Neurophysiologic Assessment of Autonomic Nervous System Functions in Children with Primary Mono-Symptomatic Nocturnal Enuresis

N. Z. El Shazly¹, R. H. Tomairek²
Departments of Clinical Neurophysiology¹, Pediatrics², Cairo University

ABSTRACT

Introduction: Previous urodynamic studies showed vesical hyperactivity in children suffering from primary mono-symptomatic nocturnal enuresis. Since the process of urination is under the control of the autonomic nervous system (ANS) hence ANS dysfunction may be responsible for the pathogenesis of this disorder. Objective: The aim of the study is to (1) investigate the possible involvement of the sympathetic or the parasympathetic nervous systems in the pathogenesis of primary mono-symptomatic nocturnal enuresis, (2) The select the patients who are potential candidates for anti-cholinergic drug therapy, (3) To monitor the efficacy of anti-cholinergic drug therapy in the control of symptoms. Methods: The study was carried on 28 enuretic children and 35 age and sex matched controls. Non invasive ANS tests [sympathetic skin response (SSR) recorded from the palms and soles, R-R interval variability on normal breathing (HRVN), R-R interval variability with deep breathing (HRVD), Valsalva ratio and 30:15 ratio] were performed in the both groups. Enuretic children were all treated with oxybutynin then they were reevaluated clinically after 3 months of treatment. Results: As compared to the control group, highly significant differences ware detected in the R-R interval variability with deep breathing, Valsalva and 30:15 ratios (P<0.0001) however non-significant difference in neither the latencies or the amplitudes of the SSR recorded from either the palm or sole were recorded in the enuretic group as compared to the control gro. On clinical follow up after 3 months, 81% of the enuretic children on oxybutynin therapy showed complete control of symptoms and 12 % showed a reduction in frequency of weekly bed wetting to ≤ 1 time per week. Conclusion: Hyperactive parasympathetic nervous system may be involved in the pathogenesis of primary mono-symptomatic nocturnal enuresis; anti-cholinergic drugs are potentially useful in the control of symptoms in enuretic children showing abnormal ANS functions. (Egypt J. Neurol. Psychiat. Neurosurg., 2005, 42(1): 201-207).

INTRODUCTION

The term enuresis is derived from the Greek word “enourein” which means voiding of urine. Enuresis is defined as repeated involuntary urine voiding into bed or clothes. The term primary mono-symptomatic nocturnal enuresis is used to denote children who have never been dry at night and night time incontinence is the only disorder they suffer from. The etiology of NE is unclear, genetic factors, developmental delay, psychological problems, arousal disorders, urodynamic disorders have all been reported as possible causes. Some previous studies demonstrated the presence of bladder hyperactivity in enuretics. Autonomic dysfunction was suggested to be the cause of the dysfunction. Some studies reported sympathetic over activity, others reported parasympathetic over activity. The efficacy of anticholinergic drugs e.g. oxybutynin and antidepressant drugs with anti-cholinergic action e.g. imipramine in treatment of NE points out towards the possible role of parasympathetic disorders in the pathogenesis of the disorder. Evidence from prospective clinical
and urodynamic studies showed that enuretic children with inadequate bladder storage function responded well to 15-20 mg daily oxybutynin hydrochloride\(^\text{15}\).

Because of the previous conflicting results the study was planned to investigate the possible role of both sympathetic and parasympathetic nervous systems in MNE.

