep enuresis in childhood. Polysomnographic evidences of sleep stage and time modulation. Arq Neuropsiquiatr 1993;51:41–5.
21. Weider DJ, Sateia MJ, West RP. Nocturnal enuresis in children with upper airway obstruction. Otolaryngol Head Neck Surg 1991;105:427–32. [CrossRef]
22. Nevéus T, Stenberg A, Läckgren G, Tuvemo T, Hetta J. Sleep of children with enuresis: A polysomnographic study. Pediatrics 1999;103:1193–7. [CrossRef]
23. Zimmerman EA, Ma LY, Nilaver G. Anatomical basis of thirst and vasopressin secretion. Kidney Int Suppl 1987;21:S14–9.
24. Vaughn BV, Quint SR, Messenheimer JA, Robertson KR. Heart period variability in sleep. Electroencephalogr Clin Neuro-

physiol 1995;94:155–62. [CrossRef]
25. Baharav A, Kotagal S, Gibbons V, Rubin BK, Pratt G, Karin J, et al. Fluctuations in autonomic nervous activity during sleep displayed by power spectrum analysis of heart rate variability. Neurology 1995;45:1183–7. [CrossRef]
26. Bonnet MH, Arand DL. Heart rate variability: Sleep stage, time of night, and arousal influences. Electroencephalogr Clin Neurophysiol 1997;102:390–6. [CrossRef]
27. Akyüz G, Türkdoğan-Sözüer D, Turan B, Canbolat N, Yilmaz I, Us O, et al. Normative data of sympathetic skin response and RR interval variation in Turkish children. Brain Dev 1999;21:99–102. [CrossRef]
28. Persson A, Solders G. R-R variations, a test of autonomic dysfunction. Acta Neurol Scand 1983;67:285–93. [CrossRef]
29. Shahani BT, Day TJ, Cros D, Khalil N, Kneebone CS. RR interval variation and the sympathetic skin response in the assessment of autonomic function in peripheral neuropathy. Arch Neurol 1990;47:659–64. [CrossRef]
30. McLeod JG. Invited review: Autonomic dysfunction in peripheral nerve disease. Muscle Nerve 1992;15:3–13. [CrossRef]