Neurophysiological Assessment of Patients with Primary Nocturnal Enuresis

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ABSTRACT

Nocturnal Enuresis is the most common pediatric urological complaint encountered by primary care physicians. Despite its prevalence, nocturnal enuresis remains incompletely understood, which can frustrate patients, family members, and physicians. This study was carried out on 20 children presenting with primary nocturnal enuresis plus 10 children who were the control group, their age range between 5-14 years old. They were subjected to thorough history taking and full neurological examination. They were also subjected to the following investigations: Neurophysiological investigations: Electroencephalography, P300, Somatosensory evoked potential from the posterior tibial nerve, and Bulbocavernosus reflex, other investigations: urine analysis, I.Q. assessment and lumbosacral plain radiography. Our study aims at assessment of possible nervous system affection in child with primary nocturnal enuresis. It also aims at detection of the value of those neurophysiological techniques in detecting abnormalities in this group of patients. (Egypt J. Neurol. Psychiat. Neurosurg., 2005, 42(2): 301-309).

INTRODUCTION

School-age children with nocturnal enuresis are being labeled with ill-defined condition and forced to follow numerous therapeutic avenues, all with high failure rates. It is not uncommon for a child with a bed wetting problem to spend years in the wrong medical channels before being referred and cured correctly. Part of failure in the treatment of a child with nocturnal enuresis is caused by a lack of knowledge about the clear pathology of nocturnal enuresis.

Several investigations have been applied to clarify the real pathology of enuresis, and for assessment of bladder function, including urine analysis and culture, Post void residual urine, filling cystometrogram, voiding cystometrogram (pressure-flow study).¹

Many neurophysiological abnormalities were reported for those patients in many studies. Combination of different neurophysiological methods might show the level of the neurological lesion.²

These investigation include electroencephalograph for the assessment of the possible epileptic cause of primary nocturnal enuresis and for assessment of cerebral maturation regarding the theory that cerebral maturation is known to be important in the pathogenesis of this disorder regarding the theoretical basis that in some children there might be a delay in maturation of the normal neurological pathway involved in establishment of nocturnal continence³⁴. An innovative investigation is the measurement of the sensory input to the brain due to bladder distention i.e. Somatosensory evoked potential should be considered a useful reliable technique for assessing spinal cord function especially when no structural lesion can be demonstrated.⁵

Combination of different neurophysiological methods might show the level of the neurological lesion⁶.
PATIENTS AND METHODS

The present study is a case controlled study carried out on randomly selected 20 boys ranging in age from 5 to 14 years old with a mean age 9.3±3.04. They were suffering from primary nocturnal enuresis. The diagnosis of nocturnal enuresis based on DSM IV criteria that include significant repeated voiding of urine during night more than twice weekly for at least 3 months, which cause clinical distress.

Exclusion criteria
1. Mentally retarded patients (I.Q. < 70).
2. General medical disorders that may cause nocturnal enuresis as Diabetes mellitus, Diabetes insipidus, and Sickle cell anemia.
3. Local genitourinary diseases: as cystitis and obstructive uropathy.
4. History of drug intake or intoxication: as diuretics.

Patients also included another 10 children who are the control group who are potentially normal.

All were subjected to thorough history taking; Full neurological examination and neurophysiological studies:
- Electroencephalography was done using (Nihon Kohden-Neurofax) 14 channels
- EEG examination was carried under standard condition using the 10-20 international electrode placement system, with hyperventilation (continuously for three minutes) and photic stimulation as provocative techniques.

Parameters for evaluation:
Background activity, Focal changes, Generalized changes.

Auditory Event – related Potential (P300) was done using (Schwarzer). Recording electrodes were placed at Cz, Fz, Pz electrode sites of the 10-20 international system of electrode placement. It was done using the auditory odd ball paradigm. A headphone was used to deliver the auditory stimulus, which completely enveloped both ears. Responses to 30 target infrequent tones were obtained; The response to the infrequent tone is complex consisting of a negative N1, positive P2, negative N2 and a positive P3 deflection. Parameter for evaluation was P3 latency measured as the major positive peak after N2, within a range of 250- 350 msec.

