A Case of Nephrogenic Diabetes Insipidus Diagnosed at an Advanced Age in a Female Patient with an AVPR2 Gene Mutation and Skewed X Inactivation

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Background: Arginine vasopressin receptor 2 (AVPR2) gene mutations are the most common cause of congenital nephrogenic diabetes insipidus (CNDI), and they are inherited in an X-linked recessive manner. Women are generally asymptomatic or mildly affected, but atypically severe cases have been reported. Skewed X inactivation, in which the X chromosome is unevenly active, is a cause of this atypical severe case. X chromosome inactivation is a developmental compensation mechanism that results in equal doses of X-linked genes between XX females and XY males and has been reported to be accentuated by aging.

Clinical Case: A 69-year-old woman had no family history of diabetes insipidus. Immediately after undergoing a craniotomy for subarachnoid hemorrhage in July, she showed marked polyuria of approximately 8000 mL/day and hypernatremia of 161 mEq/L. The use of desmopressin (15 mcg/kg/day) did not improve her polyuria. She was referred to our department in September for further investigation and treatment. Her urine osmolality remained hypotonic at approximately 60–80 mOsm/kg/H O (50–1300 mOsm/kg/H 2 O) according to a water restriction test. Her urine osmolality increased slightly to 106 mOsm/kg/H 2 O in a desmopressin test. These results indicated that desmopressin was ineffective, and the patient was diagnosed with nephrogenic diabetes. Her urine output decreased to approximately 2500 mL/day with trichlormethiazide treatment. There was no significant anterior pituitary hypofunction.

Genetic examination revealed a heterozygous mutation of the AVPR2 gene (c.656T>G, p. Leu219Arg) in her X chromosome, and her X chromosome activity ratio was 79:21 in a human androgen receptor assay, indicating skewed X inactivation.

Conclusion: We observed a case of CNDI in an elderly woman with no family history of the disease. In this case, a combination of the skewed X inactivation, presumably accentuated by aging, and the onset of subarachnoid hemorrhage, reduced her drinking water and led to the diagnosis of CNDI.


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