Research paper

Impaired selective attention in patients with severe primary monosymptomatic nocturnal enuresis: An event-related potential study

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ABSTRACT

Objectives: Primary monosymptomatic nocturnal enuresis (PMNE) is a very common problem in school age children. It is thought that PMNE represents a maturational lag in the central nervous system of those children. We did this case control study to assess the selective attention and resource allocation in those children using the P300 wave of the Event-Related Potentials (ERPs) and its relation to disease severity.

Methods: Forty four patients with PMNE and twenty three healthy controls were included in this study. Patients were diagnosed according to the criteria of international children’s continence society and were classified into two groups; patients with frequent wetting (>4 episodes/week), and patients with infrequent wetting (<4 episodes/week). ERPs were recorded at Fz, Cz, and Pz locations using odd-ball paradigm. N200 and P300 peak latencies (ms), and N200/P300 peak to peak amplitudes (μV) were measured.

Results: We found significant increase of P300 and N200/P300 interpeak latencies, and significant decrease of P300 amplitudes in frequent wetting group “severe” PMNE compared to healthy controls and infrequent wetting group.

Conclusion: Abnormal selective attention and resource allocation were found in patients with severe PMNE. Measures to improve selective attention might be helpful in treatment of patients with severe PMNE.

Significance: Impaired selective attention might play a role in pathogenesis of severe PMNE and the need for the various measures to improve selective attention may be further studied as a therapeutic tool for patients with severe PMNE.

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1. Introduction

Primary monosymptomatic nocturnal enuresis (PMNE) is defined as wetting episodes that occur in discrete amounts during sleep after the age of 5 years without previous dry periods of 6 months. PMNE adversely affects the quality of life of children and their parents, which can be much improved after treatment (Neveus et al., 2006; Naitoh et al., 2012). PMNE is a very common psychosocial problem affecting school children worldwide (Novello and Novello, 1987). In Upper Egypt, the prevalence of PMNE was 18% of school children (Hamed et al., 2017).

Many factors have been described in the pathogenesis of PMNE. Genetic background has been suggested from the results of twin, epidemiological and other genetic studies (Bakwin, 1971; Eiberg et al., 1995; Bower et al., 1996; Hamed et al., 2017) which have described several possible genes that play a possible role in its pathogenesis (Eiberg et al., 1995; Arnell et al., 1997; Eiberg, 1998). Till now no single gene has been confirmed to be responsible for all cases of PMNE, with marked clinical and genetic heterogeneity (von Gontard et al., 1998; Wang et al., 2009). Nocturnal polyuria may have an important role in pathogenesis PMNE through vasopressin deficiency (Rittig et al., 1989), but this also couldn’t explain all cases of PMNE as many children with nocturnal polyuria don’t have PMNE (Mattsson and Lindstrom, 1995). Moreover, nocturnal detrusor overactivity was described in cystometric studies in many children with PMNE (Esperanca and Gerrard, 1969; Watanabe and Azuma, 1989).

Maturational delay in the central nervous system may play an important role in the pathogenesis of PMNE. This hypothesis was supported by a number of clinical observations. A higher proportion of children with PMNE were having delayed walking, speech and musculoskeletal development (Mimouni et al., 1985; Steinhausen and Gobel, 1989). Moreover, electrophysiological evidence of delayed maturation of the brain was reported in many
studies (Kawauchi et al., 1998; von Gontard et al., 2001). Deep sleep with arousal difficulties was found in most of cases with PMNE (Gumus et al., 1999; Chandra et al., 2004). A strong association between PMNE and attention deficit hyperactivity disorder (ADHD) has been established (Baeyens et al., 2004; Baeyens et al., 2007; Shreeram et al., 2009). ADHD was diagnosed as a comorbidity in about 19% of children with PMNE (Nappo, 2012). Moreover, more severe ADHD was associated with more severe manifestations in children with PMNE (Baeyens et al., 2005; Kovacevic et al., 2018). Finally, the treatment of ADHD was associated with reduction of wet nights in children with PMNE (Ohtomo, 2017). This improvement was explained by several mechanisms including: the reduction of arousal threshold (Bahali et al., 2013), the reduction of detrusor contractility and the increase in the bladder capacity (Kovacevic et al., 2018) through the adrenergic and dopaminergic effects of the drugs used in treatment of ADHD (Biederman and Spencer, 1999; Bahali et al., 2013).

