The genetic basis of inherited primary nocturnal enuresis: a UAE study

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Abstract

Objective: Nocturnal enuresis is defined as involuntary emptying of the bladder in the absence of an organic cause in a child aged 5 years or older. Primary nocturnal enuresis (PNE) is the term used if the child has never been dry. Of several factors implicated in the etiology of PNE, genetic factors appear to be the strongest. In about 75% of affected children, there is a strong family history. The purpose of this study was to examine the genetic basis of nocturnal enuresis among children in the United Arab Emirates (UAE). Methods: Chromosomes 12 and 13 were genotyped in all family members of 10 affected children in four large families. Linkage to earlier reported microsatellite markers on these two chromosomes was examined. Results: In the four families examined, we did not find evidence for linkage to the two loci reported previously. Conclusions: Among UAE children examined, no linkage was found between PNE and the loci reported previously on chromosomes 12 and 13, indicating further genetic heterogeneity in PNE.

Keywords: Inheritance; Primary; Nocturnal enuresis; UAE

Introduction

According to the International Children’s Continence Society [1], enuresis is defined as normal voiding occurring at a socially inappropriate time and place in children aged 5 years. Nocturnal enuresis is defined as voiding in bed without awakening at night. Around 10% of children at the age of 5 years experience nocturnal enuresis or bedwetting. Problems of enuresis were first described in the papyrus of Ebers around 1500 BC [2], and remedies in those days ranged from drinking bouillon from boiled combs of hen to more drastic measures such as the use of collodium for closure during the night. The current recommendation of the World Health Organization is to recognize and treat the condition if the frequency of wetting is more than twice per week when the child has started regular schooling (5–7 years), due to its effects on self-esteem, peer relationships, family environment, and others, with long-term consequences.

There are two subtypes of nocturnal enuresis: Type I [primary nocturnal enuresis (PNE)], wherein the child has always had the disorder, and Type II (secondary), wherein the child has been dry for at least a period of 6 months. Available evidence suggests that the maturation of the nervous system and the hormonal regulation (through the secretion of antidiuretic hormone) of urine production are partly genetically determined, and this explains why failure to gain bladder control at night often runs in families. It is hypothesized that, in these cases, nightly serum vasopressin level is not upregulated [3]. Other factors implicated in the etiology include reduced functional bladder capacity [4], abnormal sleep pattern, and arousability, characterized by reduced waking from sleep in response to the sensation of a full bladder, as well as a lack of inhibitory cerebral control of reflex voiding during sleep [5]. While genetic factors are believed to be important in PEN [6,7], most cases of secondary enuresis have been attributed to psychosocial...
issues [8]. In the remaining cases, physical causes, including urinary tract infection, nocturnal epilepsy, diabetes, sickle cell disease, abnormalities of urinary tract/kidney, and other neurological causes, will need to be excluded.

Family studies have shown that 77% of children with PNE have a positive family history in a first-degree relative [9], while a majority of cases of secondary enuresis are sporadic. In a recent United Arab Emirates (UAE) study [10], 72% (23 of 32 cases) of those with enuresis were found to have a family history of bedwetting in a first-degree relative compared to 6.2% in the total population. In this study, bilineal transmission (from both maternal and paternal sides) was noted in half (12 of 23) of those with a positive family history. In this regard, it is to be noted that 34% of these families were consanguineous. A further analysis of the pattern of transmission revealed that, among 10 females in the nuclear units through whom the condition was transmitted, 9 were found to be affected while 12 male transmitters were all affected. This fits the hypothesis of an autosomal-dominant mode of inheritance with high penetrance (the one presumed carrier among 22 parents reflects a 4% deviation from full penetrance).

Twin studies have shown higher concordance in monozygotic (43%) than in dizygotic (19%) twins in childhood as compared to 25% and 0%, respectively, in adulthood [11]. More recently, there have been some advances in genetic research, with the suggestion of an autosomal-dominant mode of inheritance with 90% penetrance for PNE [12]. In this study of three-generation Danish families, a multipoint linkage analysis pointed to a disease locus at chromosome 13 (q13–q14.3 labeled as ENUR1) in 5 of 11 families, but locations at chromosomes 8 and 12 could not be excluded. Linkage was noted in the same chromosomal region in 3 of 16 Swedish families, with another six families showing linkage to a region on 12q13–21 [13]. In another study, Arnell et al. [14] confirmed the second locus at chromosome 12 q13–q21, which was labeled as ENUR2. Other studies have found linkages to 8q [15] and 22q [16,17]. Loeys et al. [18] explored 32 families with enuresis and found linkage to 22q11 in nine families, linkage to 13q13–14 in six families, and linkage to 12q in four families. There was no convincing evidence for linkage to chromosome 8q in this study. Furthermore, these authors found no clear phenotype/genotype correlation in monosymptomatic enuretics versus those with underlying bladder dysfunction.

In the present study, 10 affected children in four UAE families were examined for linkage to earlier reported microsatellite markers on chromosomes 12 and 13.

### Subjects and methods

#### Clinical examination

Families were ascertained from index patients attending the enuresis clinic at the school health center in Al Ain Medical District, UAE. Four multiply affected families, in which the parents were nonconsanguineous and gave consent to participate in the study, were recruited. Only patients with at least three affected first-degree family members over two generations were included (Fig. 1). Clinical diagnosis was based on a careful history, including questions about voiding problems and micturition habits. Family history was ascertained by direct clinical interview with each of the family member concerned, following which a blood sample was collected.

#### Genotyping

Blood samples were obtained from available members of all four families after informed consent had been obtained.

### Table 1

Two-point LOD scores between PNE and markers surrounding the ENUR1 locus, as reported previously on chromosome 13, in four UAE families

<table>
<thead>
<tr>
<th>Marker</th>
<th>Position (cM)</th>
<th>LOD scores at θ</th>
<th>0.0000</th>
<th>0.0100</th>
<th>0.0200</th>
<th>0.0300</th>
<th>0.0400</th>
<th>0.0500</th>
</tr>
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<tr>
<td>D13S219</td>
<td>35.50</td>
<td>−4.4739</td>
<td>−1.5974</td>
<td>−1.2784</td>
<td>−1.0868</td>
<td>−0.9484</td>
<td>−0.8401</td>
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<tr>
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<td>39.34</td>
<td>0.5237</td>
<td>0.5081</td>
<td>0.4925</td>
<td>0.4769</td>
<td>0.4614</td>
<td>0.4459</td>
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<tr>
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<td>43.24</td>
<td>−0.0241</td>
<td>−0.6851</td>
<td>−0.8000</td>
<td>−0.0259</td>
<td>−0.1551</td>
<td>−0.0823</td>
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<tr>
<td>D13S291</td>
<td>47.23</td>
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<td>0.0000</td>
<td>0.0000</td>
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</tr>
<tr>
<td>D13S168</td>
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<td>−8.2596</td>
<td>−2.6124</td>
<td>−3.7252</td>
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<td>−1.4465</td>
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<tr>
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<td>−0.2562</td>
<td>−0.1553</td>
<td>−0.0825</td>
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