Etiology and pathology of enuresis among primary school children in Isfahan, Iran

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ABSTRACT

Objective: To determine the etiology and pathogenesis of enuresis among primary school children by using a special ultrasound (US) protocol for the assessment of bladder dysfunction and to compare excretion of urinary sodium and calcium in enuretic children.

Methods: We conducted this cross sectional study on 66 enuretic children aged 6-12 years from September 2005 to January 2006 in Isfahan University of Medical Sciences, Iran. Ultrasound (US) was designed for the evaluation of bladder parameters using bladder volume and wall thickness index (BVWI%), and expected percentage bladder volume index for kidney volume.

Results: Sixty children (90.9%) had nocturnal enuresis, 5 (7.5%) had diurnal enuresis and one child (1.6%) had nocturnal and diurnal enuresis. Urinary infection was detected in one child (1.5%). The incidence of urinary system abnormalities was 10.6% in all enuretic children. Hypercalciuria was seen in 9.2% and natriuresis in 20.3%. Normal bladder function (BVWI 70% to <130%) was seen in 67%, small bladder with a thick wall (BVWI <70%) in 27% and large bladder capacity with a thin wall (BVWI >130%) was seen in 6% of children with primary nocturnal enuresis (PNE). There was a significant difference in BVWI between children with PNE and secondary nocturnal enuresis (p=0.01).

Conclusion: Enuresis is a common problem among school children and associated urinary abnormalities are not uncommon. Our results show that US measured bladder parameters can provide useful clues for the underlying bladder dysfunction and may help to guide clinical management.

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Enuresis is the involuntary voiding beyond the age of the anticipated control.[1] It is a common problem among children and adolescents, and can lead to important social and psychological disturbance.[2] Nocturnal enuresis (NE) is defined as: 1. Bed-wetting during sleep at least 2 times per week in a child aged 5 years or more for duration of at least 3 months according to the American Psychiatry Association (DSM IV) criteria and 2. bed-wetting during sleep at least once a month in a child aged >5 years for a duration of at least 3 months according to the World Health Organization (ICD10) criteria.[3,4] Diurnal enuresis is defined as wetting while awake after the age of 3 years. When the wetting occurs continually, while asleep or awake, this condition is accepted as nocturnal and diurnal enuresis. We distinguished enuresis as primary and secondary. Primary nocturnal enuresis is bedwetting in a child aged >5 years who have never been dry for extended periods, while secondary nocturnal enuresis (SNE) is the onset of wetting after a continued dry period of more than 6-12 months.[3,4] Nocturnal enuresis is a heterogeneous disorder and there is much confusion regarding the etiology and pathogenesis of it. Three of the main causes that we considered are nocturnal polyuria, nocturnal detrusor hyperactivity and abnormally deep sleep.[5] Conflicting evidence has also been published about the possible vasopressin deficiency of bedwetters, and solute diuresis as well as water diuresis have been considered to explain the polyuria of these children.[5-7] Hypercalciuria has been claimed to be important in the pathogenesis of enuresis. This association, if true, can explain that hypercalciuria reduces the vasopressin-mediated renal concentrating ability.[8,9] Reduced functional bladder capacity and bladder dysfunction in the pathogenesis of

primary nocturnal enuresis, especially when refractory to treatment has become an important role in several studies.[10-12] Accurate assessment of bladder dysfunction associated with voiding dysfunction often necessitates invasive urodynamic (UD) studies. Yeung et al[12] demonstrated that US measured bladder parameters in patients with PNE correlated with the UD findings can provide useful predictive clues for the underlying bladder dysfunction as well as treatment outcome. The aim of this study was to determine the etiology and pathogenesis of enuresis among primary school children by measuring urinary calcium, sodium, and US measured bladder parameters.

Methods. A cross-sectional population-based study was conducted in 4500 children aged between 6 and 12 years from September 2005 to January 2006 at the Department of Pediatrics, Isfahan University of Medical Sciences, Isfahan, Iran. Permission was obtained from the Ministry of Education. Accoding to our previous study[13] there were 84951 students (41678 girls and 43273 boys) attending the primary school in Isfahan. When we took the estimated prevalence as 12% and marginal error as 1.5%, at 95% confidence interval, the least number of children needed to represent 84951 students was 3600. The sample was further increased by 25% to account for contingencies such as non-responder. Because Isfahan is a large city, a random cluster-sampling scheme was used to obtain a representative sample of primary school children from various districts. Data were collected via a questionnaire and a written informed consent was obtained.

