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## Case Report

## A Rare Case of Familial Neurogenic Diabetes Insipidus in a 22-Year-Old Man

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## ABSTRACT

**Objective:** Diabetes insipidus (DI) can be classified into 2 types: central/neurogenic DI and nephrogenic DI. Most cases of central DI occur after brain surgery, trauma, tumor, or infection. Here we report a rare case of familial central DI due to a heterozygous AVP gene mutation.**Methods:** A case of familial neurogenic DI has been described with thorough clinical, laboratory, and genetic workup. PubMed and Google scholar databases were used for literature discussion.**Results:** A 22-year-old man presented with polyuria and polydipsia. He drank about 4 gallons of water everyday and urinated large volumes very frequently. His physical examination was unremarkable. After 2 hours of water-deprivation, his serum sodium level was 147 mmol/L, serum osmolality was 302 mOsm/kg with concurrent urine osmolality of 78 mOsm/kg, vasopressin level was <0.8 pg/mL, and copeptin level was <2.8 pmol/L, suggesting neurogenic DI. His brain magnetic resonance imaging revealed the absence of the posterior pituitary bright spot but a normal anterior pituitary gland. Genetic analysis revealed a nonfunctional heterozygous mutation in the AVP gene. Further questioning revealed that his mother also had the disease and that he had been treated with desmopressin as a child; however, it was later self-stopped. The patient was reinitiated on desmopressin, which improved his symptoms.**Conclusion:** Genetic mutations in the AVP gene represent a very rare etiology of DI, and patients with DI respond well to desmopressin treatment.Published by Elsevier Inc. on behalf of the AACE. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## Introduction

Diabetes insipidus (DI) is characterized by polyuria with hypotonic urine and plasma hyperosmolality if urinary fluid loss cannot be completely compensated for by fluid intake. It is a rare disease, with a prevalence of 1 in 25 000 people.<sup>1</sup> DI is classified into 2 types, central and nephrogenic, depending on whether it responds to vasopressin (AVP) or not. Of these 2, central diabetes insipidus (CDI) is more common, and most cases are due to brain surgeries or head injuries that damage the posterior pituitary gland, the pituitary

stalk, or the hypothalamic structures, leading to inadequate AVP production.<sup>1</sup> Familial CDI with symptom onset in early childhood has been reported in only 1% to 5% of all CDI cases.<sup>2,3</sup> Genetic mutations in the AVP gene on chromosome 20p13, the WFS1 gene on chromosome 4p16.1, or the PCSK1 gene on chromosome 5q15 have been reported to cause this extremely rare entity.<sup>4,5</sup>

Diagnosis of DI is usually made after a thorough hormonal workup and a water-deprivation test. In patients with confirmed polyuria (>3 L/day or 50 mL/kg/day), hypokalemia, hypercalcemia, osmotic diuresis secondary to hyperglycemia, and mannitol, urea, or loop diuretic use should be ruled out first.<sup>1,6</sup> Depending on baseline sodium and osmolality levels, patients may or may not need a water-deprivation test. If the patient already has plasma Na<sup>+</sup>>145 mEq/L, plasma osmolality (Posm) >295 mOsm/kg H<sub>2</sub>O, and urine osmolality <Posm, desmopressin can be administered immediately to differentiate between central versus nephrogenic DI by monitoring changes in urine osmolality. Water-deprivation test may be needed to ascertain the patient's maximal ability to

**Abbreviations:** AVP, arginine vasopressin; CDI, central diabetes insipidus; DI, diabetes insipidus; ER, endoplasmic reticulum; MRI, magnetic resonance imaging; NPII, neuropeptin II; Posm, plasma osmolality; Uosm, urine osmolality.

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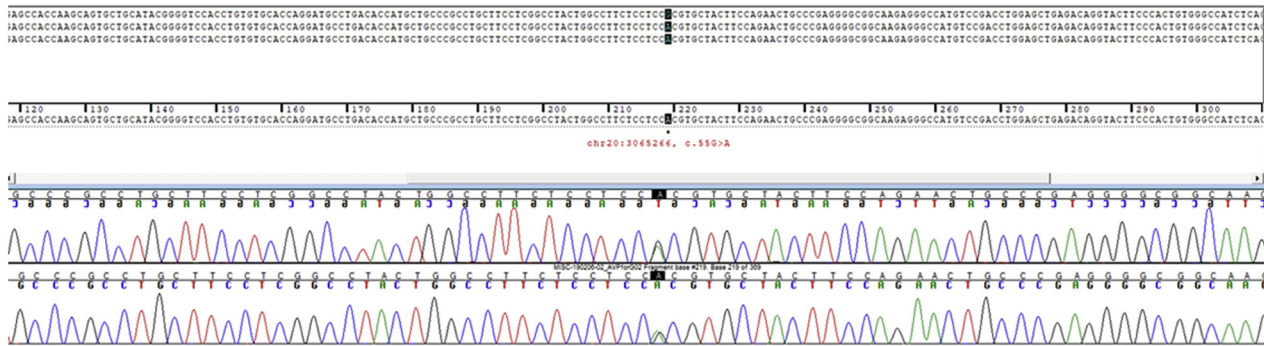


