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A Rare Case of Congenital Nephrogenic Diabetes Insipidus Associated with Aquaporin 2 Gene Mutation and Subsequent Acute Lymphoblastic Leukemia: Impact of Steroids on Kidney Function

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 9-month-old
Final Diagnosis: Nephrogenic diabetes insipidus
Symptoms: Vomiting
Clinical Procedure: —
Specialty: Endocrinology and Metabolic • Pediatrics and Neonatology

Objective: Rare disease

Background: Nephrogenic diabetes insipidus (NDI) is a rare renal disorder that can be congenital, and is caused by mutations in either aquaporin 2 or arginine vasopressin receptor 2, or it can be secondary to kidney disease or electrolyte imbalance. The clinical signs of NDI include polyuria, compensatory polydipsia, hypernatremic dehydration, and growth retardation without prompt treatment. In this report, we present the case of a patient with congenital NDI who was later diagnosed with acute lymphoblastic leukemia (ALL). With dexamethasone treatment, he had uncontrolled polyuria and polydipsia. Our aim was to concentrate on the impact of steroids on the kidneys.

Case Report: Our patient presented at the age of 9 months with signs of severe dehydration that were associated with polyuria. His laboratory examinations revealed hypernatremia and decreased urine osmolality. He was diagnosed with NDI and his exome sequence revealed a homozygous mutation at the nucleotide position AQP2 NM_000486.6: c.374C>T (p.Thr125Met). He was treated with hydrochlorothiazide and amiloride. Then, at age 19 months, he presented with gastroenteritis and a complete blood count (CBC) showed high white blood cell count and blast cells. He was diagnosed with (ALL) and began receiving chemotherapy, during which again developed polydipsia and polyuria, which could not be controlled with an increased dosage of hydrochlorothiazide.

Conclusions: We report a rare case of NDI caused by a missense mutation in the aquaporin 2 gene. One year later, the child developed ALL, and treatment with dexamethasone led to an uncompensated state of polydipsia and polyuria.

Keywords: Precursor B-Cell Lymphoblastic Leukemia-Lymphoma • Dexamethasone • Diabetes Insipidus, Nephrogenic • Aquaporin 2 • Polyuria

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Introduction

Nephrogenic diabetes insipidus (NDI) is a rare renal disorder with an incidence estimated at 8.8: 1 000 000 males for X-linked NDI based on data form the general population of Quebec [1]. It is characterized by inability to concentrate urine in the kidneys in response to vasopressin [2]. In 2022 a working group proposed to change the terminology to arginine vasopressin resistance (AVP-R) [3]. Its clinical presentation is similar to that of diabetes mellitus, which includes polyuria, polydipsia, dehydration, vomiting, and electrolyte imbalance [4]. NDI in children is most commonly congenital nephrogenic DI (CNDI) [5] resulting from either a mutation in arginine vasopressin receptor 2 (AVPR2) in 90% of patients with congenital nephrogenic diabetes insipidus or a mutation in the water channel protein aquaporin 2 (AQP2) in the remaining 10% of patients [2]. It can also be secondary to kidney diseases such as urinary tract obstruction, polycystic kidney disease, amyloidosis, sickle cell disease, granulomatous disease, chronic infection, electrolyte disturbances such as hypercalcemia or hypokalemia, and various drugs that interfere with the action of vasopressin in the renal tubules [6].

Diagnosis can be made after confirming polyuria, which is defined as urine output greater than 2 L/m^2/day [7], and excluding other causes of polyuria such as hypercalcemia, hyperglycemia, and hypokalemia. The second step is to check the sodium level (Na). If it is high (>145 meq/L) with diluted urine, this indicates a diagnosis of diabetes insipidus. The third step is the administration of desmopressin to distinguish between central DI and nephrogenic DI according to the response of urine osmolality [8]. NDI is diagnosed if urine osmolality does not increase by >50% after desmopressin administration [9]. In case of normal sodium level and plasma osmolarity, a water deprivation test is needed for the diagnosis [8].