P3 amplitude was measured peak to peak from the negative component just before P3 which represents N2, to the maximum positive peak P3.average amplitude of P300 is 10.5-15 µv.

Somatosensory Evoked Potentials for the Posterior tibial nerve was done using Nihon Kohden-Neuropack four channel. The first active electrode was placed over the space between L2 and L3 spines, the reference electrode was placed on the iliac crest. The second active electrode was placed at Cz over the scalp (located 2 cm behind Cz) with its reference electrode was located on the forehead at Fz according to the international 10-20 system of electrode placement.

The ground electrode was placed between stimulation and recording electrode in the middle of the leg. Parameters for evaluation were the Absolute latency measured from stimulus artifact to the peak of each of the waves, analyzed and expressed in milliseconds.

And Amplitude measured from the peak of one polarity to immediately following peak of the opposite polarity and expressed in micro volts Bulbocavernosus reflex was done using Nihon Kohden-Neuropack fourchannel, the ground electrode is placed near the perineum, the active electrode was a concentric needle inserted into the bulbocavernosus muscle; stimulation was applied on the dorsal side of the penile shaft, it was done using ring electrode. Voltage needed was 50-200 V, the duration was 0.1 msec. The values of the response were measured from the onset of the negative peak.

Assessment of Intelligence Quotient Using Wechsler Intelligence Scale for children (Wisc-R), Laboratory assessment includes fasting, postprandial blood sugar, and urine analysis.
**Radiological assessment:**
Plain X-ray lumbosacral (lateral and antroposterior view)

**RESULTS**

**EEG** examination of the children under the study yields a normal EEG in 12 patients (60%), on the other hand the abnormal EEG findings in the patient group were focal frontotemporal sharp waves in 3 patients (15%), these changes were focal right frontotemporal in 2 patients and focal left frontotemporal in the other one patient.

A background slowing activity of 6-7 cps theta waves with respect to age during wakefulness was seen in 3 patients (15%)

A focal tempoparietal spike and slow waves complexes were seen in only 2 patients (10%) (Table 1).

**Auditory P300:**
In the control group the normal P300 latency was 250-350 msec with a mean of 333.52 ± 4.84 msec, the amplitude of the response in the same group was 10.5-15µv with a mean 13.27± 1.93µv.

In the enuretic group the mean latency of the auditory P300 wave was 354.28±9.8 msec, the mean amplitude of the response in the same group is 9.8±1.63 µv. Nine patients (45%) showed delayed latency of the auditory P300 wave > 3 SDwith decreased amplitude < 2SD (Fig. 1), while 11 patient (55%) showed normal latency of p300 wave with normal amplitude (Figs. 2, 3 and Tables 2, 3).

**Somatosensory evoked potential of the posterior tibial nerve stimulation:**
In the control group the mean latency of SSEP:
Lumbar evoked potential 15.53±1.19 msec.
Cortical evoked potential p wave: 23.41±3.81 msec.

**The mean amplitudes were:**
Lumbar evoked potential 1.01±0.95µv
Cortical evoked potential 1.74±2.23µv

In the enuretic group, the results were abnormal in 9 patients 45%; 2 patients (10%) showed delayed cortical response with no apparent lumbar waves (Fig. 4). In the first patient the cortical evoked potential latency was 28.07 msec, the amplitude was 1.28 µv . The second patient the cortical evoked potential latency was 40.902 msec, the amplitude was 1.29 µv .

5 patients (25%) showed delayed lumbar wave latencies, while 2 patients (10%) had normal cortical waves and normal shape and latency of the lumbar wave but with diminished amplitude. In one of those 2 patients the lumbar amplitude was 0.85µv the other one showed 0.78 µv.

SSEP was normal in 11 patients (55%) (Tables 4, 5).