Autonomic nervous system (ANS) functions can be assessed by a variety of invasive and non-invasive tests\(^\text{16}\). Tests of autonomic functions are simple, noninvasive, sensitive, specific, reproducible, non-time-consuming, physiologically and clinically relevant tests, that are strongly indicated when a disorder involving the autonomic nervous system is suspected\(^\text{17}\). Sympathetic skin response (SSR) and RR interval variability are the most commonly used tests for autonomic function because of their easy application and consistent results\(^\text{18}\). SSR test of sudomotor autonomic functions\(^\text{19}\). It represents the momentary change in skin potential reflexively evoked by a variety of arousal stimuli and can be recorded in the form of a slow wave resulting from activation of the sudomotor sympathetic efferent fibers. Heart rate variability (HRV), that measures the variation in the length of the intervals between heart beats, is another non-invasive autonomic test of the neural activity of the heart. Although also influenced by the sympathetic activity of the heart, HRV is essentially determined by the vagal out flow to the heart that originates in the vagal nucleus and is conveyed to the heart by the finely myelinated vagal fibers\(^\text{20}\). HRV can be also measured in relation to deep breathing where it reflects the respiratory sinus arrhythmia\(^\text{21}\). Heart rate variability in response to Valsalva maneuver and HRV in response to standing (that is expressed in the form of 30:15 ratio) provide another window through which autonomic control of the heart can be tested\(^\text{16,22}\).

The study was designed to: (1) investigate the possible role of ANS in the pathogenesis of PMSNE. (2) Select the patients who are potential candidates for anti-cholinergic drug therapy. (3) Monitor the role of anti-cholinergic drug therapy in the control of symptoms.

**SUBJECTS AND METHODS**

The study was carried on 28 untreated children having PMNE (females15, male 13) age range 5-15 years. The cases were chosen from the nocturnal enuresis clinic in Cairo University Children Hospital. The approach to the diagnosis depended upon thorough history taking about the onset of enuresis to exclude the presence of diurnal symptoms, e.g. Incontinence, urgency, frequency, interrupted stream, dysuria, associated encorporesis, constipation, punishment by the parents or the presence of associated psychological stress or diagnosed urinary tract infection.

Physical examination included assessment of intelligence, and performing inelegance quotient if necessary, abdominal examination for masses, neurological examination for lower back reflexes, perineal sensations and gait. Simple laboratory tests were done including (1) urine analysis for specific gravity, glucose, ph, pus. cells, or ova (2) Stool analysis for oxyuris ova. The inclusion criteria for the patients included cases more than 5 years of age with mono-symptomatic nocturnal enuresis without previous treatment, IQ> 70 %, no identified etiology, (e.g. Urinary tract infection, diabetes mellitus, diabetes insipidus, spinal dysraphism, or oxyuriasis) and nocturnal bed wetting was the only presenting symptom for at least 6 months. The SSR and HRV were recorded in 28 untreated enuretic children as well as 35 healthy age and sex matched children who served as control group. Six of the enuretic children could no undergo the SSR test (could not withstand electrical stimulation). The children were subjected to thorough history taking, physical examination, and neurological assessment, urine analysis, culture, random blood sugar and urinary tract sonography, and x-ray lumbar spine to exclude any medical problems e.g. Diabetes mellitus, congenital urinary tract disorders, spinal cord disorders as well as...
neurological disorders particularly ANS disorders and epilepsy. EEG examination was carried out to all the children to exclude the possibility of a missed epileptic disorder. After explaining the test to the guardians and taking their consent, the child was seated on a comfortable chair in a quiet room and asked to relax 5 minutes prior to testing. Room temperature was maintained around 25 °C. (1) Sympathetic skin response; (SSR) was carried on a Nihon Kohden Neuropac 2 machine.

Electrode application: 1 cm stainless steel electrodes were used. Recording were obtained from the right hand; the active electrode was placed on the palm 3 cm proximal to the second web space and the reference electrode was placed on the distal phalanx of the third digit. For recording from the right foot, the active electrode was placed on the plantar surface 3 cm proximal to the first web space and the reference was placed on the second toe. The ground electrode was placed on the wrist or ankle proximal to the recording electrode.

Stimulation: Upper limb: The left median nerve is stimulated. The cathode is directed proximally. Lower limb: The cathode was placed over the left 2nd plantar interspaces in the mid foot and the anode was placed on the 2nd toe. The band pass was adjusted at 0.5-5000 Hz, stimulus intensity was set at 10-30 mA, stimulus duration was set at 0.2 msec stimuli were delivered at irregular intervals to avoid habituation. The seep was adjusted at 1 second/ division. The latency from the stimulus artifact to the first deflection and the peak to peak amplitude was measured.