Current treatments for CNDI rely on symptomatic management to limit urine output, which includes adequate fluid intake, minimizing osmotic load by restricting sodium intake to minimize obligatory urinary losses [10], and the use of drugs such as thiazide diuretics, which work on the thiazide-sensitive cotransporter SLC12A3 in the distal convoluted tubule, which decreases salt reabsorption. This then leads to a reduction in plasma volume and enhanced proximal reabsorption of the glomerular filtrate [2]. To minimize the risk of hypokalemia, potassium-sparing agents such as amiloride can be used. Other drugs, such as prostaglandin synthesis inhibitors (e.g. indomethacin and ibuprofen), reduce urine output independent of vasopressin, mainly by improving salt and water reabsorption in the proximal tubule [2].

The association between NDI and acute lymphoblastic leukemia (ALL) has rarely been reported, especially in the pediatric age group; it was reported in an adult patient as an initial presentation 1 month before the diagnosis of ALL, and disappeared with treatment [11].

In this report, we present a patient who is currently a 3-year-old boy who was diagnosed with NDI at age of 9 months. He was started on a low-sodium diet, hydrochlorothiazide (HCT), and amiloride, which significantly improved his clinical symptoms until 1 year later (at age of 19 months), when he presented with vomiting and diarrhea. His laboratory tests showed the presence of blast cells in the peripheral smear, and his bone marrow biopsy confirmed the diagnosis of B-cell ALL. Genetic analysis revealed a homozygous AQP2 mutation associated with autosomal recessive nephrogenic diabetes insipidus. When he started chemotherapy, especially dexamethasone, his symptoms worsened. He consumed approximately 6-8 L of water per day with the same amount of urine output. The aim of this case report is to emphasize the effect of steroids on the kidneys and the management difficulties encountered during management.

Case Report

A 9-month-old male patient initially presented with high-grade fever, vomiting, diarrhea, and severe hypernatremia dehydration, for which he was admitted to the pediatric ICU. During admission, his urine output was 7 ml/kg/h (3.5 L/m^2/day) despite his high sodium level (172 mmol/l) and low urine osmolality (147 mmol/L), for which he was diagnosed with diabetes insipidus. His past medical history revealed recurrent vomiting, for which he was diagnosed with a cow's milk allergy, and multiple admissions for hypernatremia dehydration. His weight was in the 15th percentile, and his length was below the 3rd percentile according to the World Health Organization (WHO)

Table 1. Laboratory results both before and after desmopressin treatment.

Laboratory parameter (units)	Before desmopressin	After desmopressin	Reference range
Sodium level (mmol/L)	172	157	135-145
Plasma osmolality (mOsm/kg)	352	322	275-294
Urine osmolality (mmol/L)	147	80	300-900

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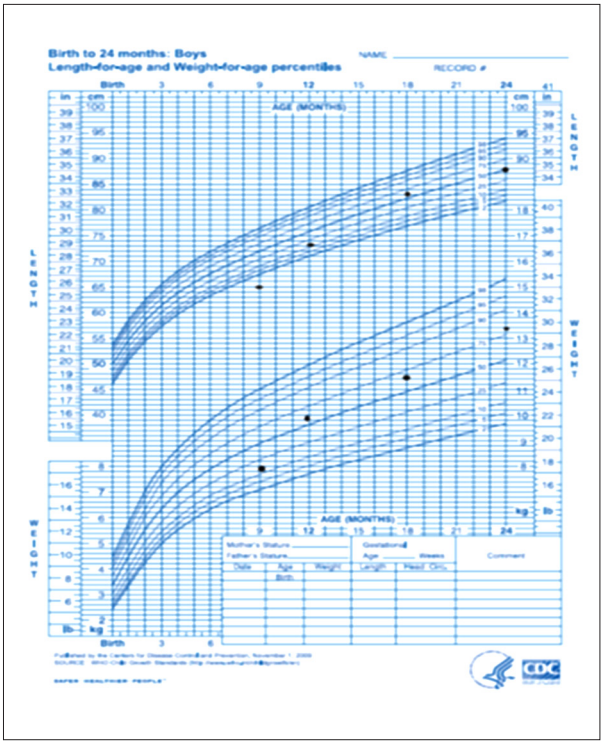