The frequency of NE was divided into 4 categories: >3 times per week, <3 times per week, one time per 2 weeks, and one time per month. From an overall response rate of 69.9%, the enuresis was reported in 216 children (7%), comprising 6.2% for nocturnal enuresis according to ICD10 and 3.3% according to DSM IV, 0.5% for diurnal enuresis, and 0.8% for combined day and night wetting. Primary nocturnal enuresis was reported in 166 children (5.3%).[13] Two hundred and sixteen enuretic children and their parents were invited to the outpatient clinic of the Pediatric Nephrology Department. We reevaluated and categorized enuretic children accurately and diagnosed and managed appropriately the probable underlying urinary abnormalities. Before initiating the study, permission was granted from the Ethics Committee of Isfahan University, Isfahan, Iran and from all the participating families. The exclusion criteria were history of cardiovascular disease, endocrinopathy (diabetes mellitus, diabetes insipidus), psychiatric problems, renal tubular acidosis and renal failure. All of the enuretic children from our previous epidemiologic study were included in this study. A detailed history was taken from 66 patients, and a pediatric nephrologist carried out a thorough physical examination. Urine specimens were analyzed, and urine cultures were performed. On day 2, we collected the morning urine sample and assessed the sodium, calcium, and creatinine. Hypercalciuria was defined as urinary calcium to urinary creatinine ratio greater than 0.21mg/mg. Natriuresis was defined as urinary sodium to urinary creatinine ratio greater than 51 mol/mol in children aged 5-7 years, 42 mol/mol in 7-10 years, and 34 mol/mol in 10-14 years.[14] In a child with clinical findings suggestive of urinary tract infection (fever, nausea, vomiting, loin pain, dysuria, frequency, urgency incontinence, so forth) the presence of more than 10^5 colony counts per deciliter confirms the diagnosis of urinary tract infection. Ultrasonographic examination of the urinary system was performed on all patients. Scans were performed with the patient supine using Toshiba Just vision 200 with a 5 MHz frequency probe. Children were scanned in a standard supine position. Both renal volumes were measured and calculated using a standard formula for an ovoid, length times maximum transverse short axis diameter times maximum transverse long axis diameter times 0.523. The transverse diameter was taken in a plane transverse to the long axis of the child and at the maximum cross-sectional area, which was usually at or near the renal hilum to give the total renal volume, The bladder volume index was calculated based on the equation, BVI = longitudinal plane (LS) times maximum transverse plane (TS) times maximum anteroposterior diameter (AP). The maximum length of the bladder (LS) was measured from the fundus of the bladder to the internal opening of the urethra. After the probe was turned 90 degrees to the transverse plane (TS), the maximum transverse diameter and maximum anteroposterior diameter (AP) were measured. The BVI was repeated and bladder emptying efficiency was calculated from BVI maximum - BVI empty/BVI maximum as a percentage. If it was >90%, the child was judged to have normally emptied and if it was >90%, the child was asked to void a second time. Bladder wall thickness measurements consider reliable if the bladder emptying was >90% of a maximally full bladder. We applied the transducer transversely in the sagittal plane of the abdomen to measure the bladder wall thickness.We calculated the mean bladder wall thickness as an average of the 3 measurements (BT = [anterior wall thickness plus lateral wall thickness plus posterior wall thickness]/3). The bladder volume and wall thickness index were calculated as bladder volume and wall thickness index (BVWI%) = (measured BVI maximum/measured BT). This volume was then expressed as a percentage of the expected from reference standard values of children with a normal urinary tract in accordance with the study of Leung et al.[15]

According to BVWI measurements enuretic children was divided into 3 groups: 1. BVWI <70% (implying smaller bladders with a thicker wall), 2. 70% to <130% (implying normal bladders), 3. BVWI >30% (relatively larger bladder capacity with relatively thinner walls).[12]

Statistical analysis. The data were compiled and analyzed using the Statistical Package for Social Sciences (version 11.5) program. The comparison between enuretic groups (primary enuresis group versus secondary enuresis and diurnal enuresis group versus nocturnal enuresis and PNE versus SNE) regarding the BVWI% was tested using x^2 test with a $p<0.05$ was considered statistically significant.

