



Adult female with symptomatic AVPR2-related nephrogenic syndrome of inappropriate antidiuresis (NSIAD)

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Summary

Activating mutations in *AVPR2* are associated with nephrogenic syndrome of inappropriate antidiuresis (NSIAD). NSIAD causes hyponatremia, decreased serum osmolality and clinical symptoms, which may present from birth or in infancy and include hypotonia, irritability, vomiting and/or seizures. Symptoms in later life are often less specific and include malaise, dizziness, confusion, tiredness and headache. NSIAD is a rare X-linked condition, which is associated with a variable phenotype in males, of whom some present in infancy but others do not become symptomatic until adulthood, or occasionally, never. Female carriers may present with episodes of hyponatremia, usually found incidentally. Literature in this field is limited; namely, two clinical reports describing a female proband, both diagnosed in infancy. We describe, for the first time, the case of an adult female proband with NSIAD, who had longstanding associated symptoms of tiredness, headache, temporary memory loss and mood changes as well as hyponatremia and decreased serum osmolality. A water load test demonstrated an inability to dilute urine and gene sequencing confirmed a recurrent activating mutation in *AVPR2*. The variant was inherited from the proband's mother who had had longstanding episodes of transient asymptomatic hyponatremia. This is the third report of a female proband with NSIAD and is the first female reported who sought medical treatment for chronic symptoms from adulthood. This case acts as a reminder of the importance of considering NSIAD as a diagnosis in females of all ages with unexplained hyponatremia.

Learning points:

- Activating mutations in the *AVPR2* gene are associated with the rare X-linked condition nephrogenic syndrome of inappropriate antidiuresis.
- NSIAD is associated with hyponatremia, decreased serum osmolality and inappropriately increased urinary osmolality. Early clinical symptoms in infancy include hypotonia, irritability, vomiting and/or seizures. Symptoms in later life include malaise, dizziness, confusion, tiredness and headache.
- NSIAD should be considered in female, as well as male, patients who present with unexplained hyponatremia and decreased serum osmolality. Family history may reveal relevant symptoms or biochemical features in other family members. However, family history may not always be informative due to the variable nature of the condition or if the proband has a *de novo* pathogenic variant.





- A water load test with measurement of AVP may be informative in distinguishing NSIAD from SIADH. Measurement of co-peptin levels may be considered, in substitution for direct measurement of AVP.
- Patients with NSIAD should be counseled about appropriate daily fluid volume intake. Potential episodes of fluid overload should be avoided.

Background

Nephrogenic syndrome of inappropriate antidiuresis (NSIAD, OMIM 300539) is associated with gain-of-function pathogenic variants in *AVPR2*, which encodes the vasopressin V2 receptor (1). Activating mutations cause constitutive activation of the vasopressin receptor resulting in antidiuresis and therefore cause the biochemical and clinical features of NSIAD. In contrast, loss-of-function mutations in *AVPR2* cause X-linked congenital nephrogenic diabetes insipidus (2).

NSIAD has been traditionally described as an X-linked recessive condition with index cases usually being male but with marked interfamilial and intrafamilial heterogeneity regarding the age of diagnosis and severity of disorder. To date, carrier females have most commonly been asymptomatic and identified during familial cascade screening. The two exceptions have been clinical reports of females who were both diagnosed with NSIAD in infancy (3, 4). However, a female proband presenting with chronic symptoms in adulthood has not been previously described until now. We describe the clinical features of our patient and describe relevant investigations and management. We outline the diagnostic utility of a water load test for NSIAD prior to molecular sequencing of *AVPR2*. Furthermore, we demonstrate that measurement of co-peptin levels can be used as an alternative to direct AVP measurement during the water load test.

Case presentation

Our patient was an only child and was born to non-consanguineous white British parents. Her mother had had difficulty conceiving, possibly due to a congenital uterine malformation and underwent hysterectomy after our patient was born. The proband was born at term after a normal pregnancy. Her development and early medical history were unremarkable. She had glandular fever at the age of 16 years and described feeling continually unwell from that time. Between the ages of 16 and 30 years she regularly experienced symptoms of nausea, headache and malaise, which were significant enough

for her to attend the local hospital emergency room. On these occasions, she was found to be hyponatremic (serum sodium around 125 mmol/L) with normal serum potassium and bicarbonate levels. Clinical management included hospital admission and fluid restriction. This resulted in normalization of her serum sodium levels and resolution of her clinical symptoms. She also reported other symptoms, related to the episodes of hyponatremia, and these included tiredness, occasional memory loss, mood changes and depressive symptoms. There was no history of seizures.

