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Anti-diuretic hormone and genetic study in primary nocturnal enuresis

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Abstract *Objective:* To investigate whether primary nocturnal enuresis (PNE) is related to a disturbance in anti-diuretic hormone (ADH) secretion pattern at night which may be genetically inherited.
Subjects and methods: This study included 121 children aged 6—18 years with PNE and 45 matched healthy children as controls. Enuretic children were subjected to genetic evaluation and cytogenetic assessment ($n = 99$). Assay of ADH levels (9—11 am & 9—11 pm) was performed for cases ($n = 99$) and controls.
Results: There was a positive family history in 82.4% (autosomal dominant in 35.4% and autosomal recessive in 64.6%). ADH morning and evening values were reversed in cases vs controls with significant difference in morning level. Reversal of circadian rhythm was present in 71.7% of cases and normal rhythm in 28.3% of them. Morning and evening ADH levels revealed significant difference between patients with reversed rhythm and those with normal one, and with controls. Mode of inheritance had no influence on hormonal level. Chromosomal abnormality was detected in 3 cases with reversed ADH rhythm, involving chromosome 22 in two of them.
Conclusion: PNE could be attributed in part to reversed ADH circadian rhythm which may be linked to chromosome 22.

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Introduction

Enuresis is defined as repeated spontaneous voiding of urine during sleep in a child that persists beyond the normative age of maturation of urinary control [1]. Enuresis is synonymous to intermittent nocturnal incontinence, meaning incontinence in discrete episodes while asleep. Enuresis (or nocturnal incontinence) is a symptom and a condition [1]. Enuresis may be classified as primary or secondary and monosymptomatic or non-monosymptomatic. Primary nocturnal enuresis (PNE) is enuresis in a child who has never established urinary continence for more than six months. It accounts for 80% of cases of enuresis. PNE is a common disorder that affects around 15–20% of 5-year-old children, 10% of 7–12 year olds and up to 2% of adults [2]. Monosymptomatic or uncomplicated enuresis is enuresis without lower urinary tract symptoms other than nocturia and without a history of bladder dysfunction [1], while non-monosymptomatic is enuresis with lower urinary tract symptoms [1,3].

PNE is caused by a disparity between bladder capacity and nocturnal urine production, and failure of the child to awaken in response to a full bladder [4]. Maturational delay and genetic influences may play a role in the pathophysiology of PNE [5].

Plasma anti-diuretic hormone (ADH) levels in normal subjects increase at night as a secondary reaction to bladder distension with reduction of urine production [6]. This normal circadian rhythm in ADH secretion may be absent in patients with PNE. These patients produce large quantities of diluted urine at night that exceeds bladder capacity, with resultant enuresis [7]. Lower ADH secretion in such patients has, however, been denied in another report [8].

Our study aim was to investigate the hypothesis that PNE could be related to a disturbance in ADH secretion pattern or rhythm at night, which may be genetically inherited.

Subjects and methods

This study included 121 children aged 6–18 years suffering from PNE (more than three wet nights weekly). They were recruited randomly from a pediatric outpatient clinic at the National Research Centre, Cairo, Egypt. Exclusion criteria were secondary nocturnal enuresis, children less than five years or more than eighteen years, daytime incontinence, neurological abnormalities, pelvic surgery, congenital anomalies of urological tract and urinary tract infection. Another 45 healthy children with good toilet control day and night of the same age and sex were recruited as control group. Written informed consents were taken from the guardians of all children. The study was approved by the ethical committee of the National Research Centre.

All enuretic children were subjected to full history taking including personal history, history to rule out any existing condition such as diabetes mellitus or insipidus, and history of encopresis, rectal itching and constipation. Urinary symptoms were assessed to differentiate between monosymptomatic and non-monosymptomatic NE (urgency, frequency, dribbling, burning, daytime incontinence…). The incidence of parental consanguinity and similarly affected family members was assessed. A three-generation pedigree was constructed to differentiate between autosomal dominant (AD) and autosomal recessive (AR) modes of inheritance. Anthropometric measurements and thorough clinical examination (abdominal, urological & neurological) were done. Urine analysis (to exclude urinary tract infection) and stool analysis (to exclude pin worm infection) were done.

Laboratory investigations

5 cc of venous blood were withdrawn from all nocturnal enuresis cases and controls by veni-puncture under aseptic technique for hormonal and cyto-genetic assessments (tissue culture was done for nocturnal enuresis cases only).

Hormonal assessment (ADH assay)

ADH was assessed in serum samples collected morning (9–11 am) and evening (9–11 pm, another 2 cc were withdrawn for night ADH assay); 22 cases did not complete their hormonal assessments (thus excluded from results). After centrifugation, sera were stored at −20 until assayed. Vasopressin (ADH) was measured in the collected serum samples using an enzyme immunoassay kit (Assay Design, Inc., Ann Arbor, MI, USA). The kit uses polyclonal antibody to vasopressin to bind in a competitive manner [9].

Cytogenetic analysis

Standard cytogenetic analysis following GTG banding technique was carried out for cases with nocturnal enuresis on metaphases derived from phytohemagglutinin-stimulated peripheral blood lymphocytes by standard methods [10] (22 of our cases did not complete the analysis and thus were excluded from the results).

Statistical methods

Data were statistically described in terms of mean ± standard deviation (±SD), frequencies (number of cases) and percentages when appropriate. Comparison of quantitative variables between the study groups was done using Mann Whitney *U* test for independent samples in comparing 2 groups. A probability value (*p* value) less than 0.05 was considered statistically significant. All statistical calculations were done using computer programs Microsoft Excel 2003 (Microsoft Corporation, NY, USA) and SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

Among the enuretic children, the number of wet nights per week was 7; that is, every case had a wet night daily. The prevalence of nocturnal enuresis decreased with increasing age, as shown by the age distribution of enuretic cases given in Table 1.

Table 2 shows the comparative clinical data between cases and controls. Sixty-four percent (64.2%) of our cases