

# Periodic limb movements during sleep are associated with a lower quality of life in children with monosymptomatic nocturnal enuresis

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**Abstract** The study investigates whether cortical arousals and periodic limb movements during sleep are related to daytime psychological functioning in children with monosymptomatic nocturnal enuresis with associated nocturnal polyuria. Psychological functioning is evaluated on five domains: attention deficit hyperactivity disorder—inattentive problems, quality of life, internalizing problems, externalizing problems, and executive functioning. This multi-informant (parents, teachers, and children) and multi-method study included overnight video-polysomnography, questionnaires, and neuropsychological testing. Thirty children (7 girls) 6 to 16 years (mean 10.43 years, SD 3.08) were selected in a

tertiary enuresis center. A high index of periodic limb movements during sleep was associated with a lower quality of life, according to the child. No significant correlations were found with attention deficit hyperactivity disorder—inattentive problems, internalizing problems, externalizing problems, and executive functioning.

**Conclusion:** This study clarifies the relationship between sleep parameters and psychological functioning of the children with monosymptomatic nocturnal enuresis and associated nocturnal polyuria according to the child, the parents, and the teachers. Periodic limb movements during sleep are associated with a lower quality of life of the child.

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## Abbreviations

AASM	American Academy of Sleep Medicine
ADHD	Attention deficit hyperactivity disorder
BRIEF	Behavior Rating Inventory of Executive Function
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBCL	Child Behavior Checklist
DBDRS	Disruptive Behavior Disorder Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
ICCS	International Children's Continence Society
MNE	Monosymptomatic nocturnal enuresis
NE	Nocturnal enuresis
NP	Nocturnal polyuria
PinQ	Pediatric incontinence quality of life
PLMS	Periodic limb movements during sleep
PSG	Polysomnography
QoL	Quality of life

TRF	Teacher Report Form
WISC-III-NL	Flemish version of the Wechsler Intelligence Scale for children, 3rd edition

## Introduction

Monosymptomatic nocturnal enuresis (MNE) is a heterogeneous disorder, caused by various pathogenic factors: a mismatch of the increased nocturnal diuresis rate and the functional bladder volume together with a failure to awaken in response to a full bladder. Several comorbidities probably play a part in the pathogenesis. Most common comorbidities are bladder dysfunction [47], disturbed circadian rhythm [38], sleep problems [13], and psychological problems, especially attention deficit hyperactivity disorder (ADHD) [5, 42].

The most common psychological disorder in children with enuresis is ADHD [5, 27], especially the ADHD-inattentive subtype [4, 32]. Children with the ADHD-inattentive subtype have a low ability to concentrate; they have no hyperactivity and impulsivity problems. The high comorbidity is observed in different study populations [44]: a pediatric setting [5], a child psychiatry setting [7, 14, 35], and in epidemiological studies [22, 43].

Children with enuresis are difficult to arouse from sleep compared to controls [46]. Subjectively, parents of children with nocturnal enuresis (NE) confirm this and often consider their child to be a “deep” sleeper. However, Yeung et al. suggested in a letter that children with enuresis, mostly due to an overactive bladder, have fragmented sleep associated with frequent cortical arousals but an inability to awaken completely [48]. The presence of increased arousals is confirmed by Dhondt et al. in a heterogeneous group of children with NE [12, 13].

Children with enuresis experience higher levels of daytime sleepiness [11]. Daytime sleepiness is associated with internal and external behavior problems [1]. Daytime dysfunction due to lower sleep quality is associated with a lower quality of life (QoL) in terms of physical and social well-being [16].

The majority of the above-mentioned studies have some limitations. Studies investigating sleep in children with NE are performed in therapy-resistant children [12, 13, 46] or in patients with bladder dysfunctions [48]. Furthermore, studies investigating psychological functioning of children with NE are performed in heterogeneous patient groups, not differentiating between MNE and non-MNE. Non-MNE is associated with a higher incidence of psychological problems [21, 43, 44]. Therefore, children with non-MNE are excluded from this study.

This is the first study investigating the association between sleep and ADHD-inattentive symptoms in a homogeneous group of patients with MNE associated with nocturnal polyuria (NP). Not only ADHD-inattentive symptoms are studied

but also broad psychological functioning, including QoL, internalizing problems, externalizing problems, and executive functioning.

This explorative study investigates in children with MNE associated with NP, if specific sleep parameters, i.e. cortical arousals and periodic limb movements (PLMS) are related to the psychological functioning of the child. Psychological functioning is evaluated on five domains: ADHD-inattentive problems, QoL, internalizing problems, externalizing problems, and executive functioning. It is expected that a disturbed sleep is associated with worse psychological functioning.

