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REGULAR ARTICLE

Association between the frequency of bedwetting and late preterm birth in children aged ≥5 years

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ABSTRACT

Aim: We examined the associations between late preterm (LPT) birth children aged ≥5 years and the frequency of bedwetting. Moreover, those who were born full-term/low birthweight (BW), LPT/low BW, LPT/normal BW and LPT/low BW were compared.

Methods: In total, we evaluated 614 patients who underwent assessments for frequent bedwetting at the three hospitals from January 2014 to December 2016. Data at the initial visit were collected from the electronic medical records. We assessed the patients' bladder diaries and questionnaires containing detailed information on demographics and frequency of bedwetting per month. Neonatal data were collected from the Maternal and Child Health Handbook.

Results: Frequency of bedwetting in the LPT/low BW group was higher than in the term/low BW group (28 vs. 22.5, $p < 0.05$). However, the frequency between the LPT/normal BW group and the LPT/low BW group was not significantly different (28 vs. 28, $p = 1.00$). Multiple regression analyses were conducted to eliminate potential confounding factors, attention-deficit/hyperactivity disorder and intellectual disability, but results were not changed.

Conclusion: This study revealed that LPT/low BW was associated with increased frequency of bedwetting in children. The results suggest that gestational age should be considered when examining patients with severe bedwetting.

INTRODUCTION

Nocturnal enuresis (NE), or pathological bedwetting, is a common health problem in childhood. Approximately 10% of 7-year-old children wet the bed regularly during sleep (1). According to the International Children's Continence Society, NE is defined as intermittent incontinence during sleep in a child aged ≥5 years in the absence of congenital anomalies of the urinary tract or congenital or acquired defects of the central nervous system (2). Although the cause of NE remains unclear, the standard view is that enuresis results from high arousal thresholds and either nocturnal polyuria or nocturnal detrusor overactivity (3). Importantly, NE is known to negatively affect the child's psychosocial status, such as declining self-esteem, and to be associated with a range of psychological or behavioural problems, such as attention-deficit/hyperactivity disorder (ADHD) (4–7). Several epidemiological surveys have been undertaken to determine the perinatal factors associated with NE; however, conflicting findings regarding the relevance of birthweight (BW) on NE have been reported, whereby NE has been shown to be associated with low BW

Abbreviations
ADHD, Attention-deficit/hyperactivity disorder; BW, Birthweight; DQ, Developmental quotient; LPT, Late preterm; NE, Nocturnal enuresis; SD, Standard deviation.

Key notes

- The association between late preterm (LPT) birth and the frequency of bedwetting is unknown.
- LPT/low birthweight (BW) is associated with an increased risk of more frequent bedwetting in children aged ≥5 years compared with those who were born full-term/low BW.
- The clinical assessment of the frequency of bedwetting in LPT birth children is important because some potential adverse sequelae later in life are associated with bedwetting severity.

(defined as <2500 g) in some studies and unrelated in others (8–15). Furthermore, little information is available regarding the relationship between NE and gestational age, especially late preterm (LPT) birth.

Late preterm birth infants are defined as those born at 34-0/7 to 36-6/7 weeks' gestational age (16,17). This population represents a growing proportion of preterm deliveries and has traditionally been neglected, because they are thought to behave similarly to term infants. However, several studies have shown that they are vulnerable not only during the first few weeks of life, but also later on in infancy and childhood (18–20). Furthermore, some potential adverse sequelae of LPT birth persist later in life, including cerebral palsy, intellectual disability, cognitive problems, attention problems and psychological or behavioural problems (18–20). However, studies estimating the prevalence of NE in LPT children aged ≥5 years are lacking. Therefore, our study aimed to examine whether NE was associated with LPT birth in children at aged ≥5 years.

PATIENTS AND METHODS

The present study was a retrospective, observational, cohort study performed at three Juntendo University hospitals: Urayasu Hospital, Chiba, Japan; Shizuoka Hospital, Shizuoka, Japan; Nerima Hospital, Tokyo, Japan.

Study population

We evaluated 614 patients who underwent assessments for frequent NE (>4 per week) at the three university hospitals from January 2014 to December 2016. The children in our study had a mean of age 8 years (5–15 years), and 65% were boys. They were all recruited from outpatient clinic.

