Katarina Krstić[1], Sanja Ognjanović, Dušan Ilić,
Bojana Popović, Valentina Elezović Kovačević,
Milica Opalić Palibrk, Lena Radić, Đuro Macut

PARTIAL DIABETES INSIPIDUS: COMPLEXITY IN DIFFERENTIAL DIAGNOSIS

A 43-year-old male was hospitalized at the Clinic for Endocrinology, Diabetes, and Metabolic Diseases, UKCS, in April 2024 due to polyuric-polydipsic syndrome. Upon admission, he reported that for the past two months he has been consuming a lot of fluids, and for the past month, he has been urinating frequently. He has an increased feeling of thirst during the day and night. At night, he urinates 5-8 times depending on fluid intake. During a one-day measurement at home, he drank 5500mL and urinated 7250mL. An MRI of the sellar region verified the descent of the suprasellar cistern into the sella turcica (differential diagnosis partial "empty sella"), the adenohypophysis with a CC diameter of 3mm, slightly heterogeneous structure, without clear differentiation of focal zones. The physiological hypersignal of the neurohypophysis is not differentiated, the stalk is of appropriate position and diameter. He also conducted biochemical analyses independently: adequate glucose regulation (glucose 5.06, HbA1c 5.97%), urea 5.4, Cr 105, normal electrolytes (Na 142.6, K 4.36), serum osmolality 294mOsmol/kg, urine osmolality 378mOsmol/kg, specific urine gravity 1015. He reported having hypertension for the last three years. On Norvasc 5mg therapy, his blood pressure is adequately regulated. In his family history, he mentioned that his mother had laryngeal cancer, which also affected her relatives, and his father had metastatic cancer of unknown primary origin, his sister is being treated for anemia.

The patient was in good general condition upon admission, eupnoic, acyanotic, and afebrile. Skin and visible mucous membranes were normally colored, without signs of hemorrhagic syndrome and without peripheral lymphadenopathy. Confrontation method showed no visual field defect. Cardiac and pulmonary findings were normal; BP 120/80mmHg, heart rate 72/min, without orthostasis. Abdomen soft and non-tender.

[1] Katarina Krstić, Clinic for Endocrinology, Diabetes, and Metabolic Diseases, UKCS.

Laboratory analyses: A pathological leukocyte formula was verified in the complete blood count (CBC), neutropenia with lymphocytosis, and mild normocytic anemia with normal platelets (high total leukocytes for the degree of neutropenia; Le 9.3 10^9/L, Ne 0.5 10^9/L, Ly 3.6 10^9/L, Hgb 111g/L, MCV 98 fL, PLT 253 10^9/L), normal CRP (1.6 mg/L), satisfactory glycemic control (glucose 5.7mmol/L, HbA1c 5.5%), mild hypercreatininemia (Cr 109 umol/L) with normal urea (urea 4.7 mmol/L), no electrolyte imbalance (Na 140 mmol/L, K 4.3 mmol/L, Cl 104 mmol/L, Ca 2.42 mmol/L, PO4 1.30 mmol/L, Mg 0.91 mmol/L), borderline ALT values (ALT 43 U/L) with normal values of other liver function tests, elevated LDH (663 U/L). Additional analyses including ACE and chitotriosidase were within normal values. Baseline hormonal status was completely normal (TSH 1.94mIU/L, fT4 14.2pmol/L, fT3 5.03pmol/L, negative organ-specific antibodies, FSH 6.0IU/L, LH 2.5 IU/L, total testosterone 14.13nmol/L, SHBG 23.8nmol/L, PRL 202mIU/L, ACTH 3.9pmol/L, cortisol 373nmol/L, IGF-1 158.6 ng/mL). A water deprivation test, during which serum osmolality increased from 298 to 305mOsmol/kg with serum Na up to 149mmol/L, while urine osmolality increased from 482 to 528mOsmol/kg. After administration of DDAVP, urine osmolality increased to 683mOsmol/kg, but due to technical reasons, two additional samples were not collected as planned by the protocol.

Based on the clinical presentation, test results, and MRI findings of the pituitary gland showing the absence of the “bright spot” in the neurohypophysis, indicative of antidiuretic hormone (ADH) deficiency in the neurosecretory granules, a diagnosis of partial diabetes insipidus was established. Desmopressin was initiated at a dose of 100 mcg (1/2 tablet) in the evening as part of the treatment regimen.

