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Association Between Non-hemolytic Anemia and Urinary Incontinence in Children Over 3 Years: A Case-control Study

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ABSTRACT

Background and Aim: Urinary incontinence represents a significant pediatric health concern affecting children beyond the age of expected physiological control, with a substantial impact on quality of life. Anemia, particularly iron deficiency, is a widespread global health issue affecting a large proportion of children worldwide. This study aimed to evaluate the association between non-hemolytic anemia and urinary incontinence in children over three years of age.

Methods: This case-control study included 260 children aged 3-16 years, divided into two equal groups: 130 children with non-hemolytic anemia (hemoglobin <11 g/dL) and 130 age- and sex-matched healthy controls. Participants were assessed for various types of urinary incontinence through structured interviews with parents using standardized questionnaires. Statistical analysis included the chi-square test, descriptive statistics, and logistic regression analysis to calculate odds ratios.

Results: While general urinary incontinence showed no significant association with anemia (OR: 1.32; 95% CI, 0.81-2.16), monosymptomatic enuresis was significantly more prevalent in the anemic group (30.8% vs. 6.2%, P<0.001), with an odds ratio of 6.77 (95% CI, 3.02-15.18). Conversely, underactive bladder was less common in anemic children (10.0% vs. 19.2%, P=0.035, OR: 0.46, 95% CI, 0.22-0.95). Among anemic children with urinary disorders, iron deficiency was the most common type, present in 49.4% of cases with urinary incontinence and 52.5% of cases with monosymptomatic enuresis.

Conclusion: This study provides evidence for a significant association between non-hemolytic anemia and monosymptomatic enuresis in children over three years of age. Anemia screening should be considered in children presenting with monosymptomatic enuresis, particularly in regions with high rates of iron deficiency. Future research should explore the mechanisms behind these associations and assess whether treating anemia can improve enuresis symptoms.

Keywords: Urinary incontinence, Pediatrics, Enuresis

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Introduction

Urinary incontinence, defined as the involuntary loss of urine, represents a significant pediatric health concern that affects children beyond the age of expected physiological control. While most children achieve urinary control by the age of five, persistent incontinence beyond this age warrants clinical evaluation and can manifest in various forms, including monosymptomatic nocturnal enuresis (MNE), non-monosymptomatic enuresis nocturna (NMNE), and isolated daytime incontinence. This condition significantly affects children's quality of life, with studies indicating that its psychological burden is comparable to other chronic conditions, such as bronchial asthma and diabetes mellitus [1]. Given its complex etiology, urinary incontinence in children may be indicative of underlying bladder dysfunction, neurological issues, or other physiological abnormalities requiring thorough clinical assessment and management.

Nocturnal enuresis (NE), commonly known as bedwetting, is a prevalent childhood disorder characterized by repeated involuntary urination during sleep in children aged five years and older who have completed toilet training. According to standardized diagnostic criteria, NE is defined as bedwetting occurring at least twice a week for three consecutive months [2]. Although highly prevalent, the underlying mechanisms of nocturnal enuresis remain incompletely understood and are likely multifactorial [3]. Bladder control generally develops by around three years of age, with nighttime dryness solidifying by age four. Consequently, deviations from expected bladder control in children over three years old are considered clinically significant, justifying the focus of research on this population [4].

Anemia, defined as a deficiency in hemoglobin—the protein essential for oxygen transport in the blood—is a widespread global health issue, affecting approximately 1.6 billion people worldwide [5]. The World Health Organization (WHO) has reported that anemia affects 30% of children aged 0-4 years and 48% of children aged 5-14 years in developing countries [6]. Hemoglobin, a vital component of red blood cells synthesized in the bone marrow, requires iron for effective oxygen binding. Anemia is diagnosed when hemoglobin levels fall below the normal reference range for age, generally defined as being 5% lower than the standard for a given population [7]. Among the various causes of anemia, iron deficiency is the most prevalent, particularly in populations with high growth rates and suboptimal nutritional intake [8]. In Iran, as in many other countries, iron deficiency anemia is the leading cause of anemia in children. Emerging evidence suggests that systemic disorders, including anemia, may influence bladder function and the prevalence of urinary disorders.

Given the systemic symptoms and potential complications of chronic anemias, such as thalassemia and iron deficiency anemia—including effects on the cardiovascular system, kidneys, bones, and cognitive function [9-12]—a deeper understanding of their relationship with urinary disorders is warranted. Several studies have investigated possible links between iron metabolism and bladder; however, findings remain inconsistent.

