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CAUSES OF POLYURIA AND POLYDIPSIA – A CLINICAL CHALLENGE

Abstract: The differential diagnosis of polydipsia and polyuria represents a challenge in clinical practice, as a wide spectrum of diseases and disorders can lead to this syndrome. The most common causes include diabetes mellitus, pituitary disorders, electrolyte imbalance, renal diseases, psychogenic conditions, and drug effects. Our patient developed a polyuric-polydipsic syndrome following embolization and stent implantation of an aneurysm of the left internal carotid artery (ICA). Computed tomography (CT) of the brain showed no pathological changes. Diabetes insipidus (DI) was initially suspected. Over the following year, the daily water balance remained unchanged at 4–5 L/24 h. At our clinic, endocrinological evaluation was performed. The daily water balance with free fluid intake was approximately 4.5 L/24 h, with no electrolyte imbalance detected. Upon fluid restriction, a gradual increase in urine osmolality was observed, with normal urine specific gravity and consistently normal serum osmolality. An infusion test demonstrated maintenance of normal serum electrolytes and osmolality, with an adequate copeptin response. MRI of the sellar region showed no pathological substrate. In primary polydipsia, fluid restriction leads to increased urine osmolality, as seen in our patient, whereas urine osmolality remains low in central and nephrogenic DI. Measurement of basal copeptin is a reliable method for diagnosing nephrogenic DI, and copeptin measurement after a hypertonic saline infusion test helps differentiate central DI from primary polydipsia.

Introduction

The differential diagnosis of polydipsia and polyuria is a clinical challenge due to the broad range of diseases and disorders that can cause this syndrome. The most

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common causes include diabetes mellitus, pituitary disorders, electrolyte imbalances, renal diseases, psychogenic states, and medication effects. Diagnostic test results may show significant overlap between these entities, and incorrect treatment can potentially lead to serious complications.

A case report

A 45-year-old female patient developed a polyuric-polydipsic syndrome (nocturia, pale urine, fluid intake 5.5 L/24 h, diuresis 4.45 L/24 h; serum Na 138 mmol/L; urinary Na excretion 38 mmol/24 h; serum K 4.1 mmol/L, urinary K excretion 42 mmol/24 h) after embolization and stent implantation of an aneurysm of the left ICA in October 2023 (Table 1). CT of the brain revealed no pathological findings. Diabetes insipidus was initially suspected. The patient's history was negative for psychiatric or renal diseases, and no medication affecting water-electrolyte balance was reported. Over the following year, the daily water balance remained stable at 4–5 L/24 h. During hospitalization at our clinic in August 2024, endocrinological testing was performed. Daily water balance under free fluid intake was about 4.5 L/24 h (intake 4.5 L/24 h; diuresis 4.1 L/24 h), with no electrolyte imbalance (Na 135 mmol/L; urinary Na excretion 153 mmol/24 h; K 4 mmol/L; urinary K excretion 42 mmol/24 h). Under fluid restriction (2.5–3 L intake), a gradual increase in urine osmolality was observed (urine osmolality 223... 126... 488 mOsm/L), with normal urine specific gravity (1.012... 1.012... 1.015) and consistently normal serum osmolality (280–292 mOsm/kg) (Table 2). An infusion test with 500 mL 3% NaCl showed maintenance of normal serum electrolytes and osmolality, with an adequate copeptin response (serum Na 141… 136… 138 mmol/L; K 4.4… 4.1… 4.6 mmol/L; serum osmolality 292…285…280 mOsm/kg; basal copeptin 4.4 pmol/L, post-infusion copeptin 10.6 pmol/L). MRI of the sellar region showed no pathological substrate.

