Behavioral problems in children with primary monosymptomatic nocturnal enuresis

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ABSTRACT

Background and objectives: Primary monosymptomatic nocturnal enuresis (PMNE) is a common distressing condition to children and parents. This study aimed to determine frequencies, severities and characteristics of behavioral problems with PMNE.

Methods: This cross-sectional study included 80 children with PMNE (age: 12.58 ± 1.24 yrs.; boys = 58, girls = 22) and 60 healthy children. Behavioral symptoms were assessed by Strength and Difficulties Questionnaire (SDQ).

Results: This study included 80 children (boys/girls ratio = 2.64:1) with PMNE. They had mean age of 12.58 ± 1.24 yrs. The majority (70%) had good response to medical treatment. Compared to controls, children with enuresis had higher frequencies of emotional, conduct and hyperactivity-inattention symptoms and peer relationship and prosocial problems and higher total ($P = 0.001$) and different subscales' scores of SDQ. There was an overlap of behavioral problems in 52.2% of children with nocturnal enuresis. Compared to children without behavioral symptoms, children with behavioral symptoms were significantly older at age at presentation ($P = 0.046$) regardless of gender, residence and type or response to medications. Multiple regression analysis showed that emotional [β = 0.053 (95%CI = 0.037–0.084), $P = 0.024$] and hyperactivity-inattention symptoms [β = 0.063 (95%CI = 0.028–0.097), $P = 0.001$] were significantly associated with enuresis independent to other problems.

Conclusion: PMNE is associated with higher risk of behavioral problems particularly emotional and hyperactivity-inattention symptoms indicating externalizing and internalizing problems, therefore, the importance of early non-pharmacological or/and drug interventions. The comorbid behavioral disorders should be treated separately according to evidence-based recommendations to prevent persistence of enuresis and the development of psychiatric disorders in the future.

1. Introduction

Bed-wetting is frequently considered by many clinicians as a self-limiting problem. It has been estimated that 20% of 5 years old children have nocturnal enuresis (NE) and this frequency decreases proportionately every year, becoming 10–15% at the age of 6, 7% at the age of 7, 5% at the age of 10, 1–2% at the age of 15 and 0.5–1% at the age of ≥18 years old [1]. Epidemiologic studies reported that primary monosymptomatic nocturnal enuresis (PMNE) is a frequent trouble among children worldwide with an estimated prevalence of 18–30% [2,3]. PMNE is defined based on the International Children's Continence Society (ICCS) as pathological bed-wetting with a wetting of at least once per month in children ≥5 years old [4]. While according to the fifth edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5), PMNE is defined as frequent urination into clothes or bed at least two times per week for three successive months in children ≥5 years old and who don't have acquired urinary continence [5]. PMNE etiology is multifactorial. PMNE is highly heritable condition and linked to some chromosomal loci (5, 13, 12 and 22) [6,7]. Endothelial nitric oxide synthase (eNOS) and neuronal (nNOS) genes polymorphisms are also associated with PMNE. Intrarenal nitric oxide (NO) regulates sodium and water excretion as endogenous diuretic [8]. Studies indicated that PMNE may be due to more nocturnal formation of urine because of insufficient vasopressin hormone formation during sleep [9], bladder dysfunction [10]; deep sleep or poor sleep arousal in response to bladder capacity cues [11]; neurodevelopmental immaturity of brainstem and motor cortex circuitry [12]; and defect in Barrington's nucleus network that connect the brain, urinary bladder and corticotropin-releasing factor (CRP) [13]. Studies observed that obesity could be a risk for NE [14]. Parental factors, including attitudes to PMNE, disciplinary behaviors, and psychiatric comorbidities in parents have been related to etiology of PMNE. Children with PMNE may warrant interventions which offer a quick,

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safe response that will allow the child to participate in peer activities. However, treatments will be unsuccessful if the family's social structure and home environment do not provide consistent support and care for the child. Non-pharmacological interventions (as alarm treatment) should be the first line if the child and the parent are motivated as it showed long-term beneficial effect. It is also important to encourage pharmacotherapy and proper follow-ups [1,4].