Figure 1. Growth chart of the patient after diagnosis with diabetes insipidus which showed catch-up after controlling his disease.

growth charts. His parents were second-degree consanguineous, and he had 2 older, healthy siblings.

Based on his clinical and biochemical laboratory results, he was diagnosed with diabetes insipidus. He was started on desmopressin therapy in addition to fluids during admission, but his urine osmolality and clinical presentation did not improve (**Table 1**). Therefore, we strongly suspected nephrogenic diabetes insipidus. His electrolytes (apart from sodium level) and kidney ultrasound results were normal; he had a normal urine analysis and a negative urine culture. He was started on hydrochlorothiazide and amiloride at a dose of 1 mg/kg (for hydrochlorothiazide) with sodium restriction.

He showed significant improvement in clinical symptoms, appetite, urine output, and night awakening to drink water. He was followed in an outpatient clinic every 3 months for fluid intake and output diary, electrolytes, and growth parameters. He had catch-up growth in his weight and height, as shown in **Figure 1**, and his urine output was maintained at approximately 2 L per day, **Figure 2** showed his Na level tracking at diagnosis and during follow up.

Later, his genomic DNA was extracted from an EDTA blood specimen using standard protocol. Exome capture was performed using xGen Exome Research Panel v2 (Integrated DNA