Fig. Genetic evaluation showing a nonfunctional heterozygous mutation in the *AVP* gene, c.55G>A, p.Ala19Thr, in the region encoding the signal peptide in exon 1.

concentrate urine before administering desmopressin. Water-deprivation test may be discontinued if the patient has 3% to 5% body weight loss, plasma  $\text{Na}^+ > 145$  mEq/L, Posm  $> 295$  mOsm/kg, or if urine osmolality normalizes.<sup>1,7</sup> AVP level is also measured to help differentiate between central and nephrogenic DI. Copeptin, which is co-secreted with AVP, is more stable in blood and can be a reliable marker of AVP secretion.<sup>4</sup>

Early diagnosis and treatment of familial DI are crucial because recurrent dehydration episodes during childhood might lead to growth and mental retardation.<sup>8,9</sup> Treatment of familial nephrogenic DI can be quite challenging, although familial CDI responds well to desmopressin treatment.<sup>1,10</sup> We report a rare case of CDI due to *AVP* mutation.

Genetic testing was performed in the DNA Diagnostic Laboratory, Keesler Air Force, MS. DNA was isolated and extracted from whole blood using the Puregene method (Qiagen). Custom primers were designed using Primer3 software. Amplicons were bidirectionally sequenced. Resequencing was performed on a 3130x sequencer using the BigDye 1.1 sequencing kit (Applied Biosystems). Reads generated by resequencing were aligned to genome build hg19 (NCBI build 37) using Sequencher (Gene Codes Corporation). Sequence analysis was performed using Sequencher and visual inspection. Copeptin (CT-proAVP) was measured by homogeneous automated immunofluorescent assay on the BRAHMS Kryptor Compact PLUS with a functional assay sensitivity of 1.08 pmol/L and detection limit of 0.69 pmol/L (Mayo Clinic Labs). AVP was measured using a competitive radioimmunoassay, using a kit manufactured by Euro-Diagnostica (Labcorp, NC). Its analytical and functional sensitivity were both 0.8 pg/mL. All other laboratory tests and magnetic resonance imaging (MRI) were performed at the Walter Reed National Military Medical Center.

### Case Report

A 22-year-old man presented for an evaluation of polyuria and polydipsia. He stated that, for as long as he could remember, he had to drink roughly 4 gallons (15 L) of water daily to avoid feeling thirsty and would urinate at least every hour, 24 hours a day. He denied any head trauma or brain surgery in the past and did not take any medications. Physical examination revealed a well-developed man with unremarkable vitals and normal cardiac, pulmonary, and abdominal examination. Neurologic examination result was normal with no visual deficit. His mucous membranes were moist; however, he was drinking water during the examination.

Initial laboratory evaluation without drinking water for 2 hours revealed hypernatremia ( $\text{Na}^+ = 147$  mmol/L) and hyperosmolality of 302 mOsm/kg, with an inappropriately low urine specific gravity of 1.001 and urine osmolality of 78 mOsm/kg. Pituitary MRI

revealed an absent pituitary bright spot and no pituitary or intracranial masses. Further laboratory evaluation revealed a serum AVP level of  $< 0.8$  pg/mL (normal, 0.0–4.7 pg/mL) and serum copeptin level of  $< 2.8$  pmol/L (cutoff for central DI,  $< 4.9$  pmol/L).<sup>11</sup> These results were suggestive of AVP deficiency consistent with CDI. Evaluation of the remaining pituitary axis was normal.

Genetic evaluation revealed a nonfunctional heterozygous mutation in the *AVP* gene, c.55G>A, p.Ala19Thr, in the region encoding the signal peptide in exon 1 (Fig.). Detailed family history revealed that his mother and 2-year-old son also had the disease, and they carried an identical familial mutation. The patient had been managed with desmopressin as a child; however, he had self-stopped when he became a teenager. He was initiated on desmopressin, which resulted in significant improvement in his polyuria and polydipsia and allowed him to sleep through an entire night without having to urinate. Follow-up results showed normal serum sodium (140–143 mmol/L), urine volume (1500–2000 mL/day), and urine osmolality (561 mOsm/kg).

