

•ORIGINAL RESEARCH ARTICLE•

Risk Factors of Nocturnal Enuresis in Children with Attention Deficit Hyperactivity Disorder

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Background: Presence of attention deficit hyperactivity disorder (ADHD) has a negative effect on the resolution of incontinence; however, there are few studies which investigated the risk factors of nocturnal enuresis (NE) in patients with ADHD.

Aims: This study was conducted to investigate the prevalence of NE and its risk factors in children with ADHD.

Methods: 331 children, aged 6 to 10 years, diagnosed as having ADHD were enrolled in this study. The diagnosis of ADHD was confirmed by an experienced child and adolescent psychiatrist according to DSM-IV-TR. NE was defined as nighttime wetting with or without daytime incontinence, at least twice a week over a period of 3 months or longer in children 5 years old and older without anatomical abnormalities. Details on demographic data, perinatal history, medical history and developmental history were collected from parents or medical records.

Results: Most of the ADHD patients with inattentive subtype (77.5%) had NE, compared to 31.7% in the hyperactive/impulsive subtype and 22.5% in the combined subtype ($p < 0.001$, $t = 42.71$). Among children with enuresis, there were significantly higher rates of history of familial enuresis (26% vs. 18%, $p < 0.001$, $t = 16.9$), cesarean delivery (47% vs. 33%, $p = 0.019$, $t = 5.84$) and history of neonatal sepsis (16% vs. 7%, $p = 0.018$, $t = 5.62$) than non-NE children. Moreover, patients with NE had lower birth weight than non-NE patients (2.93(0.65) vs. 3.09 (0.46), $p = 0.026$, $t = 2.51$). Also, low parental education was associated with increase in the rate of NE.

Conclusion: Children with ADHD have a high prevalence of NE. Male sex, low education level of parents, history of neonatal sepsis, positive family history of NE, low birth weight and caesarian delivery may be risk factors for NE in ADHD children. Most ADHD patients with inattentive subtype had NE.

Key words: nocturnal enuresis, ADHD, risk factors

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1. Introduction

Attention deficit hyperactivity disorder (ADHD) is a common neurobehavioral disorder in children, which is manifested by impulsive, hyperactive, and inattentive behaviors.^[1] The worldwide prevalence of ADHD in children is about 5%, with no significant difference

among different geographic regions.^[2] It is reported that 50 % of children with ADHD suffer from psychiatric comorbidities that often continue into adulthood.^[3,4]

Children with ADHD commonly experience sleep problems such as resistance towards going to bed and night awakenings.^[5,6] These problems are usually

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originated from non-biological causes, but can also be the result of undiagnosed biological sleep problems such as restless leg syndrome (RLS), sleep disordered breathing (SDB) or nocturnal enuresis (NE),^[7] which are associated with poorer daily functioning.^[6] NE is defined as urinary incontinence during sleep in children older than 5 years after excluding organic causes.^[8]

The prevalence of NE in patients with ADHD has been estimated to be 28-32%.^[9, 10] The association between NE and ADHD has been investigated in several previous studies.^[11-16] The etiology of NE has been demonstrated to be associated with neurological maturation. Previous studies have reported that children with NE had a higher incidence of delayed language and gross motor development.^[17-21] It was shown that the presence of ADHD had a negative effect on the resolution of incontinence and treatment of urinary incontinence in children with ADHD compared to those without ADHD.^[22]

Although, different studies demonstrated the role of neonatal sepsis,^[23] head injury,^[24] low birth weight,^[25] prematurity and gestational age^[25, 26] as risk factors for ADHD, there are few studies which investigated the risk factors of NE in patients with ADHD. This study was conducted to investigate the prevalence of NE and its risk factors in children with ADHD.