The P300 component of the event related potential (ERPs) is an objective measurement of cognitive processing. It is well known neurophysiological test which assesses selective attention and resource allocation (Salisbury et al., 2002; Polich, 2007). Three previous studies assessed the ERPs in children with PMNE (Iscan et al., 2002; Karlidag et al., 2004; Freitag et al., 2006). The results of these studies were contradictory with one showing significant changes of the P300 wave in children with PMNE compared to healthy controls (Iscan et al., 2002) and the other did not show any difference between the two groups (Karlidag et al., 2004; Freitag et al., 2006).

We did this case control study to further testing the changes in the ERPs in children with PMNE compared to healthy controls and to try to explain the previous contradictory results of the previously mentioned previous studies based on diseases severity.

2. Materials and methods

2.1. Subjects

Forty four patients diagnosed with PMNE and 23 healthy controls participated in this study (Table 1). All patients and controls were right handed. Patients were recruited from Neurology and Urology outpatient clinics of Sohag University Hospital in the period from October 2019 to June 2020. Patients were diagnosed according to the criteria of International Children’s Continence Society (ICCS) which is detailed in Gontard 2019 (Gontard and Kuwertz-Broking, 2019). Specifically, patients with intermittent (non-continuous wetting during sleep (including naps) without previous dry period of >6 months, with exclusion of organic causes of nocturnal enuresis (neurogenic, structural, or other medical causes), in patient >5 years old with minimum duration of 3 months of disease. Patients were further classified into two groups; patients with frequent wetting (>4 episodes/week), and patients with infrequent wetting (<4 episodes/week) (Austin et al., 2016; Gontard and Kuwertz-Broking, 2019). All patients attended regular primary, middle, or secondary schools, with normal performances. All patients achieved scores of >75 in Intelligence Quotient (IQ) testing. All patients undergone detailed medical history, urologic and neurologic examinations, full blood count, renal function tests, blood sugar, urine analysis, stool analysis, ultrasonographic examination of urinary system with pyelography if necessary. Patients who suffer organic causes of enuresis (such as urinary tract infection, intestinal parasitic infection and urinary calculi etc), those with renal, neurologic, or psychiatric disorders, or those with diurnal lower urinary tract symptoms were excluded from the study. All patients and controls were drug naïve (no previous treatment of enuresis or psychoactive drugs). Informed consent was obtained from patients and controls and the study protocol was approved by local ethics committee of Sohag University.

2.2. Event related potentials measurement

An “odd-ball” stimulus paradigm (Neupack X1- MEB2300, Nihon Kohden Co. Japan) was used to test the auditory ERPs. The auditory ERPs were recorded at Fz, Cz, and Pz locations using international 10–20 system by Ag/AgCl electrodes. The recording electrodes were placed at the Fz, Cz, and Pz locations and linked earlobe electrodes were used as the reference electrodes. The electrodes impedances were kept below 5 kΩ and the EEG signals were amplified and bandpass filtered (0.01–40 Hz), and were stored for further off-line analysis at a sampling rate of 256 Hz. The averaging epoch was 1024 ms, including 200 ms pre-stimulus baseline.

The subjects were tested while sitting in a comfortable chair with their necks support in a quiet room with dim light. First, the binaural auditory thresholds were determined at 1000 Hz for each subject. Bilateral ear stimulation over headphones at 80 dB (each 20 ms in duration) was done for each subject. The auditory stimuli consisted of 1000 Hz pure tone bursts as the standard stimuli and 2000 Hz pure tone bursts as the target stimuli. The inter-stimulus intervals were delivered at variable time intervals between 1 and 2 s. The probabilities of each sound category were 84.62% for the standard and 15.38% for the target stimuli (50 target trials in each block, 2 blocks with 325 trials in each block). The two sound types were presented randomly. The subjects were asked to press a button using the right thumb as quickly as possible on presentation of the target stimulus. Event-related potentials were recorded at the same hours of the day (between 9 and 12 AM) for each study participants. Patients and controls were asked to relax and to look at a particular point on the front wall to minimize the ocular artefacts and to improve their concentration during recording.

