CASE REPORT

Thirst perception and arginine vasopressin production in a kindred with an activating mutation of the type 2 vasopressin receptor: the pathophysiology of nephrogenic syndrome of inappropriate antidiuresis

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Abstract

Background: Activating mutations of the vasopressin receptor gene on the X chromosome cause the nephrogenic syndrome of inappropriate antidiuresis (NSIAD). We describe a male child who presented with persistent hyponatraemia and whose mother was also found to be hyponatraemic. She had learnt to avoid excess fluid consumption because of associated malaise. Both individuals had a subnormal ability to excrete a water load with mother also demonstrating a heightened sense of thirst at low serum osmolalities.

Results: Mother and child were found to have the previously characterised activating mutation (p.Arg137Cys) of the arginine vasopressin receptor type 2 gene (AVPR2), but had measurable levels of AVP when hyponatraemic.

Conclusions: We conclude that female carriers of activating mutations of the vasopressin receptor are susceptible to hyponatraemia and therefore need to be provided with advice regarding fluid intake. An altered thirst perception may increase susceptibility to hyponatraemia. We confirm that the presence of measurable amounts of AVP in patients with hyponatraemia does not exclude the diagnosis of NSIAD.

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Introduction

The arginine vasopressin (AVP) type 2 receptor (V2R) is a G protein-coupled receptor expressed in the collecting ducts of the renal tubule. AVP binds to the V2R and stimulates water reabsorption by the activation of intracellular cyclic AMP. Inactivating mutations of the V2 gene (AVPR2) on the X-chromosome result in congenital nephrogenic diabetes insipidus in males (1). Patients with nephrogenic diabetes insipidus cannot generate appropriately concentrated urine and are susceptible to hypernatraemic dehydration if denied free access to hypotonic fluid. To date, more than 180 inactivating mutations of AVP2R have been described. Although female carriers of AVP2R mutations were originally thought to be asymptomatic, it is clear that their ability to concentrate urine is compromised.

Feldman et al. (2) have recently reported hemizygous gain of function point mutations (p.Arg137Cys and p.Arg137Leu) in AVPR2 in two male infants who presented with a picture suggestive of the syndrome of inappropriate antidiuretic hormone production (SIADH), but in the presence of undetectable AVP levels. They called this condition the ‘nephrogenic syndrome of inappropriate antidiuresis’ (NSIAD). The mother of one of the boys was heterozygous for the p.Arg137Cys mutation but had normal plasma sodium and plasma and urine osmolalities, suggesting rescue of the phenotype through co-expression of the normal allele, thereby indicating a gene dosage effect. More recently, Decaux et al. (3) have described the mutation p.Arg137Cys in three hemizygous adult males and four heterozygous adult females in a large five generation family identified during the phase III clinical trials of oral inhibitors of V2R. They identified high phenotypic variability in adult males and females in the presence of this mutation.

Here we describe a male infant with hyponatraemia in early infancy who was found to have NSIAD. The subsequent studies conducted in mother and child...
provide insight into pathophysiology of NSIAD including the significance of an activating mutation of AVPR2 in female heterozygotes.

Case histories

A male infant presented at 7 months of age with a generalised tonic clonic seizure. He had been exclusively breastfed until 6 months of age before being changed to bottle feeds. Initial investigations revealed hyponatraemia with a plasma sodium of 120 mmol/l. The fractional excretion of sodium (FeNa) was 4.2% and his plasma osmolality was 250 mOsm/l. Plasma potassium, renal function, blood pressure and 17-OH progesterone were all normal. Atrial natriuretic peptide (ANP) was 16 pmol/l (reference range <11 pmol/l). Renal ultrasound scan and micturating cystourethrogram did not reveal any pathology. In view of the high FeNa and ANP level, he was initially thought to have a salt-losing nephropathy. Plasma sodium stabilised between 134 and 141 mmol/l on treatment with oral sodium supplementation in the range of 18–22 mmol/kg per day, although FeNa remained high with measurements between 1.0 and 9.1%.

Shortly afterwards, the child’s 33-year-old mother was noted to have persistent hyponatraemia (128 mmol/l) on routine medical review. She did not have any significant past medical history and she was not on any regular medication. Clinical examination was normal. Routine investigations, including thyroid function, were normal and she demonstrated a normal cortisol response to 250 µg synacthen. Urinary sodium was 143 mmol/l at the time of corresponding plasma sodium of 130 mmol/l with a FeNa of 0.76%. Further systematic enquiry revealed that large fluid intakes had made her feel unwell, and she had learnt to avoid excess fluid intake. Furthermore, she had become markedly oedematous during pregnancy.

Methods

Assessment of free water excretion: water load test

Free water excretion was assessed by water load test according to a standard protocol (4). In brief, an oral water load (20 ml/kg) was administered over 15 minutes. Urine output, urine osmolality, plasma osmolality and plasma AVP were measured at baseline and then hourly for 4 h. Normal subjects excrete 70–92% of ingested water load in the 4-h period following ingestion (normal range 70–92%). The mother also demonstrated reduced clearance of a water load, excreting only 47% of the ingested load over the corresponding time period. The relationship between serum osmolality and urine osmolality and the relationship between serum osmolality and AVP in mother and child are shown in Table 2. Plasma AVP was detectable throughout the water load test in both subjects, with nadir values of 0.7 and 0.4 pmol/l for the child and mother respectively.