Physician in clinical practice reported behavioral troubles in children with PMNE which include emotional instability, hyperactivity and inattention complaints [2,15,16] and peer-relational [17] and conduct [16] problems. The ICCS documented that approximately 20–30% of children with enuresis might have at least one psychological/ psychiatric problem which is approximately 2-folds higher than non-wetting children [1–4]. However, research studies which assessed behavior in children and adolescents with PMNE have mixed findings or contradictory results which may reflect some relevant cultural factors that should be considered in the context of PMNE and child emotional and behavioral functioning.

Evaluation of behavioral problems in children and adolescents with PMNE is an understudied area in our locality. Therefore, this study aimed to determine frequencies, severities and characteristics of behavioral problems in children and adolescents with PMNE and the independent demographic, clinical and treatment predictors which differentiate children with behavioral problems from those without.

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2. Material and methods

2.1. Participants

This was a cross-sectional study. It included 80 children (boys = 58, girls = 22) with PMNE. Patients were recruited over a period of one year (January 2018 to February 2019) from the out-patient clinic of the Hospital of Neurology and Psychiatry, Assiut University Hospital, Assiut, Egypt. Diagnosis of PMNE was carried out according to DSM-5 which is also in accordance to the definition of ICCS [4,5]. The appropriate sample size was estimated using G*power program 3.1. It has been reported that an average of 25% of children with NE has one psychological/ psychiatric problem (2-folds higher than general population), a value that was incorporated into the power testing. When, the accepted minimum level of significance (α) of 0.05, the accepted level power for the test (1-β) of 0.80 and the effect size chosen to be 0.1, therefore, the sample size of 80 children with PMNE was considered appropriate [19]. For statistical comparisons, this study also included 60 healthy children matched for sex, age (mean age: 13.67 ± 1.02), residence and socioeconomic status. They were recruited from children's classmates and neighborhoods. **Inclusion criteria were:** (1) age ≥ 7 years old, (2) children with PMNE or uncomplicated NE, (3) children on regular drug treatment for NE for at least 6 months before participation in the study, and (4) children with normal intelligence (Intelligence quotient or IQ ≥85). **Excluded criteria were subjects (patients and controls) with:** (1) secondary enuresis (i.e. regressive wetting after acquired control), (2) lower urinary tract infections, (3) structural abnormalities or malformations of urinary tract or urogenital system (complicated enuresis), (4) chronic illness (e.g. renal failure, hypertension, congenital heart disease, diabetes mellitus and diabetes insipidus), (5) gastrointestinal tract symptoms (e.g. constipation or encopresis), (6) neurological or psychiatric diseases (e.g. mental retardation, pervasive developmental abnormalities, sleep disorder), (7) low intelligence (i.e. IQ < 85), and (8) history of lumbosacral trauma or operations.

Data collection included sex, age, residence, and body weight, socioeconomic state, detailed medical, neurological, urological and psychological histories and examinations; detailed pre- and post-natal and developmental histories, family history of NE, frequency and timing of bed-wetting (bed-time and day-time) and response to medical treatment. For statistical analyses, children were further classified into

groups according to the frequency of enuresis (less frequent <2 times per week; frequent ≥2 times per week) and response to medical treatment (partial or good response, i.e. frequency of ≥1 or none in the last 3 months before the study, respectively). Children with NE were subjected to urodynamic study, urinalysis, electroencephalography (EEG), and ultrasonography on kidneys and pelvis.

2.2. Behavioral assessment

Interviewing of parents and children was done by a psychiatrist (MF). Behavioral assessment was done using Arabic translated and validated version of parent-reported Strength and Difficulties Questionnaire (SDQ) [20]. SDQ is a brief behavioral screening questionnaire for children 3–16 year olds. SDQ provides balanced coverage of children and adolescents' behavior, emotions, and relationships. It highly correlates with Child Behavior Check list (CBCL) and is equally effective in detecting internalizing and externalizing problems. SDQ is considered more sensitive than CBCL in detecting inattention and hyperactivity. SDQ covers 25 attributes which are divided into 5 subscales of 5 items each, generating scores for (1) Emotional symptoms (5 items), (2) Conduct problems (5 items), (3) Hyperactivity-inattention (5 items), (4) Peer-relationship problems (5 items), and (5) Prosocial behavior (5 items). Each item is scored from zero to 2. All subscales except for the last one are summed to generate a total difficulties score (range, 0 to 40). SDQ score can be used as continuous variables (total score) or by classifying as normal, borderline, and abnormal according to the range of each subscale or total scores.