### Discussion

In DI, patients lose the ability to concentrate urine due to inadequate AVP secretion or action, resulting in polyuria and polydipsia. Physiologically, about 180 L of fluid is filtered through the glomeruli per day, and 90% of this filtered fluid will be reabsorbed at the proximal tubules and the Henle loops. The remaining 10%, or 18 L, will reach the distal tubules and collecting ducts.<sup>8</sup> Without AVP action, patients cannot reabsorb free water and lose this amount of hypotonic fluid in the urine; hence, they have compensatory polydipsia of approximately 18 L per day to maintain homeostasis, as seen in our case.

Both central (neurogenic) and renal (nephrogenic) DI may have genetic or acquired etiologies (Table).<sup>1</sup> Hereditary central DI is a very rare etiology,<sup>12</sup> and most cases are caused by an autosomal dominant mutation in the *AVP* gene, resulting in abnormal pro-hormone formation. AVP is encoded in the *AVP*-neurophysin II gene on chromosome 20p13. This gene has 3 exons. Exon 1 encodes the signal peptide, AVP, and the aminoterminal region of neurophysin II (NPII). Exon 2 encodes the central region of NPII. Exon 3 encodes the carboxyterminal region of NPII and copeptin.<sup>6</sup> The gene's product, called prepro-vasopressin, is produced in the magnocellular neurons of the supraoptic and paraventricular nuclei of the human hypothalamus and is transported to the posterior pituitary gland, where it is proteolytically processed to create AVP-NPII prohormones and the mature hormone—AVP.<sup>6</sup> More than 70 mutations of this gene have been described since it was first reported in 1991.<sup>4,13</sup> A very high or complete penetrance of these mutations has been observed.<sup>4,14</sup> Most mutations occur in the region encoding NPII<sup>1</sup>—an intracellular carrier protein for AVP, leading to abnormal

**Table**  
Diabetes Insipidus Etiologies

	Central diabetes insipidus	Nephrogenic diabetes insipidus
<b>Acquired</b>	<ul style="list-style-type: none"> <li>• Trauma: brain injury, neurosurgery</li> <li>• Vascular: cerebral hemorrhage, infarction, aneurysm</li> <li>• Tumor: craniopharyngioma, meningioma, germinoma, pituitary tumors</li> <li>• Infiltrative disorders: histiocytosis, sarcoidosis</li> <li>• Inflammatory/autoimmune: lymphocytic hypophysitis, granulomatosis with polyangiitis</li> <li>• Infectious: meningitis, encephalitis</li> <li>• Drug/toxins: ethanol, diphenylhydantoin, snake venom</li> <li>• Other: hydrocephalus, suprasellar cyst</li> <li>• Idiopathic</li> </ul>	<ul style="list-style-type: none"> <li>• Drugs: demeclocycline, lithium, cidofovir, foscarnet, cisplatin, methoxyflurane</li> <li>• Electrolyte imbalance: hypercalcemia, hypokalemia</li> <li>• Kidney diseases: cystic kidney diseases, sickle cell disease, sarcoidosis, amyloidosis, multiple myeloma, Sjogren's disease</li> </ul>
<b>Hereditary</b>	<ul style="list-style-type: none"> <li>• Arginine vasopressin-neurophysin II gene mutation: on chromosome 20p13               <ul style="list-style-type: none"> <li>- Signal peptide region: autosomal dominant</li> <li>- Arginine vasopressin region: mostly autosomal dominant, rarely autosomal recessive</li> <li>- Neurophysin II region: autosomal dominant</li> </ul> </li> <li>• <i>WFS1</i> gene mutation - Wolfram syndrome: autosomal recessive, on chromosome 4p16.1</li> <li>• <i>PCSK1</i> gene on chromosome 5q15</li> <li>• X-linked recessive mutation</li> </ul>	<ul style="list-style-type: none"> <li>• Vasopressin V2 Receptor gene mutations: X-linked recessive, on chromosome Xq28</li> <li>• <i>Aquaporin-2</i> gene mutation: Autosomal recessive/dominant, on chromosome 12q12-q13</li> </ul>

