Circadian Rhythm of Glomerular Filtration and Solute Handling Related to Nocturnal Enuresis

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Abbreviations and Acronyms

dDAVP = desmopressin

FBC = functional bladder capacity

ICCS = International Children's Continence Society

MNE = monosymptomatic nocturnal enuresis

NMNE = nonmonosymptomatic nocturnal enuresis

NP = nocturnal polyuria

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Purpose: Although nocturnal polyuria in patients with monosymptomatic enuresis can largely be explained by the decreased nocturnal vasopressin secretion hypothesis, other circadian rhythms in the kidney also seem to have a role. We recently documented an absent day/night rhythm in a subgroup of desmopressin refractory cases. We explore the importance of abnormal circadian rhythm of glomerular filtration and tubular (sodium, potassium) parameters in patients with monosymptomatic enuresis.

Materials and Methods: In this retrospective study of a tertiary enuresis population we collected data subsequent to a standardized screening (International Children's Continence Society questionnaire), 14-day diary for nocturnal enuresis and diuresis, and 24-hour concentration profile. The study population consisted of 139 children with nocturnal enuresis who were 5 years or older. Children with nonmonosymptomatic nocturnal enuresis were used as controls.

Results: There was a maintained circadian rhythm of glomerular filtration, sodium, osmotic excretion and diuresis rate in children with monosymptomatic and nonmonosymptomatic nocturnal enuresis, and there was no difference between the 2 groups. Secondary analysis revealed that in patients with nocturnal polyuria (with monosymptomatic or nonmonosymptomatic nocturnal enuresis) circadian rhythm of glomerular filtration, sodium and osmotic excretion, and diuresis rate was diminished in contrast to those without nocturnal polyuria ($p < 0.001$).

Conclusions: Circadian rhythm of the kidney does not differ between patients with nonmonosymptomatic and monosymptomatic enuresis. However, the subgroup with enuresis and nocturnal polyuria has a diminished circadian rhythm of nocturnal diuresis, sodium excretion and glomerular filtration in contrast to children without nocturnal polyuria. This observation cannot be explained by the vasopressin theory alone.

Key Words: enuresis, kidney, kidney concentrating ability, nocturnal enuresis, polyuria

Nocturnal enuresis is characterized by involuntary loss of urine during the night at an age at which bladder control should be achieved. This condition is caused by a mismatch between nocturnal diuresis volume and functional bladder capacity, in the absence of arousal and waking up. Small bladder volume is caused by bladder dysfunction (mainly overactive bladder).[1–3] The deficient arousal theory does not explain the majority of sleep disturbances involved in nocturnal enuresis.[4] Sleep

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patterns in children with nocturnal enuresis were recently studied and showed increased sleep fragmentation and periodic limb movements during sleep.[4–6] Increased nocturnal diuresis may reflect an abnormal circadian rhythm of diuresis.[7]

Nocturnal polyuria is considered a major characteristic of monosymptomatic nocturnal enuresis.[1–3] The initial findings of decreased vasopressin levels associated with increased urine production with low osmolality overnight were recently confirmed.[7,8] Due to the reduction of nocturnal polyuria and enuresis by the vasopressin analogue desmopressin, the decreased nocturnal vasopressin secretion hypothesis became widely accepted.[1]

Although evidence based results demonstrate superiority of dDAVP over placebo, only 30% of patients achieve complete continence, suggesting that probably not all patients with MNE have polyuria or are dDAVP responsive.[7,9] This phenomenon has been related to a variety of pathogenetic factors, including several other blunted renal circadian rhythms. Such a nyctohemeral rhythm of glomerular and tubular function is well documented in humans.[10] Abnormalities in sodium and potassium handling, increased 24-hour osmotic excretion and deregulation of the circadian rhythm of prostaglandins, blood pressure and hypercalciuria have been documented,[11–19] all having a potential role in the circadian rhythm of renal function.

In a pilot study we previously observed a deficient circadian rhythm of glomerular filtration in a highly select population with MNE and dDAVP resistant nocturnal polyuria.[20] The finding was subject to criticism because of the limited number of patients and potential selection bias, thereby limiting extrapolation to a more general population. In the present study we evaluated whether there is evidence for disturbances in the circadian rhythm of glomerular function (glomerular filtration) and possible correlation to renal tubular functions (water and solute handling) in children with nocturnal enuresis.

MATERIALS AND METHODS

Data Collection

The study was approved by the ethical committee of Ghent University Hospital. Data from the hospital files were extracted and transcribed to a chart review form designed to collect data relevant to this review in a structured format.

Study Population

We retrospectively reviewed 1,687 hospital files covering the period July 2005 to June 30, 2009. Among the inclusion criteria was severe nocturnal enuresis, defined as bedwetting at least 8 nights recorded in a 2-week diary at home. Exclusion criteria were age younger than 5 years, mental disability, height and body weight outside normal reference frame (below 5th or above 95th percentile) and incomplete data set (missing samples and/or values). A total of 139 patients followed at our department of pediatric nephrology were included. If patients were referred to our tertiary center and received dDAVP in the past, they had no treatment at the time of referral. All patients received no medication or special diet for at least 48 hours before the investigation.

Maximum voided volume was obtained during 1 day of forced diuresis, during which patients were asked to drink as much as possible, postpone voiding for as long as possible and measure the voided volume. Maximum bladder volume was defined as the mean of the 3 greatest endurable voided volumes. Maximum bladder volume was considered small if less than 65% and large if greater than 150% of estimated bladder capacity.

Circadian rhythm of diuresis was evaluated by a simple home test that has been described by Dehoorne et al.[14] A 24-hour urine collection was performed in 8 timed portions to limit losses during the daytime and nighttime. Daytime and nighttime were each divided into 4 more or less equally timed intervals, starting in the morning with the first daytime collection (number 1) and ending with the last nighttime collection (number 8). Urine volume, osmolality, creatinine, sodium and potassium were measured in each urine sample. Because nocturnal diuresis volume is dependent on patient duration of sleep, age and size, and because of large age and body size differences, values are presented in ml (absolute values) and ml/kg or ml/kg per hour (diuresis rate). Because hourly creatinine excretion in an individual is rather stable, this parameter was suitable to identify incomplete or incorrect sample collections.

When the night-to-day creatinine excretion ratio exceeded 150% or was less than 50%, an error was estimated in the collection. A total of 27 children were excluded from further analysis due to these findings.

According to the ICCS, nocturnal polyuria is defined as nocturnal diuresis greater than 130% of estimated bladder capacity for age using the formula, [age + 1 year] $\times$ 30 ml, with a maximum of 390 ml. Nocturnal diuresis was calculated as the sum of the nighttime portions and volume of the first morning voided urine during the night of the 24-hour urine collection.

Calculations and Statistical Analysis

Values are expressed as mean $\pm$ 1 SD. Statistical analysis was performed by Wilcoxon test for the differences between daytime and nighttime data.

Patients were divided into 2 groups, ie those with MNE and those with NMNE. Each group was subdivided according to the absence or presence of nocturnal polyuria. Mann-Whitney U test was used to compare the 2 groups. Correlation was calculated with the Spearman correlation coefficient, with $p < 0.001$ considered significant.

RESULTS

Table 1 outlines demographic data for patients with MNE and NMNE, and table 2 outlines data for patients with and without NP. Of the 81 children