2.3. Data analysis

Data were analyzed using SPSS version 16.0 for windows (Statistical Package for the Social Sciences Inc., Chicago III). The distribution of data was evaluated by Kolmogorov-Smirnov test. Data were expressed as mean ± standard deviation (SD) as they were normally distributed. Comparative statistics were done using Student's t- (two-tailed) and Chi-square tests. Bonferroni adjustment was used for multiple testing corrections. Multiple regression analysis was done to determine the SDQ behavioral problem subscale (abnormal) which was significantly and independently associated with enuresis independent to other problems. Data were expressed as β values and 95% confidence intervals percentage (CI%). Statistical significance was considered with $P < 0.05$.

3. Results

This study included 80 children (boys/girls ratio = 2.64:1) with PMNE. They had mean age of 12.58 ± 1.24 yrs. Only 15% had combined bed-time and day-time wetting. The majorities were classified as having less frequent enuresis and had good response to medical treatment. None received behavioral interventions for NE, such as a bed-wetting alarm. None did psychotherapy. Positive family history of first degree relative with NE was reported in 70%. The majority of parents (85%) reacted patiently and supportively to their children's enuresis regardless to residence. Only 15% had abnormal urodynamic findings (Table 1). Compared to healthy children, children with enuresis had higher frequencies of emotional, conduct and hyperactivity-inattention symptoms and peer relationship and prosocial problems and higher total and different subscales' scores of SDQ (Table 2). Boys had more severe conduct symptoms ($P = 0.036$) and prosocial problems ($P = 0.032$) compared to girls, while the latter had more severe emotional symptoms ($P = 0.046$). Higher total and SDQ subscales scores were reported in children with frequent NE ($P = 0.0001$). Conduct ($P = 0.001$) and hyperactivity-inattention ($P = 0.0001$) symptoms and poor relationship and prosocial problems ($P = 0.0001$) were significantly higher in patients with partial response to medical treatment while patients with good response showed marked emotional symptoms ($P = 0.001$) (Table 3). There was an overlap of behavioral

Table 1
The demographic and clinical characteristics of the studied groups.

Demographic and clinical characteristics	Patients (n = 80)	Controls (n = 60)	P-value
Age at presentation; years			
Range	11.00 - 16.00	10.00 - 16.00	
Mean ± SD	12.58 ± 1.24	13.67 ± 1.02	0.632
Gender			
Male	58 (72.50%)	29 (48.33%)	0.563
Female	22 (27.50%)	31 (51.67%)	0.648
Body weight; kg			
Range	15.00 - 35.00	17.00 - 40.00	
Mean ± SD	26.53 ± 2.50	24.53 ± 2.50	0.347
Order of birth			
Firstborn	34 (42.5%)	-	-
Others	46 (57.5%)	-	-
Residence			
Urban	33 (41.25%)	22 (36.67%)	0.227
Rural	47 (58.75%)	38 (63.33%)	0.342
Type of wetting			
Bed-time wetting	68 (85.00%)	-	-
Combined (day and bed-time wetting)	12 (15.00%)	-	-
Frequency of Enuresis			
Less frequent (<2 times per week)	67 (83.75%)	-	-
Frequent (≥2 times per week)	13 (16.25%)	-	-
Family history of enuresis			
First- and second-degree relatives	56 (70.00%)	22 (36.67%)	**0.001**
Reaction of the parents towards child bed wetting			
Punishment for bedwetting	12 (15.00%)	-	-
React patiently and supportively	68 (85.00%)	-	-
Urodynamic findings			
Normal	68 (85.00%)	-	-
Decreased cystometric capacity	8 (10.00%)	-	-
Detrusor over activity	4 (5.00%)	-	-
Type of treatment			
Imipramine (Tofranil)	18 (22.50%)	-	-
Oxybutynin (Ditropan or uripan)	5 (6.25%)	-	-
Desmopressin (minirin)	44 (55.00%)	-	-
Combined (imipramine and oxybutynin)	13 (16.25%)	-	-
Duration of treatment; years			
Range	0.50 - 6.00		
Mean ± SD	4.05 ± 1.23	-	-
Response to treatment			
Good response	56 (70.00%)	-	-
Partial response	24 (30.00%)	-	-

problems in 52.2% of children with NE. Compared to children without behavioral symptoms, children with behavioral symptoms (total score of SDQ was 20 to 40) were significantly older at age at presentation ($P = 0.046$) but did not differ in relation to gender, residence (rural versus urban) and type or response to medications. Multiple logistic regression analysis showed that emotional [β = 0.053 (95% CI = 0.037–0.084), $P = 0.024$] and hyperactivity inattention symptoms [β = 0.063 (95% CI = 0.028–0.097), $P = 0.001$] were significantly associated with enuresis independent to other behavioral problems (Table 4).