In her twenties, she was given a provisional diagnosis of SIADH based on the biochemical profile of persistent hyponatremia with plasma serum sodium of 125–132 mmol/L (reference range 133–146 mmol/L) associated with a low serum osmolality of around 270 mosmol/kg (reference range 275–295 mosmol/kg) while euvoletic. Management included fluid restriction and sodium chloride supplements, which had variable effect, possibly due to tolerability. Due to lack of consistent improvement, she underwent a trial of demeclocycline, but again with limited sustained benefit.

Additionally aged 16 years, she was investigated for primary ovarian insufficiency but no cause was identified. Genetic testing failed to identify either a Fragile X syndrome premutation or any chromosomal abnormalities. She also underwent investigations for autoimmune disorders, which were negative. The premature ovarian failure resulted in sub-fertility, and she later adopted two children. She underwent investigations for chronic fatigue syndrome and was diagnosed with fibromyalgia.

Investigation

She was further investigated as no underlying cause had been found for her symptoms and biochemical profile. At this time, she remained euvoletic, with a plasma sodium of 133–136 mmol/L, but urine osmolality was raised (626 mosmol/kg). Adrenocortical and thyroid function



Table 1 The results of the water load test for our patient using a protocol adapted from a previous publication (10).

(min)	Urine output (mL)	Venous gas Na (mmol/L)	Lab Na (mmol/L)	K (mmol/L)	Glu (mmol/L)	Urea (mmol/L)	Creatinine (μ mol/L)	Serum osmolality (mosmol/kg)	Urine osmolality (mosmol/kg)	Co-peptin (pmol/L)
0		136.0	134	4.4	5.1	5.9	48	280	710	<1.3
60	300	131.1	128		4.9	4.3	43	272		
120	300	129.1	128		4.9	4.2	43	264		<1.3
180	200	128.1	129	3.8	4.8	3.9	37	266		
240	40	131.1	128	3.8	4.6	3.9	37	262		<1.3
360	100	130.5	128	3.9	4.6	3.9	39	267	495	
09:00h following morning	N/A	N/A	134	4.4	4.6	5.9	48	287	609	

A water load based on the following calculation (20 mL/kg = 1508 mL) was performed. Within 60 min of the water load consumption, serum sodium dropped to 128 mmol/L from 134 mmol/L but co-peptin remained suppressed consistent with a diagnosis of nephrogenic SIAD. Furthermore, the patient failed to excrete the expected 70–80% (1056–1206 mL) of the water load volume within four hours, as indicated by the urine output (840 mL in 4 h).

tests and an acute intermittent porphyria screen were normal. She was taking no medication which could be responsible for her symptoms. Cross-sectional imaging of the head, chest and abdomen did not identify an infectious or neoplastic cause for SIADH and an octreotide isotope scan was also normal.

A water load test was therefore considered to determine if the hyponatremia was due to an inability to dilute urine in the presence of a relative excess of free water (Table 1). This test was carried out in a controlled environment and under direct supervision, given the risk of exacerbating hyponatremia associated with this test. This investigation demonstrated a marked inability of the patient to excrete a free water load (40% of a 20 mL/kg oral fluid load by 240 min post ingestion). Normal subjects excrete 78–82% of the water load in 4 h. There was onset of hyponatremia at 128 mmol/L and a persistently elevated urine osmolality during the test. However, serum co-peptin, a peptide released together with AVP, was undetectable throughout the test (<1.3 pmol/L), which indicated that our patient did not have SIADH. The water load test was therefore important in establishing that NSIAD was the most likely diagnosis in our patient. The value of the water load test in the diagnosis of NSIAD is described by Ranchin and coworkers (5).

To confirm the diagnosis, next-generation sequencing (NGS) was carried out with the Illumina TruSight One sequencing panel using the MiSeq Illumina NGS platform. Reads were aligned; variants were called and initial pre-filtering was carried out using an in-house bioinformatics pipeline. This pipeline filtered the data to only show *AVPR2* variants. Variants with a population frequency greater than 1 in 50 were automatically deemed as insignificant.

Variant interpretation of the remaining variants was carried out using the Alamut Visual software. All variants of class 4 or above, according to the current ACMG guidelines, were then confirmed by Sanger sequencing (6). The recurrent mutation c.409C>T, p.(Arg137 Cys) was identified in *AVPR2*, confirming the diagnosis of NSIAD. X-linked inactivation studies were requested and showed an unskewed pattern in blood.

The pathogenic variant was found to be maternally inherited. On review of the medical records, our patient's mother had experienced recurrent episodes of hyponatremia during illness, for example, after an episode of shingles, but also on routine medical review, with the lowest serum sodium recorded at 130 mmol/L. She also had a history of lupus and Hashimoto's thyroiditis but did not display any symptoms of NSIAD. Her parents were



deceased, and her two brothers (one deceased) did not have any relevant symptoms. However, predictive genetic testing has been offered to the wider family.