In the enuretic group the mean latency and amplitude of SSEP were:
- Mean lumbar evoked potential latency & amplitude: 20.27 ±3.3 msec, 1.13±1.26 µv.
- Mean Cortical evoked potential latency and amplitude: 36.08±3.78, 1.22±1.48 µv.

**Bulbocavernous reflex:**
As regard BCR findings in our control group; it was elicited in 8 subjects (80%); the other two patients were non cooperative as their age was 5 and 5.5 years. Absolute latency was within normal range (28±40) msec. with the mean latency was 30.5±8.2.

While in the patient group it was elicited only in 9 patients (45%) and it wasn’t elicited in the other 54% (11 patients), and this is relatively in agree with Podnar et al. who stated BCR could not be elicited in 14% of enuretics. In patient group 2 patient (25%) had delayed bulbocavernous reflex latency > 40 msec, while 6 patients (75%) showed normal latency.

The mean latency in the patient group was 35.7±8.3 msec. (Table 6).
Table 1. Results of EEG examination of the patient group

<table>
<thead>
<tr>
<th>Patients</th>
<th>Normal</th>
<th>Abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>3</td>
</tr>
<tr>
<td>Percentage</td>
<td>60%</td>
<td>15%</td>
</tr>
<tr>
<td>Number</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Percentage</td>
<td>15%</td>
<td>15%</td>
</tr>
<tr>
<td>Number</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Percentage</td>
<td>10%</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Comparison between patient and control group in result of P300.

<table>
<thead>
<tr>
<th>Groups</th>
<th>P300</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Delayed</td>
</tr>
<tr>
<td>Control</td>
<td>0</td>
</tr>
<tr>
<td>Patient</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
</tr>
</tbody>
</table>

Fig. (1): P300 in a child with primary nocturnal enuresis showing delayed P300 latency.
Table 3. Comparison between patient and control group in the mean amplitude (µv) of auditory P300.

<table>
<thead>
<tr>
<th>P300 Amplitude</th>
<th>Control group</th>
<th>Patients group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean P300 amplitude</td>
<td>13.27±1.93</td>
<td>9.8±1.63</td>
</tr>
</tbody>
</table>

Fig. (2): Comparison between patient and control group regards the mean latency (msec) of auditory P300.

Fig. (3): Comparison between patient and control group regards the mean amplitude (µv) of auditory P300.
Fig. (4): Shows SSEP to the right posterior tibial nerve stimulation in a male patient with primary nocturnal enuresis (14 years old) showing delayed cortical response (34 msec) with no apparent spinal response.

Table 4. Comparison between patient and control group in SSEP.

<table>
<thead>
<tr>
<th>SSEP</th>
<th>Abnormal</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delayed cortical wave latency with no spinal wave</td>
<td>2 (10%)</td>
<td>0</td>
</tr>
<tr>
<td>Delayed spinal wave latency</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>Normal cortical and spinal latency but with diminished amplitude</td>
<td>0</td>
<td>11 (55%)</td>
</tr>
</tbody>
</table>

Table 5. Comparison between patients and control group as regard SSEP results (latency in msec, amplitude in µv)

<table>
<thead>
<tr>
<th>SSEP</th>
<th>Control group</th>
<th>Patients group</th>
</tr>
</thead>
<tbody>
<tr>
<td>The mean latency of lumbar evoked potential</td>
<td>15.53±1.19</td>
<td>20.27±3.3</td>
</tr>
<tr>
<td>The mean latency of cortical evoked potential</td>
<td>23.41±3.81</td>
<td>32.08±3.7</td>
</tr>
<tr>
<td>The mean amplitude of lumbar evoked potential</td>
<td>1.01±0.95</td>
<td>1.13±1.26</td>
</tr>
<tr>
<td>The mean amplitude of cortical evoked potential</td>
<td>1.74±2.23</td>
<td>1.22±1.48</td>
</tr>
</tbody>
</table>
Table 6. comparison between patients and control groups regarding the bulbocavernosus reflex latency.