(2) R-R interval variability:

The R-R interval test was carried on a DANTEC, key point, machine software version 1.6. Stainless steel surface electrodes were applied on the radial pulse bilaterally (the active electrode on the right radial pulse and the reference on the left radial pulse). The ground electrode was applied on the right forearm. The R-R interval was recorded continuously during (1) normal breathing, (2) 6 – 10 cycles of deep breathing, (3) the patient was then trained to perform the Valsalva maneuver (maintain a 40mmHg pressure by blowing into a mouthpiece connected to a manometer) and the R-R interval was recorded for 35 seconds of the maneuver and 30 seconds after the release of pressure. (4) then after 10 seconds of normal finally instructed to stand up and the R-R interval was recorded for another one minute. The R-R interval variability (RRIV) was calculated as follows:

- **R-R Interval: The time to previous peak**
  - Maximum interval – Minimum interval × 100
  - Mean interval

- **RRV during Normal breathing:**
  - Maximum interval – Minimum interval × 100
  - Mean interval

- **Valsalva ratio:**
  - Maximum interval (after 35 seconds)
  - Minimum interval (0-35 second)

- **30:15 ratio:**
  - Interval at 30th beat
  - Interval at 15th beat

Clinical follow up was carried out for all the children in the enuretic group 2-3 months after treatment with oxybutynin (uripan) in a dose of 5mg 3 times daily.

**Statistical methods:**

**Data Analysis:**

Data was coded and entered on computer for analysis. A database on Excel was developed for data entry. Data was then transferred to SPSS version 11 for analysis. Simple frequencies were used for data checking. Descriptive statistics (arithmetic mean and standard deviation) were used for summary of quantitative data. Appropriate statistical tests of significance were used to compare studied groups. Independent student’s t-test was used for comparison of means between studied groups [cases and controls], as
well as for comparison between males and females in a third group of normal children.

**RESULTS**

The study group consisted of 28 children suffering from MNE, 15 females and 13 male of a mean age 8.8±2.07 years (age range 5-15 years) and 35 healthy controls (females 21, males 14) of a mean age 7.5±2.03 years (age range 5 – 14 years). All the children were subjected to the autonomic function tests except 5 of the enuretic who could not perform the SSR test as they could not with stands electrical stimulation.

(I) **Resting Heart rate:**

The heart rate in the enuretic group ranged between 63 -103 beats/min [mean= 81.8±10.0 beats/minute] versus 70 – 97 beats / minute in the control group [mean = 80.3±7.7, range]. The difference between the 2 groups was statistically non significant (P=0.496).

(II) **HRVN:**

The HRV during normal breathing in the enuretic group ranged between 80 -184 % [mean= 138.2± 25.2%] versus 21.9 - 66.9% in the control group [mean = 44.3±14.7 %]. The difference between the 2 groups was statistically highly significant (P<0.0001) (Table 1).

(III) **HRVD:**

The HRV during deep breathing in the enuretic group ranged between 101-180% [mean = 137.0±24.2 %] versus 33.9 - 74.1% in the control group [mean = 56.7±12.3 %]. The difference between the 2 groups was statistically highly significant (P<0.0001) (Table 1).

(IV) **Valsalva ratio:**

The Valsalva ratio in the enuretic group ranged between 1.13 - 3.3 [mean = 2.1±0.5] versus 0.12 – 1.31 in the control group [mean = 1.03±0.2]. The difference between the 2 groups was statistically highly significant (P<0.0001) (Table 1).

(V) **30:15 ratio:**

The 30:15 ratio in the enuretic group ranged between 0.9 – 2.7 [mean = 1.6±0.4] versus 0.12 – 1.3 in the control group [mean = 0.92±0.3]. The difference between the 2 groups was statistically highly significant (P<0.0001) (Table 1).