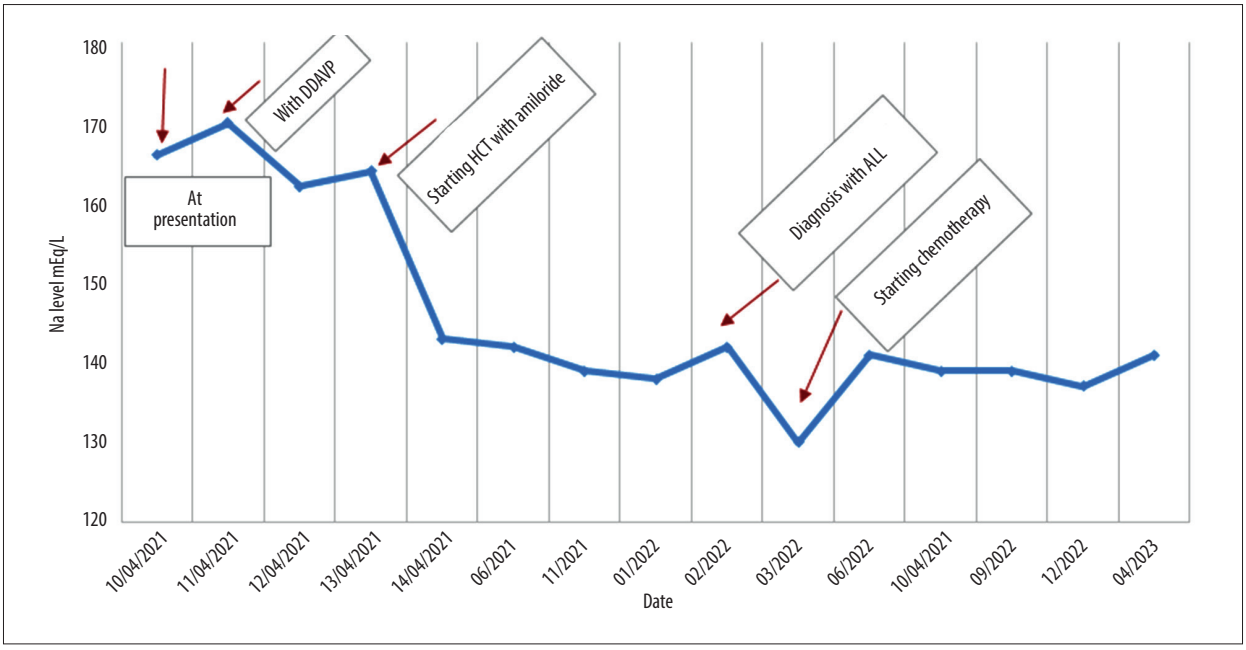

Figure 2. The patient's sodium level tracking. Arrows indicate Na level at presentation (age of 9 months), while starting DDAVP, during HCT treatment, and after starting chemotherapy. DDAVP – desmopressin; HCT – hydrochlorothiazide; ALL – acute lymphoblastic leukemia.

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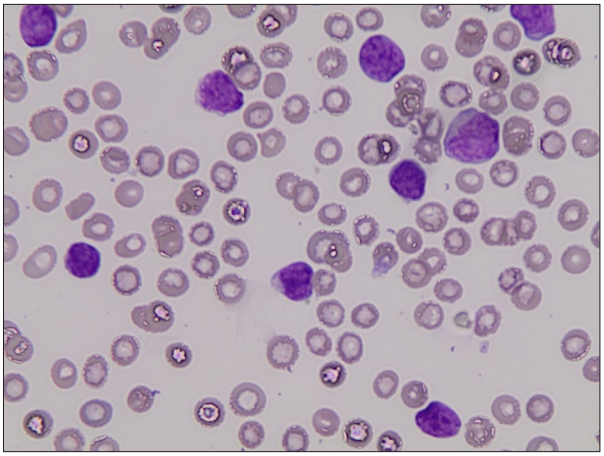

Figure 3. Peripheral blood smears exhibit a predominance of blast cells, constituting approximately 90% of nucleated cells identified within the smears. The blast cells exhibit a range of sizes, primarily appearing small-to-intermediate in diameter, with prominent nuclei occupying a significant portion of the cellular area. Notably, the nuclei display immature chromatin patterns and irregular nuclear contours associated with a thin rim of cytoplasm. Within the blast population, there are multiple occasional small nucleoli. These cellular demonstrations are characteristic morphological features consistent with a diagnosis of B-cell acute lymphoblastic leukemia (B-ALL). Within the smears, normal hematopoietic elements are markedly decreased, and megakaryocytes are visible.

Technologies, Coralville, IA, USA) and sequencing was performed using NovaSeq 6000 (Illumina, San Diego, CA, USA). It revealed an apparently homozygous mutation at the nucleotide position AQP2 NM_000486.6: c.374C>T (p.Thr125Met), which is associated with autosomal recessive nephrogenic diabetes insipidus, and this confirmed the diagnosis.

At the age of 19 months, the patient presented with a picture similar to gastroenteritis with diarrhea and vomiting of 4 days duration, for which he was evaluated in the emergency department and received normal saline bolus and blood samples were sent to the laboratory for testing. His complete blood count (CBC) showed elevated white blood cells ($32.1\times10^3/mm^3$, lymphocytes 90% (40% of them suspicious), with a decrease in hemoglobin (8.5 g/dl) and platelet count ($78\times10^3/mm^3$). His lactate dehydrogenase level was elevated, but his serum chemistry values were within the normal range. He underwent bone marrow biopsy, and the results revealed acute B-lymphoblastic leukemia (B-ALL) (**Figure 3**). Flow cytometry analysis showed that his lymphoblast expressed CD34, CD19, CD22, HLA-DR, and TdT. He was started on chemotherapy for standard-risk ALL, and an AALL0331 protocol was established by the Children's Oncology Group (COG). First, he received induction therapy with dexamethasone, vincristine, pegaspargase, intrathecal methotrexate, and intrathecal cytrabine. During that chemotherapy, his symptoms worsened; he vigorously sought water, and his urine output reached 8 L per day. His sodium level ranged from low to low-normal as shown in figure 2, and this was uncontrolled even with a higher dose of hydrochlorothiazide (3 mg/kg) or with a trial of desmopressin. Due to hematological concerns, we could not add prostaglandin synthesis inhibitors.