Due to the complete blood count findings, a hematologist was consulted, and due to the peripheral smear findings showing 16% blasts and 38% cells of the monocytic lineage, the patient was urgently transferred to the Clinic for Hematology UKCS, where a diagnosis of acute myeloid leukemia with neuroleukemia was established. Specific oncological treatment was initiated, which was accompanied by complications such as bone marrow aplasia and pulmonary aspergillosis. Finally, in September 2024, after screening the International Registry, a donor was found and an unrelated allogeneic HSC transplant was performed without complications. Prior to this, therapeutic irradiation of the CNS (craniospinal axis) was conducted as part of the pre-transplant protocol. Control myelogram indicates complete remission.

Discussion

Diabetes insipidus (DI) is a disorder characterized by excessive urine output (>3L/24h) of hypoosmolar urine (<300mOsm/kg). Under physiological conditions,

if osmolality falls below 280 mOsm/kg, vasopressin secretion is suppressed, leading to the excretion of hypoosmolar urine (<100 mOsm/kg). In healthy individuals, the osmolality level at which maximum antidiuresis occurs (295mOsm/kg) is also the thirst threshold. When plasma osmolality exceeds this threshold, vasopressin is secreted, resulting in maximum urine concentration in the renal medulla.

There are central diabetes insipidus (caused by decreased synthesis of antidiuretic hormone; 80% of arginine vasopressin-secreting neurons must be damaged to cause DI) and nephrogenic DI (caused by renal resistance to circulating ADH). Due to frequent confusion between Diabetes insipidus and Diabetes mellitus, in 2022, upon the proposal of numerous European and global endocrinology associations and with the support of patients, the terminology was changed. Central DI was renamed "Arginine Vasopressin Deficiency (AVP-D)" and nephrogenic DI to "Arginine Vasopressin Resistance (AVP-R)."

Central diabetes insipidus is a rare endocrine disorder affecting nearly 1 in 25,000 people or about 0.004% of the general population. It occurs equally in both genders and can develop at any age, with hereditary forms appearing earlier in life.

Antidiuretic hormone (ADH, arginine vasopressin (AVP)) is a nonapeptide synthesized as a preprohormone (prepropressophysin) primarily in the supraoptic nuclei and to a lesser extent in the paraventricular nuclei of the hypothalamus. It is then transported via axons to the neurohypophysis, where it is stored in secretory granules and released into the systemic circulation. Before secretion, the preprohormone is enzymatically cleaved into neurophysin and copeptin, which are biologically inert, and the active hormone AVP. These components are released into the plasma in equimolar concentrations.

The primary role of ADH is to maintain osmotic balance. Hyperosmolar states strongly stimulate ADH secretion. Osmoreceptors in the anterior hypothalamus are sensitive to changes in blood osmolality. ADH primarily acts on the kidneys by binding to V2 receptors in the distal and collecting tubules, initiating an intracellular phosphorylation cascade that leads to the phosphorylation of aquaporin-2 and subsequent water reabsorption. Increased ADH production is also induced by hypovolemia. Baroreceptors in the left atrium, carotid artery, and aortic arch detect changes in blood volume and directly stimulate ADH secretion through the vagus nerve. ADH then binds to V1 receptors on the smooth muscle cells of blood vessels, initiating phosphorylation processes. The overall effect of this signaling cascade is the contraction of smooth muscle cells in blood vessels, leading to increased total peripheral resistance and, consequently, increased blood pressure.

There are congenital and acquired factors that can lead to central diabetes insipidus (Table 1)

CONGENITAL	▪ Autosomal dominant – mutation in the AVP gene, ▪ Autosomal recessive – Wolfram syndrome (mutation in the WFS1 gene)
ACQUIRED:	▪ Idiopathic – 50% ▪ Trauma – pituitary surgery, injuries, radiation therapy ▪ Primary tumors – craniopharyngioma, meningioma, germinoma, Rathke's pouch cyst, pituitary adenoma, astrocytoma ▪ Metastatic tumors – lymphomas, leukemias, breast cancer, lung cancer ▪ Inflammatory/autoimmune – lymphocytic hypophysitis, hypophysitis associated with IgG4 ▪ Vascular – hemorrhages, Sheehan's syndrome ▪ Infectious – meningitis, encephalitis, HIV, tuberculosis, toxoplasmosis ▪ Granulomatous diseases – sarcoidosis, histiocytosis ▪ Other – osmoreceptor dysfunction, hydrocephalus, drugs/toxins

About 50% of patients with central DI have an idiopathic form. Many of these patients may have autoimmune destruction of the neurohypophysis as the most likely cause of central DI.

Trauma or surgical treatment of the neurohypophysis is followed by the appearance of DI after 1-4 days. The disease can be permanent or there may be recovery that is either definitive or transient; in the latter case, recovery lasts for several days and ends with permanent DI. This triphasic pattern in the dynamics of vasopressin secretion is characteristic of traumatic DI.