(VI) **SSR of the palm:**

Neither the latency nor the amplitude of the SSR recorded from the palm showed a significant difference between cases and controls. (P = 0.819, 0.380 respectively) the latency ranged between 1.21 – 1.78 ms in cases (mean =1.6 ± 0.1 ms) versus 1.12 – 1.96 in controls (mean 1.5±0.3 ms) while the amplitude range was 0.73 – 2.20 in the enuretic group (mean =1.5±0.4 UV) versus 0.92 – 1.96 in the control group (mean = 1.4±0.3Uv) (Table 1).

(VII) **SSR of the sole:**

Neither the latency nor the amplitude of the SSR recorded from the palm showed a significant difference between cases and controls. (P = 0.398, 0.094 respectively) the latency ranged between 1.34 – 2.40 ms in cases (mean = 1.7±0.3 ms) versus 1.44 – 2.13 in controls (mean 1.8±0.2 ms) while the amplitude ranged between 0.13 – 1.57 in the enuretic group (mean = 0.6±0.4 UV) versus 0.13 – 1.33 in the control group (mean= 0.6 ± 0.4 UV) (Table 1).

**Follow up:**

After treatment with oxybutynin for 3 months in a dose of 5 mg three times daily. Twelve (42.6%) of the enuretic children showed a complete control of symptoms with no bed wetting for. After 1 month treatment, 15 children (53.6%) showed complete control after 2 months of treatment, 21 children (75%) showed complete control after 3 months of treatment. On the other hand after 3 months of treatment 4 of the children showed a reduction in the frequency of bed wetting to ≤ 1 time per week, 3 children showed no improvement from the pre treatment wetting frequency (Fig. 1).
Table 1. The mean of non-invasive autonomic nervous system functions in enuretic group and healthy group.

<table>
<thead>
<tr>
<th>Test</th>
<th>EG</th>
<th>CG</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR</td>
<td>81.8 ± 10.0</td>
<td>80.3 ± 7.7</td>
<td>0.496*</td>
</tr>
<tr>
<td>HR VN</td>
<td>138.2± 25.2 %</td>
<td>44.3±14.7 %</td>
<td>&lt;0.00001**</td>
</tr>
<tr>
<td>HRVD</td>
<td>137.0 ± 24.2 %</td>
<td>56.7±12.3 %</td>
<td>&lt;0.00001**</td>
</tr>
<tr>
<td>Valsalva ratio</td>
<td>2.1 ± 0.5</td>
<td>1.03 ± 0.2</td>
<td>&lt;0.00001**</td>
</tr>
<tr>
<td>30:15 ratio</td>
<td>1.6 ± 0.4</td>
<td>0.92 ± 0.3</td>
<td>&lt;0.00001**</td>
</tr>
<tr>
<td>SSR palm latency</td>
<td>1.6 ± 0.1 ms</td>
<td>1.5 ± 0.3 ms</td>
<td>0.819*</td>
</tr>
<tr>
<td>SSR palm amplitude</td>
<td>1.5 ± 0.4 Uv</td>
<td>1.4 ± 0.3 Uv</td>
<td>0.380*</td>
</tr>
<tr>
<td>SSR sole latency</td>
<td>1.7 ± 0.3 ms</td>
<td>1.8 ± 0.2 ms</td>
<td>0.398*</td>
</tr>
<tr>
<td>SSR sole amplitude</td>
<td>0.6 ± 0.4 Uv</td>
<td>0.6 ± 0.4 Uv</td>
<td>0.094*</td>
</tr>
</tbody>
</table>

*non significant, ** significant, ms millisecond, Uv microvolt. EG: Enuretic group, CG: Control group.

Fig. (1): The number of fully controlled patients on anti-cholinergic drug therapy.