Frequent NE was defined as intermittent bedwetting during sleep in children aged ≥5 years and bedwetting >4 times/week according to the International Children's Continence Society (2). Patients were excluded if they had a history of congenital kidney and urinary tract abnormalities, a history of glomerular disease (e.g. nephrotic syndrome and nephritis) and intrauterine growth restriction which was weight <3% according to gestational age.

Procedure

Data at the initial visit were collected from the electric medical records of the three participating hospitals. We assessed the patients' bladder diaries and questionnaires containing detailed information on demographics and bedwetting severity (frequency of bedwetting per month). Neonatal data (birthweight and gestational age) were collected from the Maternal and Child Health Handbook, which are distributed to all pregnant women by the local government in Japan to record maternal and child medical and health information during pregnancy and after birth. A parent-reported questionnaire on ADHD and intellectual disability was also conducted at the initial visit to hospital. Consequently, parent-identified mental and behavioural problems were evaluated by a paediatric neurologist. Intellectual disability was defined as developmental quotient (DQ) <75 according to Kyoto Scale of Psychological Development test, and Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V) consensus criteria were used for ADHD diagnosis (21,22).

Statistical analysis

Results are expressed mean ± standard deviation (SD) for continuous variables and count (%) for categorical variables. For intergroup comparisons, the Student's *t*-test for continuous variables and the Pearson's chi-square test for categorical variables were performed. When data were not assumed to be normally distributed, median interquartile range values are presented, and the Wilcoxon rank-sum test was used for intergroup comparison. In addition, multiple regression analysis was performed to adjust the presence of ADHD and intellectual disability. All analyses were performed with SAS software version 9.4 (SAS Institute Inc, Cary, NC, USA), and categorical variables and differences were considered statistically significant at $p < 0.05$.

Ethics approval and consent

This study was approved by the Institutional Ethics Committees of Juntendo University Urayasu Hospital (approval No.: 290-45), Juntendo University Shizuoka Hospital (approval No.: 532) and Juntendo University Nerima Hospital (approval No.: 17-32) and performed in accordance with applicable laws and regulations, good clinical practice and the Declaration of Helsinki (23).

RESULTS

Participants' characteristics

Of the 614 identified for recruitment, 544 were enrolled in this study. Five boys were excluded because of a history of renal malformations, one boy had a history of nephrotic syndrome was excluded, and 64 cases were not added to the analysis because information on the electric medical record was uncertain. The flow chart for enrolment is shown in Figure 1. Low BW was reported for 77 (14.2%) of the 544 participants with NE and preterm birth was reported for 41 (7.5%) of the 544 participants with NE. Of the children with a low BW, 48 (8.8%) were born at term and 16 (2.9%) were born LPT. With regard to preterm birth, 11 (2.0%) were born preterm (<34 weeks) and 30 (5.5%) were born LPT. Furthermore, 12 (2.2%) LPT children had a normal BW.

Comparison between term/low BW and LPT/low BW

There were no significant differences between the term/low BW and LPT/low BW groups for age at initial visit or birthweight, except for gestational age (37.9 vs. 35.3, $p < 0.05$; Table 1). The frequency of bedwetting per month was higher in the LPT/low BW group than in the term/low BW group (28 vs. 22.5, $p < 0.05$) at the initial visit. Multiple regression analyses were also conducted to eliminate potential confounding factors, including ADHD and intellectual disability. However, no differences were observed in the results ($p = 0.0073$). On the basis of sex, birthweight was significantly higher and the frequency of bedwetting per