Results. From all the enuretic children who were invited to the outpatient clinic only 30% (66 children) attended. Sixty children (90.9%) had nocturnal enuresis, 5 (7.5%) had diurnal enuresis and one child (1.6%) had nocturnal and diurnal enuresis. The characteristics of the study population are shown in **Table 1**. Only 21% of children had no family history of enuresis. Nocturnal enuresis was more frequent in boys (44 [73%]) than in girls (16 [27%]) (p=0.593). Diurnal enuresis was more frequent in boys than girls (3 versus 2) (p=0.759). The severity of NE for the 4 categories of frequency >3 wet nights/week, <3 wet nights/week, 2 wet nights/2 weeks and one wet night/month were 75%, 11.5%, 7.8%, 5.7%. Physical examination of all enuretic children revealed no abnormal findings. The mean urinary calcium to urinary creatinine ratio was 0.10±0.08 in nocturnal and 0.14±0.11 in diurnal enuretic children (p=0.289). The mean urinary sodium to urinary creatinine ratio was 25.16±18.52 in PNE and 24.35±17.10 in SNE children (p=0.91). Seven children with PNE and natriuresis had more than 3 wet nights/week. The mean urinary calcium to

Table 1 - Characteristics of the study population.

Variable	Enuresis n=66	Nocturnal n= 60		Diurnal n= 5		Diurnal and nocturnal enuresis n=1
		Primary n=52	Secondary n=8	Primary n=3	Secondary n=2	
Age						
6-7 years	14 (21.0)	13 (25.0)	-	1 (33.0)	-	
7-8 years	15 (23.0)	10 (19.0)	4 (50.0)	1 (33.0)	-	
8-9 years	14 (21.0)	11 (21.0)	3 (37.5)	-	-	
9-10 years	14 (21.0)	11 (21.0)	1 (12.5)	-	1 (50.0)	1 (100)
10-11 years	5 (7.5)	5 (10.0)	-	-	-	
11-12 years	4 (6.5)	2 (4.0)	-	1 (33.0)	1 (50.0)	
Gender						
Male	49 (74.0)	39 (75.0)	5 (62.5)	3 (100.0)	1 (50.0)	1 (100)
Female	17 (26.0)	13 (25.0)	3 (37.5)	-	1 (50.0)	-
Positive history of enuresis in father	43 (65.2)	36 (69.0)	3 (37.5)	1 (33.0)	2 (100.0)	1 (100)
Positive history of enuresis in mother	23 (34.8)	20 (38.5)	1 (12.5)	2 (66.0)	-	-
Hypercalciuria	6 (9.2)	5 (9.6)	-	1 (50.0)	-	-
Natriuresis	12 (18.1)	9 (17.3)	2 (25.0)	1 (50.0)	-	-
BVWI						
<70%	18 (27.0)	14 (27.0)	2 (25.0)	2 (66.0)	-	-
70% to <130%	42 (64.0)	35 (67.0)	3 (37.5)	1 (33.0)	2 (100.0)	1 (100)
>130%	6 (9.0)	3 (6.0)	3 (37.5)	-	-	-

Data are expressed as number and (%). BVWI - bladder volume and wall thickness index

urinary creatinine ratio was 0.10±0.08 and 0.10±0.04 in children with PNE and SNE respectively (p=0.83). Simultaneous hypercalciuria was seen in 3 of them. Urinary infection was detected in one child (1.5%) with nocturnal enuresis. The incidence of urinary system abnormalities was 10.6% in all the enuretic patients. Urinary system abnormalities were seen in 5 children (9.6%) with PNE and in one child (12.5%) with SNE. Reflux was seen in 2 children (3.8%) with PNE. These abnormalities included the horse-shoe kidney with bilateral reflux (n=1), a small trabeculated bladder with multiple diverticula and narrowing at the junction of posterior and anterior urethra without reflux (n=1), left sided high grade reflux (n=1), small sized kidney with mild hydronephrosis (n=1), small sized and ectopic right kidney with mild pelvicalyceal stasis (n=1), kidney stone and a small ureterocele (n=1) and bilateral grade II hydronephrosis without urethral reflux (n=1). Bladder volume and wall thickness index as percentage of the expected from reference values are shown in **Table 1**. There was a significant difference in BVWI between PNE and SNE (p=0.01). There was a significant difference in BVWI between primary and secondary enuresis (p=0.04).