4. Discussion

Recent researches revealed that nocturnal enuresis is a group of conditions with different causes in which genetic factors are the most important. In this study, 70% had first degree relatives with enuresis. Previous studies have shown that 77% of children may develop enuresis if both parents have enuresis; 44% if one parent has enuresis and 15% may develop enuresis if neither parent has enuresis [6,7]. Although more than half of patients (58.75%) had rural residency, however, 85% of parents were aware that NE is a neurobiological disorder and they sought medical service for drug treatment and reacted patiently and supportively towards their child's bed-wetting. In contrast, some studies showed that parents often blame or shaming their children for bed-wetting and express different kinds of punishment (verbal and

physical) [21,22]. We observed that none of the children received behavioral interventions for NE, such as a bed-wetting alarm. It seemed that in our culture settings, the parents were not motivated to arouse the child from sleep particularly the majority were not able to identify the approximate time of NE after the child entered into a sleep state.

In this study, children with enuresis had high frequencies and scoring of emotional, conduct and hyperactivity-inattention symptoms and peer relationship problems. Nearly 50% had overlap of behavioral symptoms. The emotional and hyperactivity-inattention symptoms were independent to other behavioral problems. In accordance, not only research studies but also epidemiological cross-sectional and longitudinal studies reported emotional and hyperactivity-inattention [2,15,16], peer-relational [17] and conduct problems in children with PMNE, indicating externalizing and internalizing behavioral problems [16]. We observed that children with behavioral problems were older at age at presentation compared to those without behavioral problems and regardless to gender, residence (rural versus urban) or the type duration or degree of response to treatment [2,15,16]. Kanata et al. [23] evaluated behavior in 4478 Japanese children (with and without enuresis) using parent-reporting SDQ. The authors reported that the predictor for enuresis was hyperactivity-inattention symptoms after controlling for other behavioral abnormalities and age, gender, low birth weight, IQ, and parents' education.

We and others suggested the following possible relationships between behavioral problems and PMNE: **(1) psychiatric factors occur**

Table 2

Behavioral assessment categorization and scores of the studied groups according Strength and Difficulties Questionnaire (SDQ).

Behavioral assessment (SDQ subscales)	Patients (n = 80)	Controls (n = 60)	P-value
Emotional symptoms			
Normal (0 - 5)	25 (31.25%)	33 (55.00%)	**0.01**
Borderline (6)	12 (15.00%)	8 (13.33%)	0.665
Abnormal (7 - 10)	43 (53.75%)	19 (31.67%)	**0.01**
Score			
Range	3.00 - 9.00	2.00 - 7.00	
Mean ± SD	7.2 0 ± 1.60	3.8 ± 0.78	**0.001**
Conduct symptoms			
Normal (0 - 3)	32 (40.00%)	40 (66.67%)	**0.032**
Borderline (4)	6 (7.50%)	6 (10.00%)	0.532
Abnormal (5 - 10)	42 (52.50%)	14 (23.33%)	**0.01**
Score			
Range	3.00 - 9.00	1.00 - 5.00	
Mean ± SD	6.88 ± 1.84	3.02 ± 0.83	**0.001**
Hyperactivity-inattention symptoms			
Normal (0 - 5)	8 (10.00%)	13 (21.67%)	0.658
Borderline (6)	19 (23.75%)	23 (38.33%)	0.138
Abnormal (7 - 10)	53 (66.25%)	24 (40.00%)	**0.01**
Score			
Range	3.00 - 9.00	1.00 - 5.00	
Mean ± SD	8.55 ± 1.65	4.52 ± 1.02	**0.001**
Peer relationship problems			
Normal (0 - 3)	22 (27.5%)	41 (68.33%)	**0.001**
Borderline (4 - 5)	11 (13.75%)	8 (13.33%)	1.103
Abnormal (6 - 10)	47 (58.75%)	11 (18.33%)	**0.001**
Score			
Range	1.00 - 10.00	1.00 - 5.00	
Mean ± SD	7.55 ± 1.72 ( )	3.18 ± 1.01	**0.001**
Total			
Normal (0 - 15)	18 (22.0%)	32 (53.33%)	**0.01**
Borderline (16 - 19)	24 (27.5%)	16 (26.67%)	0.858
Abnormal (20 - 40)	38 (47.5%)	12 (20%)	**0.01**
Score			
Range	21.00 - 36.00	6.00 - 13.00	
Mean ± SD	30.13 ± 2.95	18.20 ± 1.84	**0.001**
Prosocial behavior			
Normal	32 (40.00%)	38 (63.33%)	**0.01**
Borderline	10 (12.50%)	13 (21.67%)	0.067
Abnormal	38 (45.50%)	9 (15.00%)	**0.01**
Score			
Range	3.00 - 9.00	6.00 - 9.00	
Mean ± SD	7.93 ± 0.86	5.05 ± 1.93	**0.03**