Maternal thirst response to hyperosmolar stimulation

Maternal plasma vasopressin data showed detectable plasma AVP at values of plasma osmolality below the normal osmolar threshold for AVP release (around

Assessment of osmoregulated thirst and AVP production by graded hyperosmolar stimulation with hypertonic saline

Thirst and AVP response to graded hypertonic stimulation were assessed in the mother by standard methods (4). In brief, hypertonic 5% saline (850 mmol/l) was infused over a period of 2 h at a rate of 0.06 ml/kg per min. Plasma osmolality and AVP were assessed at baseline and at 30 min intervals during the infusion. Thirst was assessed in parallel using a validated visual analogue scale (4). Plasma AVP and thirst were related to standardised normal reference ranges determined in normal volunteers.

Plasma AVP was measured by in-house RIA using a sheep anti-AVP antibody with an inter-assay coefficient of variation of 5–7%. Lower limit of detection of the assay is 0.3 pmol/l (4).

AVPR2 analysis (accession number NM_000054.2)

Exon 8 of AVPR2 was amplified from genomic DNA using the forward primer ACT TGT GCC TGG CCG ACC TG and the reverse primer AGC AGG CCC AGC AGT CAG TG. The PCR conditions used were initial denaturation at 95 ºC for 7 min, followed by 30 cycles of 95 ºC for 45 s, 62 ºC for 45 s and 72 ºC for 1 min. PCR products were sequenced using dye terminator cycle sequencing Quick Start kit (Beckman Coulter, Fullerton, CA, USA) and run on the Beckman Coulter CEQ8000 Genetic Analysis System.

Results

Water load testing

Baseline biochemistry at presentation is summarised in Table 1.

Free water clearance was reduced in the child with only 19% of a water load being excreted over a 4-h period following ingestion (normal range 70–92%). The mother also demonstrated reduced clearance of a water load, excreting only 47% of the ingested load over the corresponding time period. The relationship between serum osmolality and urine osmolality and the relationship between serum osmolality and AVP production in mother and child are shown in Table 2. Plasma AVP was detectable throughout the water load test in both subjects, with nadir values of 0.7 and 0.4 pmol/l for the child and mother respectively.
284 mOsm/kg; Fig. 1A). These data are consistent with persistent low level AVP production that is not suppressible even at low plasma osmolality. No nausea was reported or observed during hypertonic saline infusion, but the mother experienced thirst at a low plasma osmolality indicating an increased thirst component compared with normal. This sensation persisted at the same level as plasma osmolality rose into the reference range (Fig. 1B).

Identification of a p.Arg137Cys mutation associated with hyponatraemia

DNA from the child and his mother was tested by direct sequencing of AVPR2 from bases c.274 to c.564 (codons 92–188); the portion of AVPR2 shown previously to harbour gain of function mutations. Sequencing in the child confirmed a p.Arg137Cys mutation in AVPR2 (obligate hemizygote). His mother was heterozygote for the same mutation. The other maternal AVPR2 allele was confirmed as wild-type sequence.

Discussion

Gain of function mutations of a range of G-protein-coupled receptors that induce constitutive receptor activation in the absence of a hormonal stimulus are described. Such mutations can give rise to diseases such as thyrotoxicosis (an abnormal thyroid-stimulating hormone receptor), familial male-limited precocious puberty (an abnormal LH receptor) and hypercalcuric hypocalcaemia (an abnormal Ca sensing receptor) (5, 6). This group of disorders has been expanded further by the description of activating mutations of V2R leading to NSIAD (2). Details of the 12 patients now reported with NSIAD are summarised in Table 3.

Our case demonstrates that female carriers of such mutations of AVPR2 may develop a clinical and biochemical phenotype with an abnormal response to a water load. This is in contrast to a previous report (2), but in keeping with the findings of Decaux et al. (3) who demonstrated an abnormal water load test or episodes of hyponatraemia in three out of four female heterozygotes.
Table 3  Characteristics of the 12 patients with nephrogenic syndrome of inappropriate antidiuresis reported to date including baseline biochemistry.