2. Methods

2.1 Participants

This study was approved by the Research Council and Ethical Committee of the Kermanshah University of Medical Science and carried out between September 2014 and August 2015. Written informed consent was obtained from all participants' parents. During the

study period, we consecutively enrolled 344 children, aged 6 to 10 years, diagnosed as having ADHD as well as children with confirmed ADHD who presented for the follow-up in the Psychiatric Clinics of Farabi Hospital, Kermanshah, Iran. Children with other mental disorders such as mental retardation, intellectual disability (i.e., IQ<70), pervasive developmental disorder, seizure, and urinary tract infection/disorders were excluded from the study.

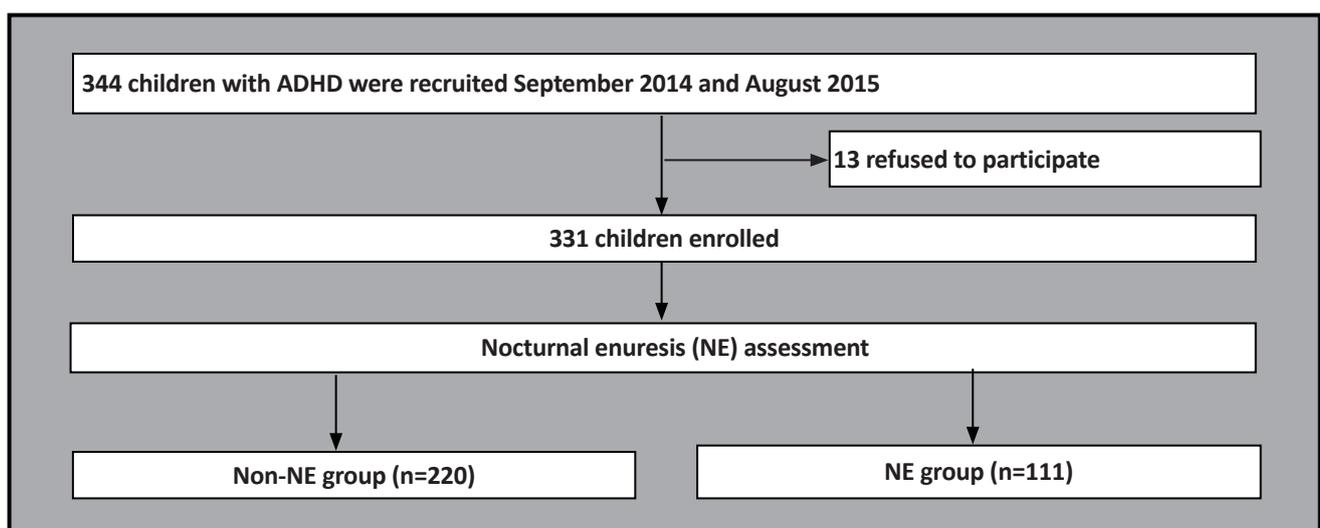
The diagnosis of ADHD was confirmed by an experienced child and adolescent psychiatrist according to DSM-IV-TR^[27] and the ADHD rating scale (ADHD-RS).^[28] The ADHD-RS includes 18 items that each shows one ADHD symptom according to DSM-IV-TR criteria. It may be used for ages ranging from 5 to 18 years and is useful for differentiation of ADHD and healthy children, and differentiates attention deficit symptoms from hyperactivity and impulsivity symptoms. The ADHD-RS has been used extensively in Iran and the reliability of this instrument showed alpha Cronbach's as 0.81.^[28]

NE was defined as nighttime wetting with or without daytime incontinence, at least twice a week over a period of 3 months or longer in children 5 years old and older without anatomical abnormalities. NE was diagnosed by a pediatric urologist and was examined by urinalysis, renal sonography, and interview with children and their parents. Details on demographic data, perinatal history, medical history and developmental history were collected from parents or medical records.

2.2 Statistical analysis

Statistical analysis was conducted using SPSS version 19.0. The Student t-test and χ^2 test were used to compare the variables between the groups. A *p* value of less than 0.05 was regarded as significant.