<table>
<thead>
<tr>
<th></th>
<th>Mean latency of bulbocavernosus reflex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control group</td>
<td>30.5±8.2</td>
</tr>
<tr>
<td>Patient group</td>
<td>35.7±8.3</td>
</tr>
</tbody>
</table>

**DISCUSSION**

As regard the Electroencephalographic monitoring of our patients group, 40% had abnormal EEG, similar results were found by Farrag et al. who reported EEG abnormalities in 43.8%. However Muttawea found only 24% of enuretics had EEG changes.

As regard the background activity in our patients group it showed generalized slowing in 15% while Fehlow found background slowing in 31.5%. The lower percentage of background slowing in our study can be referred to exclusion of mentally retarded children.

Other EEG abnormalities were in the form of focal epileptic changes in 25% this is agree with Fehlow who stated that 20% of his patients group has spikes and focal sharp waves.

Our study revealed the number of cases with abnormal EEG (8 patients), which supports the principle that primary nocturnal enuresis may be due to missed epileptic fit.

Out of those who showed abnormal EEG records, four cases were given Carbamzepine 200 mg as a trial to control their enuresis, complete cure occurred in 2 cases, appreciable improvement in one patient while the fourth failed to respond to this drug. The remarkable improvement with antiepileptic supports the principle of epileptic origin of primary nocturnal enuresis.

As regard P300; Celesia and Brigell stated that the P300 latency is known as a distinct parameter in cognitive disturbances. Our results showed that 45% of patients had delayed P300.

Longer P300 latency in primary nocturnal enuresis patients compared with non enuretics is another evidence of a maturational delay of central nervous system function.

In the present study we used SSEP of the posterior tibial nerve as a method for assessment of sacral roots and posterior column. The posterior tibial nerve and pudendal nerve share the second and third sacral segments and supraspinal course of their pathway. So when we detect any neurophysiological dysfunction through posterior tibial nerve somatosensory evoked potential in patients with normal neurological examination, we can expect a relevant dysfunction in neurophysiology of micturition.

Also normal micturition is a brainstem reflex rather than a simple sacral reflex, the interruption of this sacral to brainstem reflex pathway results in uncoordinated voiding (detrusor-sphincter dyssynergia).

The achievement of total control over the bladder function is a maturation process similar to that of other complex behavior pattern.

As regard the posterior tibial nerve SSEP we found it to be abnormal in 45% of enuretics, 10% had delayed cortical response with no apparent spinal wave which reflect affection of sacral roots or the root entry zone, while another 10% had normal cortical waves and normal shape and latency of the spinal wave but with diminished amplitude which express axonal affection of the sacral dermatomes, while 25% had delayed spinal wave latency which denotes involvement of the lumbar and sacral roots or cauda equina lesions.

The former results indicate the sensitivity of SSEPs in detection of possible lesions inspite of normal neurological examination.

On the other hand Gastaut and Broughton, Yeates, and Al shaar & Eman stated that the defect responsible of enuresis is located either in the midbrain or in the cerebral cortex.

Bulbocavernous reflex is integrated in the S2-S4 segments of the sacral spinal cord and at least oligosynaptic central integration has been
postulated. The excitatory status of motor nuclei of perineal muscles depends on afferent (e.g. bladder fullness) and descending input; the BCR can be used as an indicator of this excitatory status of the spinal cord nuclei. If the stimulation is performed under constant conditions, the changes in reflex response will be due to central integration of the reflex.

In our patients group BCR was elicited in only in 9 patients (45%) and it wasn’t easily elicited in the other 54% in spite of patient cooperation and absence of technical factors and this is relatively in agree with Pondar et al. who stated that enuretics are different from non enuretic children in percentage of successfully elicited BCR by single electrical stimuli: (86% in enuretics group).