Metastases to the pituitary gland represent rare complications of advanced malignant disease. In 1857, the first case of metastatic melanoma in the pituitary gland was identified through autopsy. Then, in 1913, Cushing published this unique phenomenon as a cause of diabetes insipidus. Pituitary metastases are rare, accounting for 1% of all operated pituitary tumors and <1% of all intracranial metastatic lesions. Most cases are asymptomatic and are discovered incidentally during autopsy or in patients in the terminal stage of malignant disease. For 20-30% of patients with pituitary metastases, this is the first manifestation of the malignant disease. Any type of cancer can metastasize to the pituitary gland. In women, it is most commonly breast cancer (50%), and in men, lung cancer (46%). Diabetes insipidus occurs in 50% of patients with pituitary metastases. Metastatic spread to the posterior lobe of the pituitary gland and infundibulum is a consequence of hematogenous spread through the inferior hypophyseal artery. Patients with pituitary metastases have a poor prognosis, and most die within 12 months of diagnosis.

Central diabetes insipidus (CDI) is a rare reported complication of acute myeloid leukemia (AML), occurring in less than 0.6% of AML cases. The onset of CDI typically precedes the diagnosis of AML by 1-2 months. However, CDI can occur at the time of AML diagnosis or as the initial manifestation of AML relapse. It is assumed that CDI associated with AML represents an unfavorable prognostic indicator of AML, even when CDI symptoms are alleviated by the administration of desmopressin (DDAVP). The mechanism is believed to involve leukemic infiltration of the pituitary gland, which is not always visible on MRI. In one study, as many as 61.4% of patients with CDI due to AML did not have changes on MRI, while autopsy revealed that 46% of AML patients had peripituitary leukemic infiltration in the absence of obvious CDI. Recently, several case series have indicated cytogenetic aberrations of chromosomes 3 and 7 in patients with AML associated with CDI. Both aberrations result in the overexpression of ectopic viral integration 1 (EVI-1). It is assumed that overexpression of this gene interferes with hypothalamic secretion of ADH or leads to its inactivation. DI can result from infiltration, infarction, infection, hemorrhage, or thrombosis of the pituitary gland. In a study of CDI associated with AML, Ladigan and colleagues analyzed 51 cases of adults with myeloid malignancies and associated CDI. The average age of patients was 48 years, while the average age of all AML patients was 65 years. AML associated with CDI is more common in the female population (59% women) compared to a slight male predominance in all AML. Most (45/51) of these cases are de novo AML, where patients do not have a previously known primary bone marrow neoplasm. The remaining cases consist of myelodysplastic syndrome (MDS), which is a common precursor to AML, or AML transformed from aplastic anemia, MDS, or chronic myelomonocytic leukemia (CMML).

Primary symptoms common to AVP-D and AVP-R include polydipsia, polyuria, and nocturia. Polyuria is defined as urine excretion greater than 3L per day. Urine is usually most concentrated in the morning due to the lack of fluid intake during the night and increased AVP secretion during the late sleep period. As a result, the first sign of mild to moderate loss of urine concentration ability is often nocturia. However, nocturia is often nonspecific and may be secondary to other factors. In patients with central nervous system (CNS) tumors, in addition to classic symptoms, headaches and vision impairments may occur. Patients with AVP-D may develop reduced bone density in the lumbar spine and femoral neck. The mechanism for this is unclear. Additional symptoms in patients with AVP-D may include nonspecific symptoms such as weakness, lethargy, fatigue, and muscle pain. Before conducting functional testing, it is necessary to exclude other conditions that cause increased thirst and urination. The diagnosis is based on hypotonic polyuria with the presence of hyperosmolar plasma. Plasma sodium concentration is at the upper limit of normal in cranial and nephrogenic DI but is reduced in primary polydipsia. Diabetes insipidus should be differentiated from primary polydipsia, where there is also a problem of excessive fluid intake and

consequent polyuria, but the level of ADH is normal. For diagnosis and differential diagnosis, a short (8-hour) and extended water deprivation test (thirst test) is used, after which DDAVP is administered intramuscularly at a dose of 2mcg (to identify the origin of diabetes insipidus, cranial or nephrogenic) with further monitoring of urine osmolality (Table 2). Before the test, it is necessary to confirm normal thyroid and adrenal gland function (since thyroid hormones and cortisol affect water and electrolyte balance). If urine osmolality remains low, it implies a problem with ADH production. If urine osmolality increases >750mOsm/kg after desmopressin administration, central diabetes insipidus is present. However, if there is no increase in urine osmolality after desmopressin administration, it indicates an inadequate response to ADH, suggesting nephrogenic DI. It is often difficult to distinguish whether it is partial DI or primary polydipsia, especially after pituitary surgery (if the patient does not have an intact thirst sensation). In this case, plasma sodium and plasma osmolality can be helpful in the presence of polyuria, as in PP, sodium is often low basally (<135mmol/L) with low plasma osmolality (<280 mOsm/kg), while in DI, Na levels are higher (>147 mmol/L) with hyperosmolar plasma (>300mOsm/kg).