as a reactive consequence to enuresis: In support, behavioral problems were more severe and frequent and correlated with older age at presentation regardless to child's gender, good response to medical treatment, supportive response of parents towards child's enuresis and residence (rural versus urban). PMNE is a troubling and distressing condition not only for children but also for families because of its burden and stigmatism [24–26]. Children with enuresis often experience a

substantial stress, feeling of shame, sense of social difference and isolation or poorer sense of belonging to society, low self-esteem and loss of self-confidence. These all result in difficulties in child/adolescent social interaction. From psychological point of view, many authors consider that the psychological impacts of bed-wetting are more important than physical considerations (emotional and behavioral) during adolescence [27]. Some suggested that increased hyperactivity-inattention could be a relapse of coping behavior due to enuresis psychological burdens that become stronger in early adolescence (about 10 years) due to social and peer-relationship meanings at that age [28]. These severe behavioral symptoms can result in chronic course or persistence of enuresis, poor scholastic achievement and impaired social activities. Studies also observed that the substantial stress to children resulted in poorly developed coping mechanisms and thus maladaptive behavior later in life to alleviate stress produced by their surroundings. Kessel et al. [29] investigated predictors, prevalence, prognostic factors, and outcomes of primary enuresis in 559 children. The authors followed-up children from the age of 3 till the age of 9. The authors observed that the child and maternal anxieties and low positive affectivity and authoritative parenting were the predictors for the development of enuresis by the age of 9. They also observed that marked anxiety and depressive symptoms at the age of 3 predicted a greater likelihood for enuresis and hyperactivity, inattention and depressive symptoms by age of 9. Vasconcelos et al. [30] assessed the behavior of 1119 healthy Chilean children at the age of ≤5 and 10. The authors observed daytime and nocturnal urinary incontinence NE in 3.30% and 11.40% at the age of 10 and 1.10% and 2.70% at adolescence. They also observed that (a) the difficult early life temperament was linked to the increased odds of 10-year daytime urinary incontinence, and (b) inattention at the age of 5 years was linked to the increased odds ratio for NE at 10 years old and adolescence. **(2) An overlap or shared biological etiology for both enuresis and behavioral problems:** Studies reported co-occurrence between enuresis or dysfunctional voiding symptom in 28.30% to 30% of children with attention deficit hyperactivity disorder (ADHD). These children also had shorter reaction time in inhibitory control domain, auditory sustained attention and working memory [31]. Mohsenzadeh et al. [18] reported anxiety disorders in 43%, sleep disorders in 34% and academic failure in 4% of children with PMNE. **(3) the presence of emotional and behavioral abnormalities before the development of enuresis:** authors observed the presence of at least one psychological, motor or neurological difficulty in 80% of children with NE [29–33]. Amiri et al. [33] reported psychiatric disorders in 79.23% of children with NE, with the highest incidence for ADHD (74.90%), followed by oppositional-defiant disorder (53%) while tic disorders were reported in 12% and bipolar affective disorder, conduct disorder and post-traumatic stress disorder were reported in only 5%.