## Material and methods

### Study population

Thirty children (7 girls) 6 to 16 years (mean 10.43 y, SD 3.08) suffering from MNE associated with NP, referred to a tertiary enuresis center, were included. NP was defined in this study as a nocturnal diuresis exceeding the expected bladder capacity according to the formula of Hjalmas [(age+1)\*30]. Patient characteristics were demonstrated in Table 1. Exclusion criteria were daytime incontinence resistant to therapy, dysfunctional voiding, urgency, diuretics, antihypertensives, uropathy, renal abnormalities, poor therapy compliance, and intelligence quotient below 75. Children who were on desmopressin stopped treatment at least 2 weeks for the start of the study. This substudy was part of a larger study investigating the influence of desmopressin on sleep, MNE, and psychology.

### Procedure

The study was approved by the Institutional Ethics Board of the Ghent University Hospital (B670201212). Written consent was obtained from all patients and their parents.

All subjects participated in one overnight standardized video-polysomnography (PSG). PLMS and cortical arousals

**Table 1** Patient characteristics

	N of patients with available data	Mean	SD
Age (years)	30	10.43	3.08
MVV (ml)	30	383	132
Number of wet nights a week	29	5.2	1.9
Nocturnal diuresis on PSG (ml)			
Wet + dry nights	29	753	355
Wet nights only	26	767	372
Dry nights only	3	633	115

MVV maximum voided volume, PSG polysomnography

were the main PSG parameters investigated in this study. PLMS were defined as rhythmic extensions and dorsiflexions of the ankle, occasionally of the knee and hips. Scored according to the American Academy of Sleep Medicine (AASM) criteria, PLMS were calculated per hour of sleep (PLMS index). A PLMS index greater than five was considered as pathologic [26]. PLMS usually cluster into episodes and could co-occur with cortical arousals.

Cortical arousals could be short (micro-arousals of 3 to 15 s) or longer (>15 s), resulting in awakening. The number of arousals during the night was manually scored according to the AASM criteria and also calculated as arousal index (number of arousals over total sleep time). Awakening index was also calculated (number of awakenings over total sleep time).

The psychological measurements were multi-method and multi-informant. Parents, children, and the teachers filled in questionnaires, and neuropsychological testing of the child was performed.

Parents provided socio-demographic information. Parents and teachers completed the Child Behavior Checklist/Teacher Report Form (CBCL/TRF), the Disruptive Behavior Disorder Rating Scale (DBDRS), and the Behavior Rating Inventory of Executive Function (BRIEF). The CBCL/TRF measured emotional, social, and behavioral problems in 6 to 18-year-old children. Problems were grouped into internalizing and externalizing problems [2, 20, 40, 41]. The DBDRS measured behavior problems in terms of DSM-IV [3] criteria in 6 to 16-year-old children [17, 29, 30]. It contained four scales: inattention, hyperactivity/impulsivity, oppositional defiant disorder, and conduct disorder. The BRIEF measured executive function behaviors for children and adolescents ages 5–18 years [18, 19, 37].

Parents and children completed two questionnaires measuring QoL of the child. The pediatric quality of life inventory measured health related QoL in children aged 2 to 18-year old [15, 39]. Scores ranged from 0 to 100 with higher scores indicating better QoL. The pediatric incontinence quality of life (PinQ) was originally developed to measure QoL in children with bladder dysfunction [8, 9]. Scores ranged from 0 to 84, with higher scores on the PinQ indicating worse QoL concerning the wetting problem.

The child performed three neuropsychological tests. First, the digit span subtest of the Flemish version of the Wechsler Intelligence Scale for children, third edition (WISC-III-NL) was used to measure auditory memory [23, 45]. Second, two subtests of the Test of Everyday Attention for children were used to measure sustained attention: score double task and code transmission [24, 25]. Third, the child underwent several subtests of the Cambridge Neuropsychological Test Automated Battery (CANTAB) [10, 36]. Motor screening and Big/little circle were two mandatory screening subtests to screen for visual, movement, comprehension, learning and reversal

difficulties. Four subtests assessed executive function, working memory and planning. More specifically, Intra/Extra Dimensional set shift assessed rule acquisition and attentional set shifting. The Stockings of Cambridge assessed spatial planning and motor control. Spatial Span and Spatial Recognition Memory tested working memory capacity. Visual sustained attention was measured by the subtest Rapid Visual Information Processing.