Figure 1. Flowchart of the study



3. Results

During the 11 month study period, from 344 children with ADHD, 13 children were excluded from the study and the 331 remaining children with a diagnosis of ADHD were enrolled in this study. Mean (sd) age of study participants was 7.9 (1.3) years (range 6-11 years) and 205 of them were boys. A total of 49 children were diagnosed with the inattentive subtype (14.8%), 104 with the hyperactive/impulsive subtype (31.4%) and 178 with the combined subtype (53.8%) according to the DSM-IV-TR criteria (Table 1). The prevalence of NE among the 331 children with ADHD was 33.5% (111/331). So, we divided the children with ADHD into two groups according to presence of NE and assessed risk factors between the two groups.

Table 1. Demographic data of participants (n=331)	
Mean (sd) age in years	7.9 (1.3)
Sex (m)	205 (61.9)
ADHD subtype	
Inattentive	49 (14.8)
Hyperactive/Impulsive	104 (31.4)
Combined	178 (53.8)
Data presented as mean (SD) or number (%)	

The mean (sd) age of ADHD diagnosis was slightly higher in the NE group, but did not reach statistical significance (5.7 (1.9) in NE group vs. 5.2 (1.9) in non-NE group; $p=0.055$, $t=2.48$). Furthermore, compared with the non-NE group, significantly more children with NE were boys ($p=0.007$, $t=7.28$).

Among children with enuresis, there was a significantly higher rate of history of familial enuresis (26% vs. 18%, $p<0.001$, $t=16.9$), cesarean delivery (47% vs. 33%, $p=0.019$, $t=5.84$) as well as history of neonatal sepsis (16% vs. 7%, $p=0.018$, $t=5.62$) compared to non-NE children. Moreover, patients with NE had a lower birth weight than non-NE patients (2.93 (0.65) vs. 3.09 (0.46), $p=0.026$, $t=2.51$). Regarding parents education level, our results showed that low parental education was associated with increase in the rate of NE ($p<0.001$, $t=56.17$) (Table 2).

There was a significant difference between the non-NE and NE groups with respect to ADHD subtype. Most of the ADHD patients with inattentive subtype (38/49 patients (77.5%)) had NE, compared to 33/104 patients (31.7%) in hyperactive/impulsive and 40/178 patients (22.5%) in combined subtypes ($p<0.001$, $t=42.7$) (Table 2).

There were no significant differences in terms of gestational age at birth, history of neonatal icter, and motor or language developmental delay, between the NE and non-NE groups. Furthermore, the rate of Ritalin

use was more among non-NE children compared with NE, however, this difference did not reach statistical significance (49% in NE group vs. 59% in non-NE group; $p=0.084$, $t=2.99$) (Table 2).

Enuresis was most common in children 7 to 9 years of age. Incidence of NE was the following: children aged <7 years, 52 children (46.8%), aged 7-7.9 years, 20 children (18%), children aged 8-8.9 years, 26 children (23.4%), children aged 9-9.9 years, children aged >10 years, only 8 (7.2%) and 5 (4.5%) children had enuresis, respectively.

4. Discussion

4.1 Main findings

The aim of this study was to better understand the correlation between nocturnal enuresis and ADHD as well as the risk factors of NE in children with ADHD. Comorbidity of ADHD and nocturnal enuresis has been shown in several studies.^[9-13] In our study, the prevalence of NE in children with ADHD was 33.5%. This is roughly in agreement with other studies which reported 32% and 28.3% prevalence rate of NE in children with ADHD.^[9,10] The exact pathogenesis of the high incidence of NE in ADHD children is not clear. It has been suggested that delay in maturation of the central nervous system could account for the association between enuresis and ADHD.^[18-20] Also, a brainstem inhibition deficit in children with enuresis, could explain why they are unable to remain dry at night.^[18] Several previous studies have suggested that primary NE happens when a child with ADHD can't wake up when the urinary bladder is full or be awake enough to get up and go to the toilet when there is an urge to urinate.^[19-21]