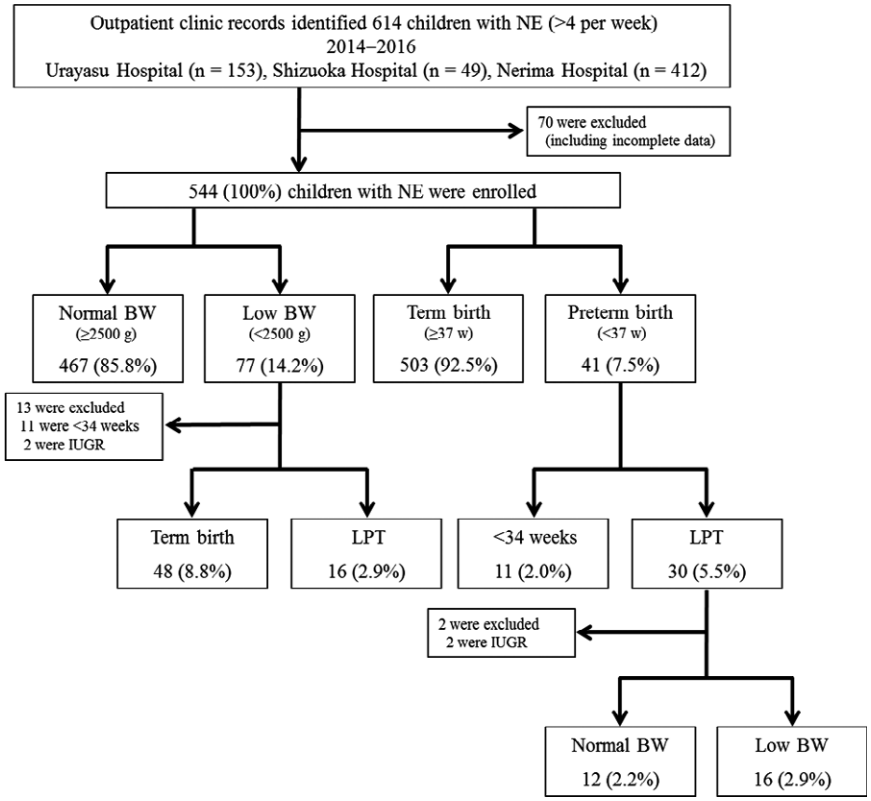

Figure 1 Flow chart for enrolment in this study. NE, nocturnal enuresis; BW, birthweight; IUGR, intrauterine growth restriction, LPT, late preterm.

month was significantly lower for boys in the term/low BW group than those in the LPT/low BW group. There were no significant differences regarding psychological or behavioural problems between the two groups or according to sex.

Comparison between LPT/normal BW and LPT/low BW

There were no significant differences between the LPT/normal BW and LPT/low BW groups for age at initial visit or gestational age, except for birthweight (2851 g vs. 2227 g, $p < 0.05$; Table 2). There was no significant difference in the frequency of bedwetting per month between the LPT/normal BW and LPT/low BW groups (28 vs. 28, $p = 1.00$) at the initial visit. Multiple regression analyses were also conducted to eliminate potential confounding factors, including ADHD and intellectual disability. However, no differences were observed in the results ($p = 0.80$). In all the factors, there was no significant difference between boys and girls.

DISCUSSION

We herein report that LPT birth is associated with an increased risk of more frequency of bedwetting in children aged ≥5 years, whereas low BW children are not at an increased risk of more frequency of bedwetting. Therefore, it is important to check the number of gestational age when examining patients with severe NE. Furthermore, on the basis of the results of this study, health providers who follow-up LPT birth children should pay attention to the coexistence of NE. Increased knowledge of the risk factors of frequency of bedwetting is needed to identify LPT birth children at risk of future problems attaining and maintaining continence. Although there is some evidence that early risk factors, including a developmental delay and premature birth, are linked to bedwetting, no previous studies have focused on the association between bedwetting frequency and LPT birth in children aged ≥5 years. Hence, we believe that our report is worthwhile.

Even decades ago, although premature birth was never specifically considered as the primary cause of NE, several studies have reported the association between BW and NE recently (8–13). A retrospective cohort study conducted in the United States showed that a low BW carries an increased risk of prolonged bedwetting (8). Furthermore, Jarvelin et al. (9) reported that low BW children had a higher frequency of bedwetting than children with a normal BW in a random sample of 3206 7-year-old Finnish children, leading the authors to speculate that NE cases with neurological damage and delayed maturation were because of the low BW. In contrast, these are some studies that report no association between low BW and NE (12,13). A large US study showed that bedwetting in children aged ≥5 years, irrespective of its frequency, was associated with increased rates of behavioural problems, but not with BW on the basis of three categories (<1500 g; 1500–2499 g; >2499 g) (12). Of note, in Japan, Kawauchi et al. reported no association between BW and NE at three and 5 years of

Table 1 A characteristic and the result of the frequency of bedwetting between term/low BW and LPT/low BW