Table 2. Interpretation of water deprivation test

Diagnosis	Urine osmolality (mOsm/kg) after the thirst test	Urine osmolality (mOsm/kg) after desmopressin administration
Normal	>750	>750
Central DI	<300	>750
Partial DI/ 1° polydipsia	300-750	<750
Nephrogenic DI	<300	<300

During a short thirst test, a partial response is often expected due to the reduced concentrating ability of the renal medulla. For this reason, the extended thirst test (according to Miller and Moses) is applied. An increase in urine osmolality by 9% or more after DDAVP administration indicates partial cranial diabetes insipidus (CDI). A normal urine osmolality response in the presence of high plasma osmolality occurs in patients with a subtle vasopressin secretion deficit. The absence of an increase in urine osmolality after DDAVP in the presence of polydipsia and polyuria indicates primary polydipsia (PP). To overcome the low sensitivity of the aforementioned test in the differential diagnosis of PP and partial CDI, direct measurement of plasma arginine vasopressin (AVP) has been proposed. AVP concentrations below normal indicate CDI, above normal suggest nephrogenic diabetes insipidus (NDI), and normal

values indicate PP. However, numerous factors have hindered the implementation of AVP measurement in clinical practice, leading to the proposal of measuring copeptin, which is secreted in equimolar concentrations. Unstimulated copeptin values are useful in the differential diagnosis of NDI versus CDI (>21.4 pmol/L; 100% sensitivity and specificity for confirming NDI), while for the differential diagnosis of PP and CDI, a stimulation test with hypertonic saline infusion (3% NaCl solution) is necessary. Stimulated plasma copeptin values <4.9 pmol/L indicate CDI (partial or total), while levels equal to or greater than 4.9 pmol/L confirm PP.

Magnetic resonance imaging (MRI) is often used in patients suspected of central DI. It was long believed that the absence of a hyperintense area in the posterior pituitary, the so-called bright spot, was pathognomonic for CDI, as it was thought to result from AVP stored in neurosecretory granules. However, the absence of the bright spot was confirmed in 70% of patients with CDI, but also in 39% of patients with primary polydipsia in a prospective study involving 92 patients with polyuric-polydipsic syndrome. Some patients with CDI showed the presence of the bright spot. Another typical MRI characteristic is a thickened pituitary stalk, which is also not specific for CDI. However, detecting these MRI findings requires a more precise evaluation of pituitary and hypothalamic disorders.

It is very important to determine whether it is central or nephrogenic diabetes insipidus, as the therapeutic approach differs. If it is central DI, the treatment of choice is desmopressin, a vasopressin analogue. In nephrogenic DI, thiazide diuretics are used, which act on the distal tubule by blocking sodium and chloride cotransport. Increased excretion of NaCl induces mild hypovolemia, leading to increased sodium reabsorption in the proximal collecting tubule, thereby increasing water reabsorption. This alleviates polyuria. If the cause of DI is discovered, the underlying disease needs to be treated.

If metastasis to the pituitary is present (sudden onset of DI, often with deficiency of other pituitary tropic hormones, in a patient with diagnosed malignancy), complete surgical resection is usually not possible because metastases are often diffuse and invasive, but substitution of deficient target hormones and DDAVP is necessary. Surgery is indicated when suprasellar expansion of the metastasis results in optic chiasm compression and visual impairment, or when histological confirmation of the sellar tumor is needed for the diagnosis of the primary tumor and selection of appropriate therapy. Stereotactic radiosurgery of the sellar region is a possible therapeutic option, representing a non-invasive and safe method for alleviating compressive symptoms of pituitary metastases. Surgical resection and radiation therapy of the pituitary serve palliative purposes, to improve local symptoms without affecting survival.

We presented a case of a young patient who exhibited polyuric-polydipsic syndrome. Through detailed diagnostic and differential diagnostic procedures, the presence of a causal hematological disease was confirmed. The diagnosis was promptly esta-

blished, and the patient was referred for further hematological evaluation. MRI of the sellar region revealed partial empty sella with displacement of the adenohypophysis, but no deficiencies in basal tropic hormones were observed. Other potential causes of neurohypophysitis were excluded. Following hematopoietic stem cell transplantation, complete remission of acute myeloid leukemia (AML) was achieved along with complete remission of partial diabetes insipidus.

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