In our study, most of the enuretic children were 6-8 years old. In a study of the prevalence of ADHD in enuretic children in Belgium, the older children (9 to 12 years), had a higher prevalence of ADHD.^[21] However, in a study by Yang et al in Taiwan, the mean (sd) ages of enuretic and nonenuretic children with ADHD were 7.53 (1.06) and 7.26 (1.03) respectively, which was not a statistically significant difference ($p=0.04$).^[9]

Yang et al found no association between NE and birth weight, gestational age, type of delivery, neonatal icter, and maternal education in children with ADHD.^[9] However we found a significant correlation between birth weight as well as type of delivery and NE in ADHD. Our data revealed that children with NE had lower birth weight than non-NE children, and also, children who were given birth by caesarian had a higher risk for developing NE. It has been shown that low birth weight was significantly associated with delay in achieving all developmental milestones including walking alone, meaning speech, and bedwetting cessation.^[29] We also investigated the correlation between parental education and NE and concluded that the lower parental educational level was associated with higher prevalence of NE in ADHD children.

Table 2. Comparison of risk factors between groups

	Non-NE group (n=220)	NE group (n=111)	Statistics	p
Age (mean [sd])	5.2 (1.9)	5.7 (1.9)	t= 2.48	0.055
Sex (Male)	125 (56.8)	80 (72)	$\chi^2=7.28$	0.007
ADHD subtype (%)				
Inattentive (n=49)	11 (22.5)	38 (77.5)	$\chi^2=42.71$	<0.0001
Hyperactive/Impulsive (n=104)	71 (68.3)	33 (31.7)		
Combined (n=178)	138 (77.5)	40 (22.5)		
Familial history of NE(%)	20 (9)	29 (26.1)	$\chi^2=16.97$	<0.0001
Delivery by cesarean section (%)	73 (33.1)	52 (46.8)	$\chi^2=5.84$	0.019
Birth weight (mean [sd])	3.09 (0.46)	2.93 (0.65)	t=2.51	0.026
Gestational age at birth (mean [sd])	37 (1.2)	37 (0.5)	t=0.78	0.938
History of neonatal icter (%)	62 (28.1)	36 (32.4)	$\chi^2=0.64$	0.424
History of neonatal sepsis (%)	17 (7)	18 (16.2)	$\chi^2=5.62$	0.018
Motor or language developmental delay (%)	9 (4)	10 (9)	$\chi^2=3.29$	0.069
Ritalin use (%)	131 (59)	55 (49)	$\chi^2=2.99$	0.084
Parents education (%)				
Illiterate	2 (1)	18 (16)	$\chi^2=56.17$	<0.0001
Elementary school	77 (35)	33 (30)		
High school	99 (45)	59 (53)		
Academic	42 (19)	1 (1)		

In our study, children who had a history of neonatal sepsis had a higher risk for developing NE compared with children without a history of neonatal sepsis. Although the association of neonatal sepsis and NE is not clear and the origin of sepsis in our cases was unknown, some studies showed that a history of infection, especially urinary tract infection, was significantly associated with NE. It may be due to the negative effects of infection on the lower urinary tract. It has been shown that vesicoureteral reflux (VUR) might be more frequent in children with NE with intermittent daytime incontinence.^[30]

In the present study, a meaningful association was seen between family history of NE and developing NE in patients with ADHD. This may indicate the role of genetics in NE in children with ADHD. Norgaard et al., in their review reported that when both parents were enuretic as children, their offspring had a 77% risk of having nocturnal enuresis. The risk was 43% when one parent was enuretic and 15% when neither parent was enuretic.^[31] Furthermore, Bailey et al., reported a positive family history enuresis in 65-85% of children with NE. If the father or the mother was enuretic as a child, the relative risk for his/her child was 7.1 and

5.2, respectively.^[32] In addition, certain chromosomal loci (5, 13, 12, and 22) have been implicated in nocturnal enuresis,^[33, 34] of which suggestive linkage to chromosomes 12 and 13 were shown in children with ADHD.^[35]