	Low BW					
	Term birth			LPT birth		
Parameters	All (n = 48)	Boys (n = 27)	Girls (n = 21)	All (n = 16)	Boys (n = 11)	Girls (n = 5)
Age at initial visit (years)	7.4 ± 1.5	7.4 ± 1.4	7.5 ± 1.6	8.1 ± 1.5	8.1 ± 1.8	8.0 ± 0.7
Gestational age (weeks)	37.9 ± 1.0*	38.1 ± 1.0*	37.7 ± 1.1*	35.3 ± 0.8	35.1 ± 0.8	35.8 ± 0.5
Birthweight (g)	2393 (2291–2446)	2410* (2304–2446)	2352 (2268–2418)	2227 (2128–2407)	2180 (2120–2402)	2305 (2178–2412)
Frequency of bedwetting (times per month)	22.5* (14–28)	14* (7–28)	28 (14–28)	28 (21–28)	28 (14–28)	28 (28–28)
Intellectual disability	1 (2.1%)	1	0	2 (12.5%)	1	1
ADHD	5 (10.4%)	3	2	3 (18.8%)	2	1

BW = birthweight; LPT = late preterm; ADHD = attention-deficit/hyperactivity disorder; SD = standard deviation.
Values are the mean ± SD, median (interquartile range) or number (%). In addition to overall comparisons, boys and girls were analysed separately. Asterisk (*) indicates statistically significant differences between groups ($p < 0.05$).

Table 2 A characteristic and the result of the frequency of bedwetting between LPT/normal BW and LPT/low BW

	LPT					
	Normal BW (>2500 g)			Low BW		
Parameters	All (n = 12)	Boys (n = 8)	Girls (n = 4)	All (n = 16)	Boys (n = 11)	Girls (n = 5)
Age at initial visit (years)	7.6 ± 1.8	7.5 ± 2.1	7.8 ± 1.3	8.1 ± 1.5	8.1 ± 1.8	8.0 ± 0.7
Gestational age (weeks)	35.7 ± 0.5	35.6 ± 0.5	35.8 ± 0.5	35.3 ± 0.8	35.1 ± 0.8	35.8 ± 0.5
Birthweight (g)	2851* (2693–3085)	3009* (2778–3202)	2672* (2643–2777)	2227 (2128–2407)	2180 (2120–2402)	2305 (2178–2412)
Frequency of bedwetting (times per month)	28 (22.5–28)	28 (22.5–28)	28 (24.5–28)	28 (21–28)	28 (14–28)	28 (28–28)
Intellectual disability	0 (0%)	0	0	2 (12.5%)	1	1
ADHD	1 (8.3%)	1	0	3 (18.8%)	2	1

BW = birthweight; LPT = late preterm; ADHD = attention-deficit/hyperactivity disorder; SD = standard deviation.
Values are the mean ± SD, median (interquartile range) or number (%) In addition to overall comparisons, boys and girls were analysed separately. Asterisk (*) indicates statistically significant differences between groups ($p < 0.05$).

age, but that head circumference for boys and developmental delays in speaking and walking maybe important enuretic factors (13). However, in these reports, the coexistence of psychological or behavioural problems in low BW children was not thoroughly investigated; thus, it is still unclear if low BW itself is strongly related to NE. Taken together, these findings suggest that debate regarding the association between low BW and NE is still ongoing.

Meanwhile, limited information is available regarding the association between gestational age and NE (14,15). Touchette et al. (14) found that females who were still bedwetting at the age of 53 months were born prematurely (<37 gestational weeks) compared with all nonbedwetting groups combined through a survey of 1666 Canadian children at the ages of 29, 41 and 53 months. The authors, however, reported that there was no association between low BW and NE. Possible reasons explaining the significantly higher prevalence of NE in 4.5-year-old girls who were born prematurely were not well discussed. In addition, Sullivan et al. (15) reported little evidence that gestational age or low BW is associated with increased risk of NE in a longitudinal study of 8769 children in the UK; however, they did not investigate the relationship between LPT birth and NE in detail.

In the past decades, the association between NE and ADHD is well recognised. In a recent review of 7-year-old children, 10% had NE and 5%–10% had ADHD, whereby ADHD and NE coexisted at much higher rates than expected by chance, and an interaction was present (24). Among children with NE, approximately 15%–19% were reported to have ADHD, and vice versa, and comorbid ADHD has been identified as a risk factor for treatment resistance in NE (25,26). By contrast, there are several reports on the relationship between NE and intellectual disability. In particular, some of these reports were about complications, including syndromes and chromosomal diseases (27,28). Recently, Basiri et al. reported that boys with primary NE had a lower intelligence quotient compared with the control group only in low-income district (29).