Pituitary and brain MRI was performed to exclude central leukemic infiltration responsible for this uncontrolled DI, which revealed no pituitary mass lesion, with normal pituitary stalk thickness.

Eventually, we tried to manage this with behavioral therapy, giving him food or milk instead of water when he asked to drink, and limiting all water sources in his room. This approach (in addition to his regular medications) achieved partial control, and his fluid intake and urine output were reduced by 50%.

Currently, he is 3 years old, in the maintenance phase of chemotherapy, and doing well. His electrolytes are normal, and urinary bladder ultrasound showed a smoothed outline of the urinary bladder and a volume of 190 ml.

Discussion

In the human body, it is critical to maintain plasma tonicity within its normal range [12], since extracellular osmolality has a crucial role in regulating cell shape and intracellular concentrations of ions and other osmolytes, as well as cell function [13].

Under physiological circumstances, this balance is regulated by the normal function of the hypothalamus and its surrounding brain tissue, the posterior pituitary, which secretes arginine vasopressin peptide (AVP), and by the kidneys [13].

Vasopressin is secreted from the hypothalamus neurons according to plasma osmolality and other non-osmotic stimuli [2]. In the kidneys, vasopressin binds to arginine vasopressin receptor (AVPR2), which is located primarily in the renal collecting tubule, along with other sites, including the thick ascending limb of the loop of Henle and periglomerular tubules [2]. This, in turn, activates adenylyl cyclase to convert ATP to cyclic AMP. Cyclic AMP, as a second messenger, induces activation of protein kinase A, which phosphorylates AQP2 tetramers [12]. Phosphorylated AQP2 tetramers are transported to the apical membrane of principal cells to form water channels for water reabsorption and this subsequently concentrates the urine [12].

Congenital nephrogenic diabetes insipidus (CNDI) is a rare genetic disease [7]. Ninety percent of cases are caused by X-linked

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recessive inheritance of the AVPR2 gene mutation, which leads to a decrease in the response of principal cells to vasopressin [2], while the remaining 10% of NDI cases are caused by AQP2 gene mutations, causing defects in the water channel in principal cells and eventually leading to inability to resorb water and concentrate urine in the kidneys [2]. To date, more than 70 AQP2 mutations have been reported [14].

Aquaporins, which are protein molecules inserted in the cell membrane, have an important function in regulating the transfer of water and other small substances such as ions, glycerol, urea, and hydrogen peroxide throughout cellular membranes [15]. There are 13 different proteins (AQP1-12A, B) that have been identified in humans, and they are present in different cells and organs [15].

Management of NDI has focused on ameliorating symptoms and limiting urine output, which includes adequate fluid intake, minimizing osmotic load by restricting sodium intake to minimize obligatory urinary losses [2], and administrating drugs such as thiazide diuretics, which work on thiazide-sensitive cotransporter SLC12A3 in the distal convoluted tubule, which decreases salt reabsorption. This then leads to a reduction in plasma volume and enhanced proximal reabsorption of the glomerular filtrate [2]. To minimize the risk of hypokalemia, potassium-sparing agents such as amiloride can be used [16]. Other drugs, such as prostaglandin synthesis inhibitors (e.g. indomethacin and ibuprofen) reduce urine output independent of vasopressin, mainly by improving salt and water reabsorption in the proximal tubules [2].

