13 Familial DI and Genetic Workup

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Case Presentation

The patient is a 14-month old male, initially evaluated for poor weight gain. He was born full term with birthweight 7 pounds 2 ounces and had no issues with neonatal hypoglycemia. He nursed well as an infant, had no illnesses during this time, and was growing appropriately until around 1 year of age. Per the parents, he began drinking excessively (greater than 40 ounces per day), including drinking bath water, flower pots, puddles, and pet water bowls. He is requiring diapers changes every 1–1.5 hours, leaking with urine. He sometimes wakes at night and cries for water, and will quickly drink 8–10 ounces if offered. He prefers to drink water over milk or juice, and has a poor appetite for solid foods.

Of note, mother was diagnosed with central diabetes insipidus at age four and has been on desmopressin. She recalls that on imaging, her pituitary was "missing something". She had no issues with growth as a child, and no fertility concerns. Father has no pertinent medical history. 3-year-old sister does not have similar symptoms, and has normal growth and development.

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Physical exam is unremarkable. Normal genitalia and descended testes bilaterally. Random and first morning labs have shown normal glucose of 75–96 mg/dl and sodium 138–142 mg/dl. Creatinine was normal, and urinalysis showed no blood, protein, leukocytes, glucose, or ketones.

The patient was admitted for a water deprivation test, and had a sodium of 146 mmol/L after 18 hours without food or liquid intake. Urine output was calculated at 2.5 mL/kg/hour. Plasma osmolality was 298 mOsms/kg and urine osmolality was 300 mOsms/kg with urine specific gravity of 1.005. A pituitary MRI showed an absent posterior pituitary bright spot. Remainder of pituitary screening tests (thyroid hormone, cortisol, growth factors) were normal.

Assessment and Diagnosis

There are familial forms of both neurohypophyseal and nephrogenic diabetes insipidus (Table 13.1). Familial neurohypophyseal DI is most often due to autosomal dominant *arginine vasopressin* (*AVP*) mutations. 72 mutations have been identified, the majority in the NPII moiety or the signal peptide, though a few mutations in the AVP moiety have been described (Fig. 13.1). Most are missense or nonsense mutations, though a few deletions, indels, and splice site mutations have been found. Mutations lead to disor-

Table 13.1 Overview of familial DI

	Affected gene	Inheritance (# of mutations)	Age of onset
Neurohypophyseal DI	AVP	AD (73) AR (3)	1–6 years Early infancy
	WSF1	AR (>170)	2nd-3rd decade
Nephrogenic DI	AVPR2	X-linked (>200)	Early infancy
	AQP2	AR (52) AD (11)	Early infancy Early childhood

Fig. 13.1 The structure of the AVP gene related to components of the AVP peptide (prepro-AVP), including the N-terminal signal peptide (SP), the AVP moiety, the NPII moiety, and the C-terminal copeptin

dered processing or folding of AVP precursors; in most cases, the mutant is expressed, but retained in the endoplasmic reticulum, leading to cell death [1–3]. This is supported by autopsy studies showing absence of vasopressinergic neurons in affected subjects [4, 5]. There is also evidence to suggest that the mutant prohormones heterodimerize with wild-type AVP, preventing processing in a dominant negative manner [6]. The only evidence of genotype-phenotype correlation is with the c.55G > A (p.Ala19Thr) mutation, which causes abnormal cleavage of the signal peptide and is associated with later onset [7].

Onset is gradual due to progressive destruction of vasopressinergic neurons; thus, in early phases of the disease, AVP may be released during water deprivation, falsely confirming a normal response [8, 9]. Patients can present from a few months to a few years of age with polyuria, polydipsia, and failure to thrive. Presentation can be variable, even within the same family. There have been 3 autosomal recessive mutations in the *AVP* gene identified. All have presented with onset of DI in infancy, and good response to desmopressin.

Autosomal recessive mutations in the *WSF1* gene are associated with Wolfram's syndrome which presents with central diabetes insipidus, diabetes mellitus, optic atrophy, and deafness, (DIDMOAD) [10, 11]. Central DI is seen in 70% of patients; there is one reported case of isolated familial DI with WSF1 mutation. DI usually presents later in Wolfram's, in the 2nd to 3rd decade of life; the mechanism of neuronal destruction has not been identified but mutant wolframin is known to cause ER aggregates and ER stress in other cell types, suggesting this may also be causal in hypophyseal cells [12]. Case reports have also described central DI due to mutations in *PCSK1* and *FGF8*. There is also a report of X-linked transmission with no mutation yet identified [13–15].

Familial nephrogenic diabetes insipidus is caused by inactivating mutations of *AVPR2* (AVP receptor) in 90% and *AQP2* (aquaporin 2) in 10% of cases. Both lead to insensitivity of the distal nephron to AVP. Mutations in *AVPR2* are associated with X-linked inheritance, and thus the majority of cases are in males with onset of complete diabetes insipidus in early infancy [16, 17]. Some female patients have been reported, with milder phenotype, thought to be related to skewed X-inactivation [18]. Over 200 mutations have been reported, mostly missense mutations causing misfolded protein and ER retention.

AQP2 mutations are autosomal recessive homozygous or compound heterozygous in the majority of cases, though some heterozygous autosomal dominant mutations are described [19]. 52 mutations have been identified. Missense mutations throughout the *AQP2* gene result in misfolding and ER retention which ultimately causes cell death and complete diabetes insipidus. A few mutations do result in some cell surface AQP2 expression, and partial DI phenotype that may respond to desmopressin [20].

11 mutations in *AQP2* are associated with autosomal dominant inheritance. These tend to be in the c-terminal, and impede cell trafficking and localization [21]. These mutations exert a dominant negative influence when mutant protein forms heterotetramers with wild-type protein, leading to misrouting, and reduced expression at cell surface. Depending on the mutation, there may still be functional wild-type homotetramers; thus onset of AD disease is later in onset and milder than other forms [22].

Management

Patients with genetic forms of diabetes insipidus should be treated similarly to those with non-familial forms, using 1-desamino-8-D-arginine vasopressin (desmopressin) for neurohypophyseal disease and thiazide diuretics or indomethacin for nephrogenic cases. There are novel therapeutics in development for X-linked nephrogenic DI, including cell-permeable AVPR2 agonists that act as molecular chaperones and prevent misfolding of protein, leading to cell surface expression [23]. Secretin receptor agonists and

phosphodiesterase inhibitors are also being targeted to activate alternate pathways (bypassing AVPR2 activity) to AQP2 surface expression [24, 25].

Outcome

After the water deprivation test, desmopressin was given and led to decreased urine output. He continued treatment with desmopressin and showed improved appetite and weight gain, decreased polyuria and polydipsia. Genetic testing revealed mutation in AVP gene in patient and mother, and no mutation in father or older sister.

Clinical Pearls and Pitfalls

- Familial forms of DI include AR, AD, or X-linked inheritance and are primary caused by mutations in *AVP* in central DI and *AVPR2* and *AQP2* in nephrogenic DI.
- Mutations in *WSF1* cause Wolfram (DIDMOAD) syndrome which is associated with DI in 70% of cases, in addition to diabetes mellitus and optic atrophy.
- Phenotypes can vary, even within a family with the same mutation.
- Diagnostic testing early in disease process may be misleading, so if family history is suggestive, the diagnosis should not be excluded.
- Treatment of familial DI is similar to non-familial forms.

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