We believe that this study has some strength: (1) It investigated the behavioral symptomatology and their predictors in a fairly unique sample of children and adolescents with PMNE at similar developmental age

Table 3

Behavioral of scores of the studied patients in relation to gender, frequency of bed-wetting and response to treatment.

Items	Emotional symptoms	Conduct symptoms	Hyperactivity-inattention symptoms	Peer relationship problems	Total score	Prosocial behavior
Gender						
Boys	5.27 ± 1.52	7.64 ± 1.30	8.42 ± 1.22	7.55 ± 1.02	29.05 ± 2.95	6.47 ± 1.46
Girls	7.34 ± 1.43	5.63 ± 1.72	7.07 ± 1.53	6.53 ± 1.42	26.45 ± 1.85	4.45 ± 1.77
P-value	**0.046**	**0.036**	0.126	0.157	**0.024**	**0.032**
Frequency of bed-wetting						
Less frequent	4.54 ± 1.32	3.55 ± 1.38	4.63 ± 1.74	5.20 ± 1.13	17.58 ± 1.43	3.54 ± 1.30
Frequent	8.25 ± 1.60	8.57 ± 1.92	8.68 ± 1.46	7.98 ± 1.03	33.57 ± 1.55	6.40 ± 1.6
P-value	**0.0001**	**0.0001**	**0.0001**	**0.001**	**0.0001**	**0.0001**
Response to treatment						
Good response	7.78 ± 1.56	4.63 ± 1.32	4.75 ± 1.07	5.25 ± 1.08	18.78 ± 1.20	3.32 ± 1.83
Partial response	5.43 ± 1.04	7.24 ± 1.74	8.56 ± 1.38	8.98 ± 1.63	31.05 ± 1.07	7.83 ± 1.55
P-value	**0.001**	**0.001**	**0.0001**	**0.0001**	**0.0001**	**0.0001**

Table 4
The multiple logistic regression for prediction of different behavioral problems in children with enuresis.

Parameters	β	95% (CI)	P-value
Emotional symptoms	0.053	0.037-0.084	**0.024**
Conduct symptoms	0.02	0.015-0.034	0.436
Hyperactivity-inattention symptoms	0.063	0.028-0.097	**0.001**
Peer relationship problems	0.018	0.011-0.033	0.462
Prosocial behavior	0.028	0.019-0.057	0.093

in a previously unstudied population or an unstudied cultural setting. (2) Patients underwent extensive medical work ups compared to many previously related studies which included urodynamic study, a quite an invasive and stressful procedure for children.

However, the study has some limitations which include: (1) The outcome variables were mainly based on parents' interviews and parents' reports. (2) Patients were recruited from a single tertiary hospital center which may result in selection bias for severe cases and high scoring of behavioral symptoms, (3) Due to the cross sectional design of the study, it is difficult to determine the temporal relation of behavioral symptoms Longitudinal research is required to determine whether de novo behavioral symptoms occur in relation to specific developmental age or NE and behavioral symptoms are a continuation of a shared pathogenic pathway or risk. It is expected that the presence of an internalizing psychopathology early in life (e.g. <7 years) could make the child more vulnerable to the distress associated with bed-wetting. The persistence of enuresis with resistance to therapy and even depressive symptoms in adulthood might also be adverse consequences, (4) some children with NE (38.75%) received imipramine as treatment for NE. Imipramine is an antidepressant and its effects on behavior/mood could potentially confound patients' outcomes.

5. Conclusion

PMNE is associated with higher risk of different behavioral problems particularly emotional and hyperactivity-inattention symptoms regardless to the child's good response to treatment indicating externalizing and internalizing problems. Physician should encourage compliance to effective modality of therapy. Behavioral comorbid disorders should be treated separately according to evidence-based recommendations as they may also contribute to the persistence of enuresis over time and the development of psychiatric disorders in the future.

Authors' contribution

SAH and MF did the design of the study, recruitment and evaluation of patients and participated in statistical analysis and drafting the manuscript. EAH assisted in statistical analysis and drafting of the manuscript.

Ethical approval

The study protocol was approved by local ethical committee of Faculty of Medicine (ID # AUFM_326/2018), Assiut University, Assiut, Egypt.

Informed consent

Written informed consents were obtained from the parents of all participants.

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