It is recommended to start with the minimal dose of thiazide that achieves a response; the starting dose of thiazides is 1-3 mg/kg/day for hydrochlorothiazide [17], and the dose is adjusted according to urine output, fluid intake, sodium level, or adverse effects. The most common adverse effects of HCT are hypokalemia and hypercalcemia, and hypokalemia can be managed by adding amiloride at a dose of 0.3 mg/kg [18].

In addition to the diuretic, prostaglandin synthesis inhibitors such as indomethacin (1-3 mg/kg), a nonselective cyclo-oxygenase inhibitor, antagonize prostaglandin synthesis and lead to enhanced proximal tubule water reabsorption, reducing urine output by 25-50% further than thiazides alone. Adverse effects of indomethacin, such as abdominal pain or gastric bleeding, should be monitored and can be minimized if the medication is taken with meals or with the addition of a proton pump inhibitor [17].

Unfortunately, current management strategies for NDI patients are symptomatic and sub-optimal; most patients still experience significant polyuria and polydipsia and require monitoring for the development of flow uropathy [17]. Novel treatments have been studied to discover targeted therapy for NDI or gene therapy involving kidney-specific delivery of wild-type AVPR2 or AQP2, which could potentially cure congenital NDI, but progress is slow [2].

The patient in this case was diagnosed with CNDI at the age of 9 months. Subsequently, exome sequencing showed a homozygous pathogenic variant in AQP2 (NM_000486.6: c.374C>T) at an extremely low frequency. This variant was previously reported in a female patient with a negative family history of NDI who presented in the neonatal period for signs of severe dehydration. It was suspected to be an autosomal recessive inheritance. It was the first case to be reported to have a compound heterozygote missense mutation involving NM_000486.5: exon2: c.374C>T (p.Thr125Met) and a gross deletion of at least exons 2 and 3 [19]. She received potassium, magnesium, and ranitidine in addition to hydrochlorothiazide, amiloride, and indomethacin. Despite this, control was difficult to achieve and she continued to have polyuria (about 6 L/day) [19].

In the present case, 1 year after diagnosis the patient presented with gastroenteritis and was diagnosed with B-cell acute lymphoblastic leukemia based on blood smear and bone marrow biopsy results. With initiation of chemotherapy, especially dexamethasone, his symptoms (polyuria and polydipsia) worsened, and were associated with a low-to-normal sodium level.

There are very few reports of polyuria and polydipsia after systemic corticosteroid treatment in patients without NDI. There is a reported case of severe polyuria after intravenous administration of dexamethasone, which was resistant to vasopressin [20], and another case reported after intra-articular steroid injection [21].

We propose 2 theories to explain this situation: one is the effect of dexamethasone on the kidneys, which increases the glomerular filtration rate, antagonizing the effect of HCT [22], and the other is that dexamethasone can lead to improvement in appetite signaling [23] but it was misunderstood in our patient with the increase in drinking water.

Eventually, we tried to manage this with behavioral therapy as a case of polydipsia, giving him food or milk instead of water when he asked to drink, and limiting all water sources in his room. By using this approach (in addition to his regular medication), we archived partial control, and his intake and urine output were reduced by 50%.

Conclusions

This report describes the case of a young child with congenital nephrogenic diabetes with an AQP-2 gene mutation and ALL.

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Additionally, he had uncompensated polyuria and polydipsia (mainly vasopressin-resistant polyuria) with dexamethasone treatment, which was mostly vasopressin-resistant polyuria.