Discussion. The overall prevalence of nocturnal hypercalciuria was lower (9.2%) in our study compared with the study of Aceto et al (39.7%).[6] Valenti et al[8] also revealed that hypercalciuria might cause enuresis in some patients, probably by altering aquaporin-2 (AQP2), trafficking and thus decreasing aquaporin excretion in the urine.[8] Pace et al[16] demonstrated that hypercalciuria can be responsible for nocturnal enuresis and can be treated with the combination of diet and Desmopressin. In contrast, Neveus et al[7] showed that hypercalciuria is not central to the pathogenesis of enuresis. We think that genetic predisposition or regional differences in the intake of sodium and calcium may explain the diversity in prevalence of nocturnal hypercalciuria. In this study, a larger amount of sodium excretion at night was seen in 15.2% children with PNE. Several studies revealed that a disturbed circadian rhythm of sodium excretion existed in children with enuresis.[17-19] Kuznetsova et al[20] suggested that a tubular defect in reabsorption of ions may explain increased nocturnal diuresis and renal sodium excretion in enuretic children. In the present study, similar to Cayan et al[21] (1.88%) and Gur et al's[2] studies (1.5%), the incidence of urinary infection was lower compared with Hansen et al[22] study (9.3% in the enuretic girls and 2.5% in the enuretic boys). Twenty-nine percent of 7-8-years-old Danish school entrants were found voiding symptoms suggesting bladder dysfunction as a predisposing factor to infections.[22] However, Cayan et al[21] also found no difference in the incidence of urinary tract infection between NE and control groups. The prevalence of reflux is higher among enuretics compared with other studies. However, the characteristics of reflux in enuretics are still unclear.[23] The incidence of reflux in our study is lower compared with Kawauchi et al[23](6.4%) and Sujka et al[24] (16 %). the higher incidence of reflux in previous reports is probably were based on data of voiding cystourethrography (VCUG), which was primary carried out on enuretic children. The incidence of urologic abnormalities was higher in our patients compared with the studies of Miguelez Lago et al[25] (5.4%) and Gur et al[2] (7.1%). However, at least one urological abnormality was detected in 20.2% of the 446 enuretics who underwent VCUG, cytometry and intravenous pyelography or renal ultrasonography in Kawauchi et al[23] study. One of the limitations of this study is the lack of control group to compare urinary system abnormalities between children with and without enuresis. Yeung et al[12] revealed statistically significant correlations between BVWI and treatment response. According to their results, a value of normal BVWI (70-130) was highly predictive of normal bladder function and good treatment response to desmopressin. Additionally, Rushton et al[26] showed that a small functional bladder capacity is predictive of a poor response to desmopressin therapy. In our study, 33% of children with PNE had abnormal BVWI. This rate is low in comparison with Yeung et al[12] study (65%). This could be explained by the fact that patients had severe enuretic symptoms and abnormal daytime urodynamic was seen in 70% of them.

In conclusion, enuresis is a common problem among school children and associated urinary abnormalities are not uncommon. Our results demonstrate that US measured bladder parameters can provide useful clues for the underlying bladder dysfunction and may help to guide clinical management. Hypercalciuria may have a role in nocturnal enuresis. There is a subset of bedwetters associated with high nocturnal natriuria. Nocturnal polyuria and natriuria may interfere with vasopressin levels during the night.

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References

1. Kanaheswari Y. Epidemiology of childhood nocturnal enuresis in Malaysia. ***J Paediatr Child Health*** 2003; 39: 118-123.
2. Gur E, Turhan P, Can G, Akkus S, Sever L, Guzeloz S, et al. Enuresis: prevalence, risk factors and urinary pathology among school children in Istanbul, Turkey. ***Pediatr Int*** 2004; 46: 58-63.

3. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. DSM IV, 4th ed. Washington (DC): American Psychiatry Press; 1995.
4. World Health Organization. The ICD-10 classification of Mental and Behavioral Disorders: diagnostic criteria for Research. Geneva: WHO; 1993.
5. Neveus T, Tuvemo T, Lackgren G, Stenberg A. Bladder capacity and renal concentrating ability in enuresis: pathogenic implications. ***J Urol*** 2001; 165 (6 Pt 1): 2022-2025.
6. Aceto G, Penza R, Coccioli MS, Palumbo F, Cresta L, Cimador M, et al. Enuresis subtypes based on nocturnal hypercalciuria: a multicenter study. ***J Urol*** 2003; 170 (4 Pt 2): 1670-1673.
7. Neveus T, Hansell P, Stenberg A. Vasopressin and hypercalciuria in enuresis: a reappraisal. ***BJU Int*** 2002; 90: 725-729.
8. Valenti G, Laera A, Pace G, Aceto G, Lospalluti ML, Penza R, et al. Urinary aquaporin 2 and calciuria correlate with the severity of enuresis in children. ***J Am Soc Nephrol*** 2000; 11: 1873-1881.
9. Martin PY, Schrier RW. Role of aquaporin-2 water channels in urinary concentration and dilution defects. ***Kidney Int Suppl*** 1998; 65: S57-S62.
10. Yeung CK, Chiu HN, Sit FK. Bladder dysfunction in children with refractory monosymptomatic primary nocturnal enuresis. ***J Urol*** 1999; 162 (3 Pt 2): 1049-1054; discussion 1054-1055.
11. Yeung CK, Sit FK, To LK, Chiu HN, Sihoe JD, Lee E, et al. Reduction in nocturnal functional bladder capacity is a common factor in the pathogenesis of refractory nocturnal enuresis. ***BJU Int*** 2002; 90: 302-307.
12. Yeung CK, Sreedhar B, Leung VT, Metreweli C. Ultrasound bladder measurements in patients with primary nocturnal enuresis: a urodynamic and treatment outcome correlation. ***J Urol*** 2004; 171 (6 Pt 2): 2589-2594.
13. Azhir A, Frajzadegan Z, Adibi A, Hedayatpoor B, Fazel A, Divband A. An epidemiological study of enuresis among primary school children in Isfahan, Iran. ***Saudi Med J*** 2006; 27: 1572-1577.
14. Guignard JP, Santos F. Laboratory investigations In: Niaudet P, Avner ED, Harmon WE, editors. Pediatric Nephrology. 5th Ed. Baltimore (MD): Williams & Wilkins Co; 2004. p. 400.
15. Leung VY, Chu WC, Yeung CK, Sreedhar B, Liu JX, Wong EM, et al. Nomograms of total renal volume, urinary bladder volume and bladder wall thickness index in 3,376 children with a normal urinary tract. ***Pediatr Radiol*** 2007; 37: 181-188. Epub 2006 Dec 15.
16. Pace G, Aceto G, Cormio L, Traficante A, Tempesta A, Lospalluti ML, et al. Nocturnal enuresis can be caused by absorptive hypercalciuria. ***Scand J Urol Nephrol*** 1999; 33: 111-114.
17. Raes A, Dehoorne J, Hoebeke P, Van Laecke E, Donckerwolcke R, Vande Walle J. Abnormal circadian rhythm of diuresis or nocturnal polyuria in a subgroup of children with enuresis and hypercalciuria is related to increased sodium retention during daytime. ***J Urol*** 2006; 176: 1147-1151.
18. Kamperis K, Rittig S, Jorgensen KA, Djurhuus JC. Nocturnal polyuria in monosymptomatic nocturnal enuresis refractory to desmopressin treatment. ***Am J Physiol Renal Physiol*** 2006; 291: F1232-F1240. Epub 2006 Jun 27.
19. Rittig S, Matthiesen TB, Pedersen EB, Djurhuus JC. Sodium regulating hormones in enuresis. ***Scand J Urol Nephrol Suppl*** 1999; 202: 45-46.
20. Kuznetsova AA, Natochin YV, Papayan AV. Osmoregulatory function of the kidney in enuretic children. ***Scand J Urol Nephrol*** 1998; 32: 132-137.
21. Cayan S, Doruk E, Bozlu M, Akbay E, Apaydin D, Ulusoy E, et al. Is routine urinary tract investigation necessary for children with monosymptomatic primary nocturnal enuresis? ***Urology*** 2001; 58: 598-602.
22. Hansen A, Hansen B, Dahm TL. Urinary tract infection, day wetting and other voiding symptoms in seven- to eight-year-old Danish children. ***Acta Paediatr*** 1997; 86: 1345-1359.
23. Kawauchi A, Kitamori T, Imada N, Tanaka Y, Watanabe H. Urological abnormalities in 1,328 patients with nocturnal enuresis. ***Eur Urol*** 1996; 29: 231-234.
24. Sujka SK, Piedmonte MR, Greenfield SP. Enuresis and the voiding cystourethrogram: a re-evaluation. ***Urology*** 1991; 38: 139-142.
25. Miguelez Lago C, Gomezese Ribero S, Garcia Merida M, Galiano Duro E, Villamizar P. Abstract [Enuresis and urinary pathology]. ***Cir Pediatr*** 1990; 3: 113-116. Spanish.
26. Rushton HG, Belman AB, Zaontz MR, Skoog SJ, Sihelnik S. The influence of small functional bladder capacity and other predictors on the response to desmopressin in the management of monosymptomatic nocturnal enuresis. ***J Urol*** 1996; 156 (2 Pt 2): 651-655.

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Azhir A, Frajzadegan Z, Adibi A, Hedayatpoor B, Fazel A, Divband A. An epidemiological study of enuresis among primary school children in Isfahan, Iran. ***Saudi Med J*** 2006; 27: 1572-1577.

Al-Harbi SM, Needlman RD, Khan AS, Patni T. Intensive behavioral therapy for primary enuresis. ***Saudi Med J*** 2004; 25: 934-940.

Eapen V, Mabrouk AM. Prevalence and correlates of nocturnal enuresis in the United Arab Emirates. ***Saudi Med J*** 2003; 24: 49-51.