The present study aimed to evaluate the association between non-hemolytic anemia and urinary incontinence in children over the age of three. If a significant relationship exists between anemia and urinary incontinence, early detection and treatment of anemia may serve as a potential strategy to improve the quality of life in affected children. Given that anemia encompasses both congenital conditions, such as thalassemia, and acquired conditions, such as iron deficiency, understanding their impact on urinary control may provide valuable insights into pediatric health management.

Materials and Methods

This case-control study was conducted in 2019 at the Pediatric Clinic of Amir Kabir Hospital, Arak, to evaluate the relationship between urinary incontinence and non-hemolytic anemia in children older than three years. Participants were selected using an accessible sampling method from children who visited the pediatric clinic. The study included two groups: The case group, consisting of children diagnosed with non-hemolytic anemia based on a pediatrician's assessment and confirmed with a blood test showing hemoglobin levels below 11 g/dL, and the control group, comprising age- and sex-matched children with no history, symptoms, or laboratory evidence of anemia.

Children in both groups were assessed for urinary incontinence and urinary disorders through structured interviews with parents. The different types of incontinence were explained in detail before parents responded to a standardized questionnaire. Systemic symptoms, such as fatigue, weakness, and lethargy were recorded to aid in anemia diagnosis. A pediatrician confirmed the anemia diagnosis through clinical evaluation and a complete blood count (CBC) test, using hemoglobin levels below 11 g/dL as the diagnostic threshold. The control group was randomly selected from children reporting urinary incontinence but with normal

hemoglobin levels. A structured checklist recorded participants' demographic information, study group assignment, urinary incontinence type, and relevant medical history. Data collection was performed by trained medical interns under the supervision of a pediatrician.

Inclusion criteria for the case group included children over three years of age diagnosed with non-hemolytic anemia, with no history of thalassemia major or underlying conditions affecting urinary continence, and whose parents provided informed consent. The control group included children over three years old attending routine pediatric check-ups without anemia or other blood disorders, and whose parents provided informed consent. Children were excluded if they had systemic diseases known to cause urinary incontinence, such as diabetes mellitus, anatomical or functional urinary tract disorders, or diabetes insipidus. Those with a diagnosis of thalassemia major, hemolytic anemia, or neuromuscular disorders contributing to incontinence were also excluded from the study. Informed consent was obtained from the parents of all study participants, and confidentiality was maintained for all personal and medical information. The study adhered to ethical guidelines and received approval from the relevant institutional review board. Descriptive statistics, including frequency, percentage, Mean±standard deviation, were used for data summarization. Normality was assessed using appropriate statistical tests. An independent t-test and ANOVA were used for normally distributed data, while the chi-square test was applied to categorical variables. Logistic regression analysis was performed to calculate odds ratios for enuresis in relation to anemia. All statistical analyses were conducted using Stata software version 11, with significance set at $P<0.05$.

Results

This case-control study included 260 children aged 3 to 16 years, with a mean age of 6.71±3.08 years. The participants were divided into two equal groups: 130 children diagnosed with non-hemolytic anemia and 130 healthy children. The mean age in the non-anemic (healthy) group was slightly higher (6.95 years) compared to the anemic group (6.47 years), but this difference was not statistically significant (P=0.211). The standard deviation for age across both groups was 3.08. Regarding gender distribution, 50% of the total participants were female. There was no significant difference in gender distribution between the case and control groups (P=0.215) (Table 1).

Among the children in the anemia group, iron deficiency anemia was the most common type, accounting for 50% of cases. Other types included anemia due to other causes (35.4%), thalassemia syndromes (12.3%), and congenital aplastic anemia (2.3%) (Table 2).

Analysis of urinary incontinence prevalence showed that its frequency was slightly higher in children with anemia compared to the healthy group. However, this difference did not reach statistical significance (P=0.261). The odds ratio for urinary incontinence in children with anemia compared to healthy children was 1.32 (95% CI, 0.81-2.16), indicating no statistically significant association. In the control group, 68 children had urinary incontinence, while 62 did not. In the anemia group, 77 children had urinary incontinence, whereas 53 did not (Table 3).

Table 1. Gender frequency in participants

Gender	No. (%)			P
	Healthy	Anemic	Total	
Female	70(53.8)	60(46.2)	130(50.0)	0.215
Male	60(46.2)	70(53.8)	130(50.0)	

Table 2. Frequency of different types of anemia in the subjects

Type	No. (%)	95% Confidence Interval
Iron deficiency	65(50)	41-58
Thalassemia syndromes	16(12.3)	2.2-7.19
Congenital aplastic anemia	3(2.3)	0.6-4.5
Other causes of anemia	46(35.4)	2.2-27.44

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Table 3. Analysis and comparison of frequency of urinary incontinence and enuresis in the study children