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Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

References:

1. Arthus MF, Lonergan M, Crumley MJ, et al. Report of 33 novel AVPR2 mutations and analysis of 117 families with X-linked nephrogenic diabetes insipidus. J Am Soc Nephrol. 2000;11(6):1044-54
2. Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. Nat Rev Nephrol. 2015;11(10):576-88
3. Arima H, Cheetham T, Christ-Crain M, et al. Changing the name of diabetes insipidus: A position statement of the working group for renaming diabetes insipidus. J Clin Endocrinol Metab. 2022;108(1):1-3
4. Huang L, Ma L, Li L, et al. Case report: A case of congenital nephrogenic diabetes insipidus caused by Thr273Met mutation in arginine vasopressin receptor 2. Front Pediatr. 2021;9:707452
5. Hui C, Khan M, Suheb K. Arginine vasopressin disorder (diabetes insipidus). StatPearls. Published online 2024
6. Moeller HB, Rittig S, Fenton RA. Nephrogenic diabetes insipidus: essential insights into the molecular background and potential therapies for treatment. Endocr Rev. 2013;34(2):278-301
7. Di Iorgi N, Napoli F, Allegri AEM, et al. Diabetes insipidus – diagnosis and management. Horm Res Paediatr. 2012;77(2):69-84
8. Patti G, Ibba A, Morana G, et al. Central diabetes insipidus in children: Diagnosis and management. Baillieres Best Pract Res Clin Endocrinol Metab. 2020;34(5):101440
9. Patti G, Napoli F, Fava D, et al. Approach to the pediatric patient: Central diabetes insipidus. J Clin Endocrinol Metab. 2022;107(5):1407-16
10. Bhattacharjee R, Ghosh S, Nath A, et al. Theragnostic strategies harnessing the self-renewal pathways of stem-like cells in the acute myeloid leukemia. Crit Rev Oncol Hematol. 2022;177(103753):103753
11. Li D, Liu Q, Feng Z, et al. Nephrogenic diabetes insipidus in initial stage of acute lymphoblastic leukemia and relapse after haploidentical hematopoietic stem-cell transplantation: A case report. Medicine (Baltimore). 2018;97(24):e11157
12. Milano S, Carmosino M, Gerbino A, et al. Hereditary nephrogenic diabetes insipidus: Pathophysiology and possible treatment. An update. Int J Mol Sci. 2017;18(11):2385
13. Knepper MA, Kwon TH, Nielsen S. Molecular physiology of water balance. N Engl J Med. 2015;372(14):1349-58
14. Gao C, Higgins PJ, Zhang W. AQP2: Mutations associated with congenital nephrogenic diabetes insipidus and regulation by post-translational modifications and protein-protein interactions. Cells. 2020;9(10):2172
15. Allegra A, Cicero N, Mirabile G, et al. Critical role of aquaporins in cancer: Focus on hematological malignancies. Cancers (Basel). 2022;14(17):4182
16. Knoers N, Monnens LAH. Amiloride-hydrochlorothiazide versus indomethacin-hydrochlorothiazide in the treatment of nephrogenic diabetes insipidus. J Pediatr. 1990;117(3):499-502
17. Dabrowski E, Kadakia R, Zimmerman D. Diabetes insipidus in infants and children. Baillieres Best Pract Res Clin Endocrinol Metab. 2016;30(2):317-28
18. Alon U, Chan JC. Hydrochlorothiazide-amiloride in the treatment of congenital nephrogenic diabetes insipidus. Am J Nephrol. 1985;5(1):9-13
19. Peces R, Mena R, Peces C, et al. Severe congenital nephrogenic diabetes insipidus in a compound heterozygote with a new large deletion of the AQP2 gene. A case report. Mol Genet Genomic Med. 2019;7(4):e00568
20. Toftegaard M, Knudsen F. Massive vasopressin-resistant polyuria induced by dexamethasone. Intensive Care Med. 1995;21(3):238-40
21. Habib G. Polyuria and polydipsia following an intra-articular steroid injection. Eur J Intern Med. 2009;20(3):e75
22. Baylis C, Handa RK, Sorkin M. Glucocorticoids and control of glomerular filtration rate. Semin Nephrol. 1990;10(4):320-29
23. Kuckuck S, van der Valk ES, Scheurink AJW, et al. Glucocorticoids, stress and eating: The mediating role of appetite-regulating hormones. Obes Rev. 2023;24(3):e13539

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