protein conformation of the prohormones. These mutant prohormones accumulate as fibrillar aggregates in the endoplasmic reticulum (ER) due to their inability to fold or dimerize properly.<sup>6</sup> These aggregates occur when any allele of the gene becomes mutated, which helps explain its dominant inheritance.<sup>14</sup> Over time, these aggregates exert toxic damage on the magnocellular neurons, which leads to their degeneration. It is only at this stage that neuronal destruction is sufficient to cause clinical manifestations, thereby explaining the gradual and delayed onset of symptoms in some cases.<sup>15</sup> Although less common, other mutations in the coding region for the signal peptide or AVP itself can also occur.<sup>2</sup> Mutations in the region coding for mature AVP with autosomal recessive inheritance, leading to weaker binding activity to AVP receptors, have been reported in 1999 in a Palestinian family.<sup>16</sup> Mutations in the signal peptide region were first described in 1993 by Ito et al.<sup>17</sup> This affected the signal peptide cleavage site and led to the production of a 23 kd uncleaved prohormone protein instead of the normal 21-kd protein.<sup>17</sup> As our patient's mother and son also had CDI, molecular testing with targeted sequencing of exon 1 of the *AVP* gene was performed, and a familial p.Ala19Thr mutation was identified. This is the most common gene mutation in the signal peptide region leading to CDI. This mutation eradicated the restriction site for endonuclease-based cleavage, which in turn disabled signal peptide cleavage from preproAVP. These uncleaved precursor products were trapped and had accumulated in the ER, where they exerted their cytotoxic effects by impeding the processing of other essential proteins in the ER, leading to neuronal apoptosis.<sup>18</sup> This signal peptide gene mutation is reported to be associated with the variation in age-at-symptom-onset in affected families because cells expressing the p.Ala19Thr prohormone are still able to produce some normal AVP. Compared to kindreds with NPII region mutations, kindreds carrying the signal peptide mutation, such as in our case, seem to have later DI onset.<sup>19</sup> Our patient and his mother are doing well with desmopressin; however, his son is being monitored and followed up by a pediatrician and is not taking desmopressin yet.

*WFS1* is another gene related to familial neurogenic DI. Typical patients with Wolfram syndrome have central DI, insulin-dependent diabetes mellitus, optic atrophy, and neurosensory deafness.<sup>4,6</sup> These are usually caused by autosomal recessive mutations of the *WFS1* gene that affect the quantity and/or quality of wolframin, an essential protein for maintaining intracellular Ca

homeostasis and reducing ER stress.<sup>20</sup> In patients with mutated genes, some cell types, such as pancreatic beta cells and neurons, including supraoptic and paraventricular nuclei, are more susceptible to apoptosis, leading to diabetes mellitus and DI.<sup>20</sup> Currently, our patient does not have diabetes mellitus; his levels of fasting blood glucose, HbA1C, C-peptide, GAD-65 antibodies, islet cells, and insulin antibodies were all normal. Although most reported cases have a family history of neurogenic DI, which prompts genetic analysis, there have been reported cases of "idiopathic" early-onset DI due to de novo mutations in *AVP-NPII* or *WFS1* genes.<sup>21</sup>

That the absence of the posterior pituitary bright spot on MRI is suggestive of neurohypophyseal dysfunction has been reported in many familial CDI cases, as in our patient. However, this finding varies with the approximately 60% to 100% prevalence of posterior pituitary bright spot absence in CDI cases of all causes.<sup>22</sup> The bright spot might be present at the onset of familial CDI; however, it may disappear over time due to gradual progressive degeneration of the magnocellular axons in the posterior pituitary gland.<sup>9</sup>

Although the exact prevalence of familial CDI is unknown given its rarity, genetic analysis in families with suspected hereditary CDI is essential because it can identify members with positive mutations even if they are asymptomatic.<sup>14</sup> Sometimes, they have symptoms, but because of similarity of their symptoms with those of other affected family members, they may consider it "normal" and may miss the chance for early diagnosis.<sup>23</sup> These subjects will need a hormonal workup for diagnosis and treatment to prevent complications. Once diagnosis is established, patients will require life-long hormonal replacement. Treatment for hereditary CDI is desmopressin, similar to other subtypes of CDI. Patients usually respond well to desmopressin therapy, such as in our case. Interestingly, it has been reported from studies in animal models with autosomal dominant central DI that reducing the stimulus for intrinsic AVP synthesis by desmopressin treatment not only improves polyuria but also decreases toxic aggregates of mutant prohormones in the neurons.<sup>4</sup>

## Conclusion

DI is a disease process that can be caused by a multitude of different etiologies. Genetic mutations in the *AVP* gene comprise a very rare etiology of this condition. Most cases show autosomal dominant inheritance. Fortunately, patients suffering from this

condition respond well to desmopressin therapy. Genetic counseling/evaluation should be considered not only in individuals with early-onset CDI, but also in young adult CDI patients without a clear etiology, such as previous history of hypothalamic pituitary trauma/surgery or presence of infiltrative/inflammatory diseases.

## Disclosure

The authors have no multiplicity of interest to disclose. The views expressed in this article are those of the authors and do not reflect the official policy of the Department of Army/Navy/Air Force, Department of Defense, or the U.S. Government.

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