Trials with eye blink artifacts (>50 mV of peak-to-peak amplitude) were all excluded from the averaging. The P100, N100, P200, N200, and P300 waves were determined. P100 was determined as the first positive deflection that occurs after the stimulus artifact; N100, is the first negative deflection that occurs after P100; the P200 is the first positive deflection after N100; the N200 is determined as the negative deflection that occurs after P200; and finally, the P300 which is determined as a positive deflection after N200. Interpeak latencies were measured between

Table 1

| Parameter                        | Healthy controls (N = 23) | Patients (N = 44) | P value |
|---------------------------------|---------------------------|-------------------|---------|
|                                 |                           | Infrquent wetting group (N = 24) | Frequent wetting group (N = 20) |
| Age in years (mean ± SD)        | 10.4 ± 3.2                | 9.6 ± 3.1          | 11 ± 3.5 | 0.833 |
| Sex                             | 14 males and 9 females    | 16 males and 8 females | 12 males and 8 females | 0.921 |
| Wetting frequency (wet nights/week) | 102 ± 11.3               | 2.2 ± 0.7          | 5.6 ± 1.04 | 0.005 |
| IQ (mean ± SD)                  | 453 ± 73 msec            | 467 ± 81 msec      | 475 ± 86 msec | 0.182 |

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the peaks of the consecutive waves. Peak amplitudes (μV) were measured relative to the 200 ms pre-stimulus baseline. The N200 and P300 peak latencies (ms), and the N200/P300 peak to peak amplitudes were measured.

2.3. Statistical analysis

Kolmogorov-Smirnov Z test was used for normality testing of numerical data and revealed that all the data were normally distributed. All data were presented as mean ± SD. One-way ANOVA was used for testing statistical differences between the three groups. Student t-test with Bonferroni correction was used for post-hoc comparisons between groups.

3. Results

There were no statistically significant differences between patients and controls as regard age and sex. The mean ± SD of IQ scales and reaction times were presented in (Table 1) without statistically significant differences among various groups. The numbers of wet nights/week were 5.6 ± 1.04 and 2.2 ± 0.7 for the frequent wetting and the infrequent wetting groups, respectively (Table 1). One-way ANOVA revealed statistically significant differences in P300 latency, N200/P300 interpeak latency, and P300 amplitudes and insignificant difference of N200 latency between the three groups in general at all recording locations (Fig. 1 and Table 2). Further post-hoc comparative testing between various groups using Student t-test with Bonferroni correction revealed that those significant differences were found between the patients with frequent wetting and the healthy controls, and between the patients with frequent wetting and others with infrequent wetting in P300 latency, N200/P300 interpeak latency, and P300 amplitudes in all recording locations. However, there were no statistically significant differences between the patients with infrequent wetting and the healthy controls for any of the measures of ERPs in all recording locations. Factorial ANOVA taking the “Group” as the between subject variable and recording “Location” as the within subject variable revealed insignificant Group X Location interaction meaning that the significant changes in various parameters of ERPs were not dependent on the recording electrode sites; namely Fz, Cz, and Pz. The various variables of ERPs; namely, the P300 latencies, amplitudes, N200 latencies, and the N200/P300 interpeak latencies and groups’ comparative P values were presented in (Table 2).

4. Discussion

We found significant increase of the P300 and N200/P300 interpeak latencies, and significant decrease of the P300 amplitudes in frequent wetting group “severe” PMNE compared to healthy controls and infrequent wetting group. This is the first study to test and classify the changes of ERPs according to the wetting frequency “severity” of PMNE. We found that the significant changes in the various parameters of the P300 wave occurred in patients with severe PMNE compared to patients with mild disease and healthy controls.