<table>
<thead>
<tr>
<th>Author</th>
<th>Patient number</th>
<th>Age at diagnosis</th>
<th>Sex</th>
<th>Mutation</th>
<th>Clinical findings</th>
<th>Sodium (mmol/l)</th>
<th>Lowest AVP (pg/ml)</th>
<th>Urine osmolality (mOsm/kg)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feldman et al.</td>
<td>1</td>
<td>3 months</td>
<td>M</td>
<td>R137C</td>
<td>Symptomatic hyponatraemia Bottle fed</td>
<td>123</td>
<td>&lt;1</td>
<td>284</td>
<td>Fluid restriction and urea</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2.5 months</td>
<td>M</td>
<td>R137L</td>
<td>Symptomatic hyponatraemia Bottle fed</td>
<td>118</td>
<td>&lt;1</td>
<td>390</td>
<td>Fluid restriction and urea</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Mother of patient 1</td>
<td>F</td>
<td>R137C</td>
<td>Asymptomatic, normal plasma sodium and osmolality Water load test not performed</td>
<td>140</td>
<td>Not done</td>
<td>795</td>
<td>No treatment</td>
</tr>
<tr>
<td>Decaux et al.</td>
<td>4</td>
<td>74 years</td>
<td>M</td>
<td>R137C</td>
<td>Symptomatic hyponatraemia (diagnosed as idiopathic SIADH) Abnormal water load test</td>
<td>124 (140 on urea)</td>
<td>0.9</td>
<td>615</td>
<td>Fluid restriction and urea</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>72 years</td>
<td>M</td>
<td>R137C</td>
<td>Asymptomatic Abnormal water load test Abnormal water load test</td>
<td>140 (132 post-water load)</td>
<td>1.1</td>
<td>792</td>
<td>Fluid restriction (self-learnt behaviour)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>48 years</td>
<td>F</td>
<td>R137C</td>
<td>Asymptomatic Abnormal water load test</td>
<td>141 (135 post-water load)</td>
<td>0.6</td>
<td>702</td>
<td>No treatment</td>
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<tr>
<td></td>
<td>7</td>
<td>41 years</td>
<td>F</td>
<td>R137C</td>
<td>Symptomatic hyponatraemia with high fluid intake</td>
<td>124 (on high fluid intake)</td>
<td>0.6</td>
<td>432</td>
<td>Fluid restriction</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>47 years</td>
<td>F</td>
<td>R137C</td>
<td>Asymptomatic Abnormal water load test First presentation at 7 months of age with hyponatraemia (119 mmol/l)</td>
<td>140</td>
<td>Not done</td>
<td>699</td>
<td>No treatment</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>21 years</td>
<td>M</td>
<td>R137C</td>
<td>First presentation at 7 months of age with hyponatraemia (119 mmol/l)</td>
<td>143 (on salt therapy + fluid restriction)</td>
<td>1.8</td>
<td>730</td>
<td>Salt tablets, fluid restriction and urea</td>
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<tr>
<td></td>
<td>10</td>
<td>22 years</td>
<td>F</td>
<td>R137C</td>
<td>Asymptomatic Normal water load test Skewed X inactivation</td>
<td>143</td>
<td>Not done</td>
<td>250</td>
<td>No treatment</td>
</tr>
<tr>
<td>Gupta et al.</td>
<td>11</td>
<td>7 months</td>
<td>M</td>
<td>R137C</td>
<td>Symptomatic hyponatraemia Breast fed for 6 months</td>
<td>120</td>
<td>0.7</td>
<td>930</td>
<td>Salt supplement and later fluid restriction</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>33 years</td>
<td>F</td>
<td>R137C</td>
<td>Asymptomatic Abnormal water load Abnormal thirst response</td>
<td>130</td>
<td>0.4</td>
<td>328</td>
<td>Fluid restriction (self-learnt behaviour)</td>
</tr>
</tbody>
</table>
from their kindred. A skewed X inactivation pattern was identified in the fourth, asymptomatic individual. Perhaps of greater interest in our report is the assessment of thirst dynamics and AVP production in response to graded hypertonic stimulation. This has not been assessed by previous investigators, and our studies demonstrate that both AVP and thirst dynamics can be abnormal in patients with activating V2R mutations. We have shown that AVP production can persist despite the low plasma sodium and plasma osmolality associated with V2R activation. This may represent non-osmoregulated AVP production, although the fact that AVP was detectable under most circumstances in the absence of feelings of nausea is still surprising. The osmolality of voided urine will normally reflect AVP secretion over the preceding hours rather than AVP osmolality. This may indicate that infants breastfed ‘on demand’ can regulate their fluid intake more effectively, in contrast to bottle fed babies who are frequently offered an obligate volume of feed. The relatively low urine osmolality of the very young child may also reduce susceptibility to hyponatraemia, as highlighted by Decaux et al. (3). The serum sodium value increased as the index case matured, presumably also reflecting a relative reduction in fluid intake per square metre with advancing years. Children with NSIAD have been managed successfully with oral urea (8), and although our child’s sodium concentrations rose with sodium supplements and the passage of time, oral urea might have been an appropriate therapy had he remained symptomatic. Urea is not licensed for use in the management of hyponatraemia in the UK.

In summary, a clinical picture of hyponatraemia with ongoing AVP release is compatible with an activating mutation in AVPR2. Hyponatraemia may reflect altered thirst as well as altered renal water handling. Although water restriction improves plasma sodium concentrations in such individuals, this could compromise calorie intake in young infants. Finally, female heterozygotes may need to exercise some caution with regard to their fluid intake throughout their lives.

Declaration of interest
There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References


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