**DISCUSSION**

The etiology of NE has been widely debated. The Deeper insights and more specific studies can lead to better identification of clinical subtypes of enuresis this, in turn, leads to better individualization of treatment algorithms and thus reducing the incidence of trials and errors, and spares the patient the unneeded side effects without benefit. Nocturnal urinary continence is dependent on 3 factors: 1) nocturnal urine production, 2) nocturnal bladder function and 3) sleep and arousal mechanisms. The group of enuretic children are,
however, pathogenically heterogeneous, and two main types can be discerned: 1) Diuresis-dependent enuresis - these children void because of excessive nocturnal urine production and impaired arousal mechanisms. 2) Detrusor-dependent enuresis - these children void because of nocturnal detrusor hyperactivity and impaired arousal mechanisms. Detrusor function is governed by the autonomic nervous system which is under central nervous control\(^1\). The study aimed at identifying the possible role of the autonomic nervous system dysfunction in Mono-symptomatic nocturnal enuresis children and figuring out those who are potential candidates for anti-cholinergic drug therapy.

Previous studies using Holter ECG for evaluation of the ANS functions reported conflicting results, power spectral analysis of 24 hours HRV in non-treated mono-symptomatic enuretic children showed parasympathetic hyperactivity as well as abnormal circadian rhythm of ANS functions\(^{11}\), using time dependant analysis only demonstrated dominant sympathetic activity\(^{10}\). On using both time domain and spectral analysis dominant parasympathetic activity in MNE children was demonstrated\(^{12}\). In the spectral analysis there were significantly increased high frequencies (reflects the respiratory function arrhythmia) and a decrease in the low frequency bands (that is modulated by baroreceptor activity and is dually controlled by parasympathetic and sympathetic activity).

In this study four non-invasive tests (HRVN, HRVD, Valsalva and 30:15 ratios) were used to assess parasympathetic activity reflecting the vagal afferent and efferent functions, the values of these tests increase in parasympathetic hyperactivity and decrease in hypoactivity. If the results of 2 or more of these tests are abnormal, this indicates parasympathetic system dysfunction\(^{24}\). The SSR of the palm and sole were used as well to access sympathetic activity, non-elicited responses, delayed latencies or reduced amplitudes reflect sympathetic dysfunction. In agreement with Yakini et al., we found a highly significant abnormal increase in both the Valsalva ratio and 30:15 ratio in the enuretic children as compared to control group (Valsalva ratio = 2.1 versus 1.03, 30:15 ratio = 1.6 versus 0.92 in the enuretic group and the control groups respectively, P value < 0.00001) in addition we demonstrated a highly significant abnormal HRV during normal breathing as well as deep breathing. (HRVN= 138.2% versus 44.3% RRVD= 137.0% versus 56.7%, in the enuretic group and the control groups respectively, P value < 0.00001) Our findings denote the presence of parasympathetic hyperactivity in the enuretic group. On the other hand SSR of neither the palm nor the sole showed a significant difference between cases and controls (SSR palm latency = 1.6±0.1 ms, versus 1.5±0.3 ms, P value = 0.819, amplitude = 1.5±0.4 Uv versus 1.4±0.3 Uv, P value = 0.380, SSR sole latency = 1.7±0.3 ms versus 1.8±0.2 ms P value = 0.398, amplitude = 0.6±0.4 Uv versus 0.6±0.4 Uv P value =0.094 in the enuretic group and the control groups respectively) indicating a more or less normal sympathetic activity in the enuretic children.

Previous studies showed that the effectiveness of the anti-cholinergic drugs was in the range of 5-40% and therapy was not at all different from the placebo effect. The success rate increased to approximately 90% in enuretic patients with bladder storage dysfunction\(^{25}\). The anti-cholinergic drug Oxybutynin was used to treat the enuretic children in a dose of 15-20 mg per day, clinical follow up of the children was carried out after 1, 2, 3 months of treatment. After 3 months of treatment clinical improvement of 25 children (89.3%) was noted, 21 children (75%) showed complete control of symptoms, 4 children (14.3) showed a reduction in the frequency of bed wetting to less than once per week.

In conclusion this study verified the presence of hyperactive parasympathetic nervous system as an etiological factor in MNE and a more or less normal sympathetic activity. Neuropsychologic testing of the ANS is recommended in enuretic children to select those who manifest parasympathetic over activity and hence are candidates for anti-cholinergic drug therapy.

**REFERENCES**