In the present study, the coexistence rate of ADHD and intellectual disability was not significantly different between the two NE groups of term/low BW and LPT/low BW. Similarly, there was no significant difference in the coexistence rate of ADHD and intellectual disability between the two NE groups of LPT/normal BW and LPT/low BW. We regarded these reasons as follows. First, the number of NE patients who had coexistence ADHD and/or intellectual disability was small. Second, paediatric neurologists could not evaluate the parent-reported questionnaire because of underestimation. Lastly, NE patients with mild psychological and behavioural symptoms did not meet the diagnostic criteria were included. In addition, almost all of the patients were aged around 8 years at the initial visit; therefore, the study population may have included cases in which behavioural problems and learning difficulties became apparent after the school life progressed. Overall, when examining NE patients in clinical practice, even if ADHD and/or intellectual disability is not recognised at that time, the course of NE and coexistence of ADHD and/or intellectual disability caused by LPT birth should be followed if the patient has a high frequency of bedwetting. It may be important to pay attention to symptoms that appear late or delayed.

Strengths and limitations

The present study has key strengths. To the best of our knowledge, this is the first report that focused on the association between the frequency of bedwetting and LPT birth in children aged ≥5 years. However, a larger sample size would have increased the significance of our results.

The present study involved several limitations that should be considered. First, this study was not a prospective study and the participants do not reflect the general population, but rather visit university hospitals with a referral letter. However, in this study, among patients with NE, 41 out of 544 (7.5%) were born prematurely, and 77 (14.2%) of 544 were born with a low BW. These demographic data show similar prevalence rates to those previously reported (4–15). Taken together, it can be considered to show a general tendency in the proportion of enuresis patients who were born prematurely. Second, a potential limitation of this study is the reliance on parental reports of children's bedwetting frequency. It is unlikely that a child's bedwetting would go entirely unnoticed by parents, and most parents will be able to provide a reasonably accurate estimate of the frequency of bedwetting because of being woken by these occurrences and having to deal with wet sheets. Errors in paternal reporting of bedwetting frequency are, however, possible, especially if there is an inconsistent pattern of bedwetting. Third, we did not determine if the NE children had monosymptomatic NE or nonmonosymptomatic NE. Monosymptomatic NE is defined by International Children's Continence Society as enuresis in children without any other lower urinary tract symptoms (2). Even if the patients with congenital kidney and urinary tract abnormalities were excluded from this study, patients with underlying bladder dysfunction, for example overactive bladder, may have been included. Fourth, the individual administration of NE treatment at the initial visit was not unified. Epitropakis et al., however, reported that medication is even more difficult when the population has intellectual and behavioural disabilities (30). Furthermore, behavioural factors, such as hyperactivity and inattention, likely play an important role, as they can affect the child's ability to appropriately respond to the need to urinate. Thus, when LPT children have underlying coexistence of psychological or behavioural problems, it is assumed that there is a difficulty of treatment that it is difficult to adhere to medication compliance, cannot keep drinking restrictions before sleep or does not urinate before going to bed. Therefore, regardless of whether the condition is under treatment or not, the possibility that the frequency of bedwetting had increased was considered. Fifth, medical complications, treatments, special schooling and medications were not considered because we were unable to collect data about these factors due to the retrospective nature of the study. Finally, we were unable to analyse the complete group and compare term, normal BW children with the NE patients in the risk groups born at term or with normal BW because we did not routinely assess the perinatal history of this normal NE patient group.

However, these limitations would not explain the association between bedwetting frequency and LPT birth. Although considered benign, NE can affect children emotionally, socially, and cognitively (4,5), and in LPT children with developmental problems, it may be better to actively intervene with treatment in order to maintain a healthy mental state when NE is severe. The secondary psychological consequences of bedwetting, although not a life-threatening symptom as such, should not be underestimated. Suffering from NE has a major impact on the child and his/her family. This secondary effect of enuresis is often underestimated. As demonstrated in the present study, we may need to focus on NE and LPT birth children from both prospective and longitudinal viewpoints. In addition, healthcare providers who have the opportunity to care for LPT birth children should be conscious of association with NE in later life.

CONCLUSION

Late preterm birth is a predictive factor for frequent bedwetting in children. We believe that the clinical assessment of the frequency of bedwetting in LPT birth children is

important, because some potential adverse sequelae of LP birth persist later in life, including developmental problems that are associated with bedwetting frequency.

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CONFLICT OF INTERESTS

All authors have no personal or financial conflict of interests to disclose.

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