#### Statistical analyses

The relationship between psychological and specific sleep parameters (cortical arousals and PLMS index) was explored by pairwise correlations using R version 3.0.2 [33]. Variables with more than 20 % missing observations were excluded from the correlation analyses. Correlations were corrected for multiple testing per psychological domain and per physical measure using false discovery rate control [6]. False discovery rate control examines the expected number of false discoveries among all discoveries.

## Results

Mean PLMS index was 10.83 (SD 4.99; min 3.6–max 23.3). Arousal index ranged between 1.2 and 13.9 (mean 6.433; SD 3.31) and awakening index between 1.8 and 15.2 (mean 8.720; SD 3.76).

Scores on the pediatric quality of life inventory in children and parents ranged, respectively, between 51.41 and 97.50 (mean 72.87; SD 12.08) and between 42.97 and 100 (mean 79.96; SD 14.75). Mean scores on the PinQ for children and parents were, respectively, 26.17 (SD 12.07; min 8–max 54) and 23.1 (SD 14.86; min 3–max 63).

Normscores on the Test of Everyday Attention for Children on the score double task and the code transmission task ranged, respectively, between 2 and 14 (mean 9.03; SD 2.65) and between 2 and 15 (mean 8.83; SD 3.36). The mean *z*-score on the CANTAB Rapid Visual Information Processing was 0.45 (SD 1.06; min –1.86–max 1.69). According to the parents, 5 of the 30 children had a (sub)clinical score on the DBDRS inattentive scale, compared to 1 of the 25 children with available teacher data.

Overall, 11/30 children had a (sub)clinical score on the CBCL on internalizing problems. The same number of children had a (sub)clinical score on externalizing problems. According to the teachers, 4/26 and 5/26 children had a (sub)clinical score on internalizing and externalizing problems, respectively.

The behavioral regulation index scores were (sub)clinical for 6/30 children according to the parents. Of the 25 children with evaluable data, none of them had a (sub)clinical score on the behavioral regulation index. The mean *z*-scores on the

CANTAB Intra/Extra Dimensional set shifting and Stockings of Cambridge were 0.40 (SD 1.03; min  $-1.25$ –max 3.88) and  $-0.22$  (SD 0.99; min  $-3.21$ –max 1.24), respectively. The  $z$ -scores on the CANTAB Spatial Recognition Memory and Spatial Span ranged, respectively, between  $-0.88$  and 1.79 (mean 0.52; SD 0.67) and between  $-2.84$  and 2.77 (mean 0.23; SD 1.32). Finally, normscores on the WISC-III-NL Digit Span ranged between 2 and 17 (mean 9.4; SD 3.5).

A high PLMS index was associated with a high score on the PinQ, indicating a lower QoL according to the child. The association between a high arousal index and a lower QoL

was only marginally significant. There were no correlations found between the sleep parameters (i.e., PLMS and cortical arousals) and ADHD-inattentive problems, internalizing problems, externalizing problems, and executive functioning. Details were demonstrated in Table 2.

## Discussion

This study investigates whether specific sleep parameters, i.e., cortical arousals and PLMS are related to the psychological

**Table 2** Sleep parameters, pairwise correlations with psychological domains

Psychological domain	Measurement	PLMS	Cortical arousals	
		PLMS index	Arousal index	Arousal—awakening index
Quality of life	Pediatric incontinence Questionnaire			
	Children	0.517*	0.431 <sup>a</sup>	0.317
	Parents	0.048	0.012	0.014
	Pediatric quality of life inventory			
	Children	0.065	0.231	0.325
	Parents	$-0.078$	0.118	0.208
ADHD-inattentive symptoms	CANTAB Rapid Visual information Processing	0.270	0.138	0.068
	Test of everyday attention for children			
	Score double task	0.388	0.320	0.240
	Code transmission	0.256	0.133	0.154
	DBDRS inattentive subscale			
	Parents	$-0.107$	$-0.195$	$-0.148$
Internalizing problems	Teachers	$-0.103$	$-0.207$	$-0.229$
	Child behavior checklist/teacher report form			
	Parents	0.078	$-0.153$	$-0.199$
Externalizing problems	Teachers	$-0.120$	$-0.145$	$-0.219$
	Child behavior checklist/teacher report form			
	Parents	0.140	$-0.054$	$-0.149$
Executive functioning	Teachers	0.095	$-0.050$	$-0.203$
	CANTAB			
	Spatial Recognition Memory	$-0.030$	0.150	0.035
	Spatial Span	0.016	$-0.035$	$-0.056$
	Intra/Extra Dimensional set shift	0.167	0.267	0.340
	Stockings Of Cambridge	0.013	0.020	0.149
	WISC-III-NL Digit Span	0.361	0.233	0.180
	BRIEF			
	Parents (total score)	0.016	0.017	$-0.045$
	Teachers (total score)	Missing	Missing	Missing