Variables	Groups	No. (%)		P*	Odds Ratio	Confidence Interval
		Present	Absent			
Urinary incontinence	Anemic	77(59.2)	53(40.8)	0.261	1.32	0.2-81.16
	Healthy	68(52.3)	62(47.7)	0.261	1.32	0.2-81.16
Non-monosymptomatic enuresis	Anemic	16(12.3)	113(87.7)	0.555	1.26	0.2-58.74
	Healthy	13(10.0)	113(90.0)	0.555	1.26	0.2-58.74
Monosymptomatic enuresis	Anemic	40(30.8)	90(69.2)	0.000	6.77	Present=3.02 Absent=0.18-15
	Healthy	8(6.2)	122(93.8)	0.000	6.77	Present=3.02 Absent=0.18-15
Vaginal voiding	Anemic	2(1.5)	128(98.5)	0.151	0.32	0.1-6.63
	Healthy	6(4.6)	124(95.4)	0.151	0.32	0.1-6.63
Underactive bladder	Anemic	13(10.0)	117(90.0)	0.035	0.46	0.0-22.95
	Healthy	25(19.2)	105(80.8)	0.035	0.46	0.0-22.95
Overactive bladder	Anemic	4(3.1)	126(96.9)	0.096	0.37	0.1-11.23
	Healthy	10(7.8)	119(92.2)	0.096	0.37	0.1-11.23
Pollakiuria	Anemic	16(12.3)	114(87.7)	0.999	1	0.2-47.09
	Healthy	16(12.3)	114(87.7)	0.999	1	0.2-47.09
Giggle incontinence	Anemic	17(13.1)	113(86.9)	0.856	0.93	0.1-45.90
	Healthy	18(13.8)	112(86.2)	0.856	0.93	0.1-45.90

*The significance limit was calculated using the chi-square test and at the confidence level of 95%.

Further analysis of enuresis subtypes revealed that the prevalence of asymptomatic bedwetting was slightly higher in the anemic group compared to the healthy group, but this difference was not statistically significant (P=0.555). However, the frequency of monosymptomatic enuresis was significantly higher in the anemic group (P=0.000), with an odds ratio of 6.77 (95% CI, 3.02-15.18). The prevalence of non-monosymptomatic enuresis was slightly higher in the anemia group, but this difference was also not statistically significant (P=0.555) with an odds ratio of 1.26 (95% CI, 0.58-2.74) (Table 3).

Among children with anemia and urinary incontinence, iron deficiency anemia was the most frequently observed type, affecting 49.4% of cases. The second most common category, accounting for 38.4% of cases, included children with anemia due to causes other than iron deficiency (e.g. thalassemia syndromes and congenital aplastic anemia). In children with asymptomatic enuresis and anemia, iron deficiency anemia was observed in 43.8% of cases. Similarly, in children with monosymptomatic enuresis and anemia, iron deficiency anemia was the most prevalent type, present in 52.5% of cases.

Regarding other urinary disorders, of the total patients with urinary issues, 77 had urinary incontinence, 16 had non-symptomatic nocturia, 40 had symptomatic nocturia, two had vaginal voiding, 13 had underactive bladder, four had overactive bladder, 16 had pollakiuria, and 17 had urge incontinence. In the anemia group, 68 children had urinary incontinence, 13 had non-symptomatic nocturia, eight had symptomatic nocturia, and six had vaginal voiding. Among children with urge incontinence and anemia, iron deficiency anemia was present in 58.8% of cases. The prevalence of underactive bladder in children with anemia was 53.8% for those diagnosed with iron deficiency anemia. However, in children with pollakiuria and anemia, the proportion of iron deficiency anemia decreased to 31.3% but remained the most common type.

The odds ratio of vaginal voiding in children with anemia compared to healthy children was 0.32 (95% CI, 0.06-1.63), which was not statistically significant (P=0.151). The prevalence of underactive bladder was significantly lower in the anemia group compared to the healthy group (P=0.035), with an odds ratio of 0.46 (95% CI, 0.22-0.95). The frequency of overactive bladder was lower in the anemia group compared to the healthy group, but this difference was not statistically significant (P=0.096), with an odds ratio of 0.37 (95% CI, 0.11-1.23). Pollakiuria was equally prevalent in both the anemia and healthy groups (P=0.999), with an odds ratio of 1.00. The frequency of giggle incontinence was slightly lower in the anemia group compared to the healthy group, but this difference was not statistically significant (P=0.856), with an odds ratio of 0.93 (95% CI, 0.45-1.90) (Table 4).

Discussion

This study investigated the relationship between non-hemolytic anemia and urinary incontinence in children over three years of age. While no significant association was found between anemia and general urinary incontinence, we observed a strong link between anemia and monosymptomatic enuresis. Children with anemia were nearly seven times more likely to experience monosymptomatic enuresis compared to their healthy counterparts. Additionally, an unexpected inverse relationship was noted between anemia and underactive bladder.