To the best of our knowledge, only three previous studies have tested the changes in the various parameters of the ERPs between patients with PMNE and healthy controls (Iscan et al., 2002; Karlidag et al., 2004; Freitag et al., 2006). The results of those studies were contradictory. In the first study by Iscan et al. (2002) a significant prolongation of the P300 latency was found in patients with PMNE in comparison to healthy controls group at Cz and Pz locations. However, they did not find any significant difference in latencies of N200. Moreover, this study did not find any relation of those significant differences in P300 latency in relation to the age of the patients with PMNE (Iscan et al., 2002). This was also shown in previous studies (Pearce et al., 1989; Polich et al., 1990; Sangal and Sangal, 1996). Another study by Karlidag et al. (2004) did not find such difference in P300 latency, between the enuretic and non enuretic groups. Despite that they have found a significant difference in the amplitude of P300 recorded at the Pz

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Table 2

| Parameter          | Location | Patients Group | ANOVA results | Intergroup comparisons (P value) |
|--------------------|----------|----------------|---------------|----------------------------------|
|                    |          | Frequent wetting | Infrequent wetting | F       | P                | Frequent VS Infrequent Groups | Frequent wetting VS Control Groups | Infrequent wetting VS Control Groups |
| P300 Latency in msec | Fz       | 411.9 ± 29.9    | 368.3 ± 26.9   | 493.75  | <0.0001          | 0.015  | 0.003 | 0.233 |
|                    | Cz       | 407.6 ± 33.1    | 363.9 ± 30.1   | 396.26  | <0.0001          | 0.013  | 0.007 | 0.322 |
|                    | Pz       | 401.3 ± 25.8    | 357.9 ± 29.1   | 51730.1| <0.0001          | 0.013  | 0.007 | 0.549 |
| N200 Latency in msec | Fz       | 259.3 ± 32.3    | 251.7 ± 25.2   | 20311  | 0.01362          | 0.934  | 0.489 |
|                    | Cz       | 253.1 ± 26.9    | 247.7 ± 24.5   | 243.2 ± 33.4 | 1.215 | 0.3007 | 0.745 | 0.489 |
|                    | Pz       | 251.7 ± 27.1    | 243.9 ± 25.8   | 51730.1| <0.0001          | 0.013  | 0.007 | 0.734 |
| Interpeak Latency in msec | Fz       | 153.2 ± 24.3    | 117.6 ± 22.5   | 51042.9 | <0.0001          | 0.013  | 0.007 | 0.366 |
|                    | Cz       | 154.1 ± 23.9    | 116.6 ± 23.4   | 44530.1| <0.0001          | 0.013  | 0.007 | 0.378 |
|                    | Pz       | 149.8 ± 21.7    | 113.9 ± 21.3   | 51042.9| <0.0001          | 0.013  | 0.007 | 0.256 |
| P300 Amplitude in μV | Fz       | 15.7 ± 4.7      | 18.9 ± 5.3     | 5.299   | 0.006            | 0.024  | 0.026 | 0.145 |
|                    | Cz       | 16.9 ± 5.1      | 19.1 ± 5.6     | 3.741   | 0.027            | 0.032  | 0.036 | 0.167 |
|                    | Pz       | 17.3 ± 5.7      | 19.8 ± 4.6     | 5.911   | 0.004            | 0.034  | 0.021 | 0.178 |

* We tested the event-related potentials parameters of the target stimuli representing 15.38% of stimuli.
site being less in the enuretic group (Karlidag et al., 2004). On the other hand, Freitag et al. did not find any significant differences between patients with PMNE and healthy controls in both P300 wave latency and amplitude (Freitag et al., 2006).

In our study, the significantly prolonged P300 latency and reduced P300 amplitude in patients with PMNE with frequent wetting compared to both healthy controls and patients with infrequent wetting groups suggest a more profound maturational delay in development of the central nervous system in patients with frequent wetting. This is the same findings reported by Iscan et al (Iscan et al., 2002) who used P300 component as an objective measure of cognitive function. They have suggested a functional maturation delay in the thalamus in enuretic children (Iscan et al., 2002). Koff et al. also have suggested that PMNE might be caused by a delay in the maturation in some tracts in the central nervous system which gradually recover leading to the disappearance of enuresis with advancement of age (Koff, 1996).

On the other hand, in both the studies of Karlidag et al. and Freitag et al., who tested patients with PMNE of nearly the same age group as our study, they did not find any difference in the P300 latency (Karlidag et al., 2004; Freitag et al., 2006). They have suggested that there was no difference between the speed of cognitive processing of the target stimulus determination in this age group (Karlidag et al., 2004; Freitag et al., 2006). However, the difference between the studies and our study can be explained on the fact that we have classified our patients according to severity of the disease, according to the standards of ICCS (Gontard and Kuwertz-Broking, 2019), which was not done in the other studies. This classification of disease severity may have an impact on the pathogenesis and management of those patients (Gontard and Kuwertz-Broking, 2019).