Treatment

Our patient is now asymptomatic on daily fluid restriction of 1–1.5L. This recommended volume of fluid was based on the lowest daily fluid volume our patient felt she could tolerate, while ensuring that her sodium levels remain just under or within the normal range (usually between 132 and 135 mmol/L).

Outcome and follow-up

Our patient has been followed up for a further 12 months, since she received her genetic diagnosis. She remains asymptomatic on fluid restriction.

Discussion

NSIAD was first described in 2005 in two infant boys (1). Since then, around 30 cases have been reported. Several activating mutations have been described but our patient's mutation, R137C, causing an arginine to cysteine change, is the most commonly reported to date.

NSIAD is inherited in an X-linked manner and the majority of index patients have been males. However, there have been several reports where females with NSIAD have been identified on cascade screening (3, 7, 8). Asymptomatic carrier females have been reported who have normal plasma sodium and osmolality (1). In contrast, other asymptomatic female carriers have had documented episodes of hyponatremia and/or when investigated with a water load test, have had impaired ability to dilute urine (3, 7, 8). Decaux and coworkers described a female who had molecularly-confirmed NSIAD but did not have episodes of hyponatremia or an abnormal water load test. X-inactivation studies were compatible with preferential inactivation of her mutated allele (7). Gupta and coworkers reported a male infant and his mother who both had NSIAD. The mother had learned to avoid excess fluid consumption because of associated malaise. Both family members had a subnormal ability to excrete a water load, with the mother also demonstrating a heightened sense of thirst at low serum osmolalities (8). Ranchin and coworkers described the value of the water load test in helping to diagnose NSIAD and distinguish it from cases of SIADH. The paper describes the results of the water load test that would be expected in both

hemizygous males and heterozygous females with an activating *AVPR2* pathogenic variant (5).

There have been two reports of female probands who both presented in infancy (3, 4). A 1-year-old girl was referred for persistent hyponatremia, which was first noted incidentally during an intercurrent infection. She had global developmental delay, although it is unclear if this was related to her diagnosis of NSIAD. Her mother reported a strong aversion to fluids, because she subsequently would experience headaches, which could be relieved only by eating salty foods. She passed urine only once or twice a day. The maternal grandmother reported similar symptoms. Genetic studies confirmed NSIAD in all family members (3). In the second case, the infant presented with diarrhea and poor feeding at 23 days of age. She was found to have mild hypertension and continuing episodes of hyponatremia. Her brother was known to have NSIAD and the diagnosis was also confirmed in her, with chromosome inactivation studies showing an unskewed X-inactivation pattern (4).

Identifying patients with NSIAD is important for symptom control as well as long-term management of fluid restriction. It is especially important to consider the diagnosis in infancy if a child presents with irritability, vomiting and/or seizures and a biochemical picture of SIADH, as SIADH is rare in pediatric patients and NSIAD is more likely, especially if the patient has low or undetectable AVP levels. Immediate management includes fluid restriction and possibly medication, including the osmotic agent urea and inverse agonists for specific variants, e.g. p.(Phe299Val) and p.(Ile130Asn) (9, 10). It is important to counsel patients on appropriate daily fluid volume intake and to ensure that episodes of fluid overload can be avoided, such as increased fluid intake in summertime or during sports activities or excessive intravenous fluid administration during hospital admissions.

In conclusion, we propose that NSIAD should be considered as a diagnosis in female, as well as male, patients who present with unexplained hyponatremia and decreased serum osmolality. A water load test may be informative, and measurement of co-peptin levels may be considered, in substitution for direct measurement of AVP, to aid diagnosis and guide diagnostic sequencing of *AVPR2*. In families with a known history of NSIAD, we would recommend that both females and males, from birth onwards, should be offered genetic testing for the familial variant and, if positive, referred to endocrinology for long-term management. Due to the increasing availability of genetic testing, confirmation of diagnosis is becoming easier. We conclude that, as with many other



X-linked disorders, the concept of a truly recessive X-linked inheritance is becoming blurred. This is explained by the random and mosaic nature of X-inactivation in females.

Declaration of interest

The authors of this clinical report declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent

We express our gratitude to our patient for her written consent for the publication of this case report.

Author contribution statement

Jennifer Hague wrote the manuscript. Ruth Casey wrote Table 1 and reviewed the paper. Andrew S Powlson, Mohamed Majeed and Mark Gurnell were the patient's endocrine physicians and reviewed the paper. Tom Legerton, Jonathan Bruty and Stephen Abbs performed and interpreted the molecular sequencing and X-inactivation studies. Susan Oddy performed the biochemical analysis. Soo-Mi Park was the patient's clinical genetics physician and contributed to the manuscript. Helen Simpson was the patient's primary endocrine physician and contributed to the manuscript. Dr Simpson gives permission for this clinical report to be published.

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