ADHD attention deficit hyperactivity disorder, BRIEF Behavior Rating Inventory of Executive Function, CANTAB Cambridge Neuropsychological Test Automated Battery, DBDRS Disruptive Behavior Disorder Rating Scale, PLMS periodic limb movements during sleep, WISC-III-NL Flemish version of the Wechsler Intelligence Scale for children, 3rd edition

\*Corrected  $p < 0.05$

<sup>a</sup>  $p < 0.1$  ~ marginally significant

functioning of the child in a homogeneous group of children with MNE associated with NP. Psychological functioning is evaluated on five domains: ADHD-inattentive problems, QoL, internalizing problems, externalizing problems, and executive functioning.

The study demonstrates a high incidence of disrupted sleep and an association between a high PLMS index and a low QoL of the child. More specific, a high PLMS index is associated with a high score on the PinQ, indicating a lower QoL associated with the wetting problem, according to the child, not according to the parents. This confirms previous literature based on questionnaires that a low quality of sleep is associated with a lower QoL [16].

Our pilot study demonstrated previously an increased PLMS index and cortical arousability in children with refractory nocturnal enuresis [12]. PLMS are infrequent in normal children, a PLMS index higher than five is considered as pathological [26]. Of the thirty children in the pilot study, all except one had a pathological PLMS index. These findings were confirmed in our case–control study, where it was demonstrated that children with NE displayed higher sleep fragmentation (more cortical arousals) and PLMS than the control children with a possible sleep disorder without NE [13].

The results of the present study confirm the findings of our pilot [12] and case–control study [13] in a more benign population of enuresis with NP: a high incidence of PLMS and cortical arousals and an increased comorbidity with psychological problems. However, this study only finds a significant correlation with QoL. ADHD-inattentive problems, internalizing problems, externalizing problems, and executive functioning are not associated with PLMS and cortical arousals.

The first advantage of the study is the carefully selected group of children with MNE associated with nocturnal polyuria without daytime symptoms. Second, this study is the first using objective sleep parameters by video-polysomnography while investigating the association with psychological functioning. Third, previous studies in children with enuresis investigated only 1 or 2 domains of psychological functioning [5, 42], assuming that children with enuresis only have problems on the investigated domains. This study investigates extensively the psychological functioning in a homogeneous group of children with MNE in an explorative way.

However, this study has some limitations. First, the lack of a control group of children without enuresis and without sleep problems. Due to financial and ethical reasons, this was not achievable. Second, the definition of NP of >100 % expected bladder capacity does not follow the International Children's Continence Society (ICCS) standardization paper and may be subject for criticism [28]. To our defence, we want to emphasize that the ICCS definition of >130 % is an expert opinion-based definition. The recent data from the Aarhus group in a control population demonstrates that the 100 % definition is more relevant in defining NP and/or desmopressin response

[34]. These recent data are not yet incorporated in the ICCS paper [28]. Patients with NP of >130 % expected bladder capacity are at the end of the spectrum. This would neglect a major proportion of the population with a mismatch between an increased nocturnal diuresis and a normal bladder volume.

Third, the male-to-female ratio is not according to literature. During inclusion period, more male children were eligible for the study. This selection bias could influence the results. Finally, the sleep is not measured in the natural environment of the children. The possible influence of a first night can be a limitation, a bias that was also present in the reference population. An individual night-to-night variability of PLMS in children is demonstrated. However, it is random and not likely to skew the group-level analysis [31]. Moreover, our study group investigated previously children with NE and controls; both groups have a possible first night effect. Even though, children with NE have a higher PLMS index and a more fragmented sleep than controls [13].

This study identifies in children with MNE associated with NP the relationship between sleep parameters and psychological functioning of the child according to the child, the parents, and the teachers. In children with MNE associated with NP, PLMS index is associated with a lower QoL of the child. Further research should elucidate the association between sleep and psychological functioning.

**Ethical standards** The study was approved by the Institutional Ethics Board of the Ghent University Hospital (B670201212). Therefore, it has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Written consent was obtained from all patients and their parents prior to their inclusion in the study.

**Conflict of interest** The authors declare that they have no conflict of interest.

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