In our study, 77.5% of ADHD children with inattentive subtype had NE, compared to 31.7% in the hyperactive/Impulsive subtype and 22.5% in the combined subtype. Baeyens et al showed that 15% of all enuretic children were diagnosed with the full syndrome of ADHD, an additional 22.5% and 2.5% met the DSM-IV criteria of the ADHD predominantly inattentive and predominantly hyperactive impulsive subtypes, respectively. Their study revealed a brainstem inhibition deficit in children with enuresis, which could explain why they are unable to remain dry at night. When additional attention is allocated to specific trials in the task, children with attention deficit hyperactivity disorder of the predominantly inattentive subtype, failed to optimize sensory gating. With respect to enuresis, this could result in an identification problem of bladder signals, leading to an inadequate or absent arousal effect in attention deficit hyperactivity disorder of the predominantly inattentive subtype.^[36]

4.2 Limitations

The main limitation of this study is that the findings were based on interviews with children and their parents and in using this retrospective method some details may have been overlooked.

4.3 Implications

The investigation of the risk factors of NE in patients with ADHD provides useful information about neonatal, familial and environmental factors affecting the prevalence of NE in ADHD patients.

5. Conclusions

Children with ADHD have a high prevalence of NE. Factors like male sex, low educational level of parents, history of neonatal sepsis, positive family history of NE, low birth weight and caesarian delivery may be risk factors for NE in ADHD children. Most of the children diagnosed as having ADHD inattentive subtype had NE.

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No funding was obtained for this study.

Conflict of interest statement

The authors declare no conflict of interest related to this manuscript.

Ethical approval

All procedures were approved by the institutional ethics committee of the Kermanshah University of Medical Sciences (KUMS)

Informed consent

Written consent and/or assent were obtained from the parents.

Authors' contributions

Study design: HK & HA

Assessments: HK, FE, HA & MRM

Data analysis: MRG

Questionnaire evaluation: HK, MRG, FE, HA & MRM

Manuscript writing: HK & MRG

儿童注意缺陷多动障碍夜间遗尿的风险因素研究

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背景: 儿童注意力缺陷多动障碍 (attention deficit hyperactivity disorder, ADHD) 的存在对其夜间遗尿 (nocturnal enuresis, NE) 的治疗不利; 然而, 较少有研究对 ADHD 患者的夜间遗尿的危险因素进行研究。

目的: 本研究旨在探讨儿童 ADHD 患者夜间遗尿的患病率及其危险因素。

方法: 研究对象为 331 名 6-10 岁的儿童, 由儿少精神病学专家根据 DSM-IV-TR 的诊断标准明确诊断 ADHD。NE 的诊断标准为年龄 5 岁以上, 每周夜尿至少两次, 持续 3 个月或更长时间, 夜间不自主排尿, 伴有或不伴有日间尿失禁, 无任何神经系统症状和体征, 无泌尿系统疾病。有关人口数据、围产期病史、既往病史的详细资料均从父母或医疗记录中收集的。

结果: 注意力缺陷亚型的 ADHA 患儿有 77.5% 伴发夜

间遗尿症, 而在多动 / 冲动亚型为 31.7%、混合亚型为 22.5% 的 ($p < 0.001$, $t = 42.71$)。在有遗尿症的患儿中, 家族性尿失禁的发生率明显较高 (26% 比 18%, $p < 0.001$, $t = 16.9$), 剖腹产率 (47% 对 33%, $p = 0.019$, $t = 5.84$), 新生儿败血症史 (16% 与 7%, $p = 0.018$, $t = 5.62$), 高于非 NE 患儿。此外, 有 NE 的患者的出生体重低于非 NE 患者 (2.93(0.65) 和 3.09(0.46), $p = 0.026$, $t = 2.51$)。此外, 父母低教育程度与 NE 的高发生率有关。

结论: ADHD 患儿的 NE 患病率较高。男性、父母低教育程度、新生儿败血症史、家族性尿失禁史、低出生体重和剖腹产都可能是 ADHD 患儿的 NE 患病的危险因素。大多数注意力缺陷亚型的患儿都伴发 NE。

关键词: 夜间遗尿; ADHD; 危险因素

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