The ERPs are electroencephalographic signals time-locked to an environmental and/or internal events (Valakos et al., 2020). The most studied part of the ERPs is the P300 wave (Sutton et al., 1965). The generators of the P300 wave include; the reticular formation, pre-frontal cortex, centro-parietal cortex, temporal cortex, limbic system, with some thalamic contribution which are the same structures involved in processing of attention. The most famous model for the generation of P300 wave is the context updating theory (Polich, 2007). In this model a new stimulus enters a memory comparison process to determine whether it is different from the usual stimulus (non-target stimulus) or not. Non-target stimulus is responsible for the generation of the sensory evoked potentials (N100, N200 and P200). This is not the case when the target stimulus is applied which generates the P300 by activating neural circuits of updating attention and working memory. Thus the P300 wave reflects an updating process that results from a discrepancy between the current stimulus and the task context and not only to target probability. The P300 component is related to the processing of the working memory and context updating. It is generally known that P300 latency decrease with age to reach its mature value at or after the 2nd decade (Donchin, 1981; Donchin and Coles, 1988; Polich, 2007; Gomez et al., 2019).

The P300 wave has two measured parameters. The first is the amplitude which related to the attentional processing of the target stimulus that is dependent on the working memory process (Thabit et al., 2016). The second is the P300 latency which reflects the speed of this attentional processing and memory updating process (Gonsalvez et al., 2007; Polich, 2007; Duncan et al., 2009). Based on these data, P300 wave depends mainly on event categorization, attentional resource allocation as well as attentional reorientation and working memory.

The relation between ERPs and ADHD has been established since long duration (Jonkman et al., 1997; Kilpeläinen et al., 1999). This relation was established due to the following facts; children with PMNE and comorbid ADHD were suffering more severe voiding symptoms (Baeyens et al., 2005; Kovacevic et al., 2018), poorer response to treatment (Crimmins et al., 2003), and moreover, some studies found beneficial effects of pharmacological therapy for ADHD on voiding dysfunction symptoms in patients with PMNE (Nappo, 2012; Kovacevic et al., 2018). In children with ADHD, voiding symptoms are related to both inattention behavior, and other mechanisms including failure to detect bladder signals by decreased brain stem inhibition and decreased arousal to full bladder and impaired central adrenergic stimulation in ADHD patients causes sphincter overactivity leading to failure to relax during voiding (Duel et al., 2003; Baeyens et al., 2006; Baeyens et al., 2007; Nappo, 2012).

The finding of prolonged P300 latency in the frequent wetting group in comparison to infrequent wetting group in our study suggests that deficits in attention is correlated with more severe presentation of PMNE and may dictate the trial of treatment of attention deficits in children with frequent wetting. It is well known that treatment of ADHD is associated with improvement of symptoms of PMNE (Ohtomo, 2017). Our findings also may explain why some cases don’t respond to desmopressin and anticholinergic therapy.

We found a significant difference in P300 amplitude in the frequent wetting group in comparison to both infrequent wetting and control groups suggesting a widespread difference in processing. In comparison to previous studies, Karlidag et al. found this difference in the parietal records only suggesting only a regional difference in rate/quality processing (Karlidag et al., 2004). Our findings suggest that testing P300 in cases with frequent wetting may detect subtle cognitive abnormalities that may play a role in increasing severity of nocturnal enuresis.

5. Conclusion

In conclusion, we found significantly prolonged P300 latency and reduced P300 amplitude in frequent wetting patients with PMNE in comparison to both healthy controls and PMNE patients with infrequent wetting. The limitations of our study include: the small sample size, the lack of inclusion of other secondary monosymptomatic nocturnal and polysymptomatic enuresis groups, and the small number of recording electrodes, namely 3 midline electrodes, used to test ERPs in our patients and healthy controls. Future studies including larger multicenter studies including larger number of patients and other types of enuresis and comorbidities, especially patients with comorbid ADHD and PMNE, and the use of multiple bihemispherically distributed electrodes to test the distribution of the delayed neural networks in patients with severe PMNE are needed.

Conflict of interest

None.

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