33% of patients with elicited BCR had delayed BCR latency > 40 msec while 6 patients (66%) showed normal latency, this is supportive for the previous finding with SSEP that the lesion (66%) showed normal latency, this is supportive for the previous finding with SSEP that the lesion mainly in the sacral roots or the sacral centers.

In conclusion, Neurophysiological techniques are helpful tools for assessment of patients with primary nocturnal enuresis.

- Primary nocturnal enuresis may be attributed to a focus in the brain in a high percentage of cases as the study showed increased number of enuretics with EEG changes. Beside the highest frequency of attacks of nocturnal enuresis was detected among patients with EEG changes.

- Delayed Somatosensory evoked potential of the posterior tibial nerve which was detected in 45% of enuretics gives a spotlight on the organic causes of primary nocturnal enuresis and support the theory that in patients with primary nocturnal enuresis there is a generalized neuromotor delay.

- Cognitive impairment in primary enuretics is supported by reduced I.Q. and delayed P300 latency in a considerable percentage of patients in this study.

- Bulbocavernosus was much sensitive to detect a sacral centers or sacral roots lesion as a probable cause of primary nocturnal enuresis.

The study concludes that different levels of maturational delay should be considered in Monosymptomatic primary nocturnal enuresis.

REFERENCES


الملخص العربي

يعتبر السلس البولي الأولي من أكثر أمراض فترة الطفولة انتشاره ورغم اكتشافه إلا أن السبب الأساسي وراءه مازال مثيرا للأبحاث. وقد أجريت الدراسة على 20 طفل يعانون من السلس البولي الأولي بالإضافة إلى 15 طفل أصحاء طبيعياً. وقد كانت أعمارهم تتراوح ما بين 5-14 عاماً. وقد أجريت الفحوص الإكلينيكية شاملة للجهاز العصبي وأبلغت على الفترات العصبية والجزوية، حيث اكتشفت بعض الاختلاقات الكهروفيزيولوجية مثل رسم المخ الكهربائي، اختبارات الجهاز العصبي، اختبار الموجة الموجية 300، واختبار القفز المعتدل عبر العضلة البصرية الإسفنجية. وقد أظهرت النتائج أن التأكل في السلس البولي الأولي يحدث في 45% من الحالات، وأظهرت النتائج إلى وجود تأثير في التاريخ النزاعي بنسبة 30% من المرضى. ولم تسفر الفحوص الإكلينيكية للجهاز العصبي عن أي اضطرابات واضحة.

وقد أظهرت النتائج للفحص المعملي لعينات البول المأخوذة من مجموعة المرضى عن وجود حالات التأكل في الجهاز البولي التناسلي وقد تم علاج هذه الاضطرابات ولكن لم يحدث أي تحسن واضح في السلس البولي مما يشير إلى أن التأكل في الجهاز البولي التناسلي لم يكن هو السبب وراء السلس البولي في هذه الحالات.

وقد أظهرت النتائج في 45% من الحالات ارتفاع في نسبة الياقة. وقد أظهرت النتائج إلى أن تخطيط المخ الكهربائي أظهر اختلافات غير طبيعية بنسبة 40% من الحالات وقد كانت هذه الاختلافات في صورة موجات عددها في المنطقة الأمامية و الصدفي، وفي بعض الحالات كانت هذه الاختلافات في صورة مركب ترورة و الموجة البطينية بالإضافة إلى بقاعهم في بعض الحالات الأخرى.

وقد أظهرت النتائج وجود اختلافات في رسم المخ الكهربائي في عدد من الحالات أكبر من 300 موجة متأخرة في حوالي 45% من المرضى.

أما عن نتائج الدماء فقد اكتشفت مجموعة المرضى عن مجموعة الأطفال الأصحاء فقد كانت نتائج الدماء غير طبيعية في 40% من الحالات، أما عن نتائج الفحص عبر العضلة البصرية الإسفنجية فقد اكتشفت عصبية في 45% فقط من الحالات.

وقد استنتجت النتائج وجود تأثير عام في الجهاز العصبي في مرضى السلس البولي الأولي.

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