Our findings align with prior research suggesting a possible connection between anemia and nocturnal enuresis. For instance, Esezobor et al. and Field et al. reported an increased prevalence of nocturnal enuresis in anemic children, supporting our observed association with monosymptomatic enuresis [13, 14]. In contrast, Albayrak et al. did not find a similar association [15], and such discrepancies may be explained by differences in study populations, definitions of enuresis, or methodological approaches.

Iron plays a key role in dopaminergic neurotransmission, which regulates bladder control. Although a direct link between iron deficiency and bladder innervation is not well established, studies have shown that iron deficiency reduces neuronal nitric oxide synthase (nNOS) levels in smooth muscle, impairing relaxation [16]. This suggests a potential mechanism, through which iron deficiency may contribute to increased monosymptomatic enuresis.

These findings suggest a potential role for iron deficiency in enuresis. Although conventional treatments for nocturnal enuresis, such as tricyclic drugs and alarm therapy, have shown varying degrees of short-term efficacy—with many children relapsing once treatment ceases [17]—addressing underlying iron deficiency may provide an additional avenue to improve outcomes for children with monosymptomatic enuresis. Further research is needed to determine whether treating iron deficiency can improve enuresis outcomes.

Conclusion

This study provides evidence for a significant association between non-hemolytic anemia and monosymptomatic enuresis in children over three years of age. While anemia was not predictive of urinary incontinence in general, it substantially increased the likelihood of

Table 4. Frequency of different types of anemia in children with urinary incontinence and enuresis

Type	No. (%)							
	Urinary Incontinence	Non-monosymptomatic Enuresis	Monosymptomatic Enuresis	Vaginal Voiding	Underactive Bladder	Overactive Bladder	Pollakiuria	Giggle Incontinence
Iron deficiency	38(49.4)	7(43.8)	21(52.5)	1(50.0)	7(53.8)	1(25.0)	5(31.3)	10(58.8)
Thalassemia syndromes	8(10.4)	2(12.5)	1(2.5)	0(0.0)	2(15.4)	1(25.0)	3(18.8)	2(11.8)
Congenital aplastic anemia	3(3.9)	0(0.0)	3(7.5)	0(0.0)	0(0.0)	0(0.0)	0(0.0)	0(0.0)
Other causes of anemia	28(36.4)	7(43.8)	15(37.5)	1(50.0)	4(30.8)	2(50.0)	8(50.0)	5(29.4)
Total	77	19	40	2	13	4	16	17

monosymptomatic enuresis. Conversely, anemia was associated with a lower prevalence of underactive bladder, suggesting a complex interplay between hematological health and urinary control.

Our findings suggest that anemia screening should be considered in children presenting with monosymptomatic enuresis, particularly in regions with high rates of iron deficiency. Future research should explore the mechanisms behind these associations and assess whether treating anemia can alleviate enuresis symptoms. By advancing our understanding of the connections between systemic conditions and urinary function, this study contributes to more comprehensive and effective management strategies for pediatric urinary disorders.

Despite its strengths, this study has several limitations. The case-control design precludes definitive conclusions about causality, and although our sample size was adequate for initial analysis, larger and more diverse populations may be needed to uncover subtler associations. Additionally, the reliance on parental reporting for enuresis history introduces potential recall bias, which may affect the accuracy of the data.

Suggestions for future studies

To further clarify the relationship between anemia and enuresis, future studies should focus on conducting longitudinal studies to determine whether treating anemia leads to improvements in enuresis symptoms. Additionally, exploring biological mechanisms that link iron metabolism to bladder function through neurophysiological assessments would provide further insights. Another important avenue of research would be investigating the impact of anemia treatment, such as iron supplementation, on the resolution of nocturnal enuresis.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Arak University of Medical Sciences (Code: IR.ARAKMU.REC.1399.225).

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Authors' contributions

Conceptualization: Parsa Yousefichaijan and Vahid Falahati; Methodology: Hassan Taherahmadi; Software: Hassan Taherahmadi; Validation: Parsa Yousefichaijan, Vahid Falahati, and Nooshin Sadjadei; Formal analysis: Hassan Taherahmadi; Investigation: Nooshin Sadjadei; Resources: Parsa Yousefichaijan; Data curation: Negin Adimi; Writing and original draft preparation: Negin Adimi; Writing, review, and editing: Arshia Mobini and Amir Mahdi Mohamadi Kamal; Visualization: Hassan Taherahmadi; Supervision: Parsa Yousefichaijan; Project administration: Negin Adimi; Funding acquisition: Negin Adimi.

Conflict of interest

The authors declared no conflict of interest.

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