Discussion

Primary polydipsia is a disorder characterized by excessive water intake, leading to hypotonic polyuria. In the general population, primary polydipsia is a relatively rare condition, most commonly seen in patients with psychiatric disorders, especially schizophrenia, but it can also be idiopathic without a clearly identified mental illness. Some potential causes of primary polydipsia include dysfunction of the thirst center as well as the effects of certain medications such as antipsychotics, anticholinergics, and diuretics. Clinically, this condition may present with symptoms similar to diabetes insipidus (DI), contributing to the diagnostic challenge of differentiating DI. Primary

polydipsia and DI together are referred to as the polyuric-polydipsic syndrome, characterized by hypotonic polyuria. The diagnostic approach involves confirming hypotonic polyuria, differentiating among the various types of polyuric-polydipsic syndrome, and identifying the underlying causes [1, 2]. First, it is important to confirm increased diuresis (more than 3.5 L per day), thus excluding misinterpretation caused by nocturia or incontinence. The second step in establishing the diagnosis involves determining whether the diuresis is water-related, as opposed to osmotic diuresis, which occurs in hyperglycemia, use of SGLT-2 inhibitors, or administration of mannitol in the treatment of elevated intracranial pressure [3, 4, 5]. Elevated serum osmolality is characteristic of DI, while decreased serum osmolality is typical for primary polydipsia. Low urine osmolality indicates either DI or primary polydipsia. Elevated serum sodium levels suggest DI, while low serum sodium is specific to primary polydipsia. Elevated serum potassium and calcium levels can cause nephrogenic DI [6, 7, 8]. To establish the diagnosis and distinguish between central DI, nephrogenic DI, and primary polydipsia, clinical overlap must be considered, and more than one form may coexist in a single patient. The diagnostic process includes evaluation of clinical presentation and diagnostic test results, as well as the potential coexistence of other conditions. A detailed diagnostic approach aids in identifying the correct cause of polyuria and polydipsia, which will allow for appropriate treatment. Testing includes fluid restriction (water deprivation test) and administration of desmopressin, as well as measurement of baseline copeptin and copeptin after an infusion test. During limited fluid intake (2.5–3 L), patients with primary polydipsia are able to concentrate urine, as was the case with our patient, whereas those with central or nephrogenic DI excrete dilute urine. As a confirmatory test, measurement of baseline copeptin and copeptin after infusion was of particular importance. Copeptin is the precursor of vasopressin (also known as antidiuretic hormone – ADH). Unlike vasopressin, which is unstable and difficult to measure in blood, copeptin is stable and easy to measure, making it a reliable surrogate marker for the presence and levels of vasopressin [9]. Plasma copeptin levels correlate with plasma ADH levels in both healthy individuals and in those with DI or primary polydipsia. Measurement of baseline copeptin is a reliable method for diagnosing nephrogenic DI when baseline copeptin is >21.4 pmol/L, with 100% sensitivity and specificity. It also helps differentiate primary polydipsia from central DI when copeptin values are ≥2.9 pmol/L (with 82% sensitivity and 78% specificity), and to distinguish central DI from primary polydipsia when copeptin is <2.6 pmol/L (with 95% sensitivity and 100% specificity) [10, 11]. The infusion test can be used to differentiate primary polydipsia from central DI, and its value increases when combined with copeptin measurement, which represents a newer method of choice. Medications such as diuretics, SGLT-2 inhibitors, desmopressin, carbamazepine, chlorpropamide, glucocorticoids, and NSAIDs must be discontinued 24 hours before testing. Prior to initiating the infusion test, two intravenous lines are

established—one for infusion and the other for collecting baseline values of copeptin, serum sodium, glucose, and serum osmolality. The infusion test begins with 500 mL of 3% NaCl according to the standard protocol. At the midpoint of the test, sodium and potassium levels are checked, and serum osmolality is measured; then at the end of the test, sodium, potassium, and serum osmolality are measured again along with copeptin. According to protocol, the test lasts about three hours or until the target sodium level of ≥150 mmol/L is reached. Upon completion, 5% glucose infusion is administered at a rate of 500 mL/hour for one hour. Serum sodium is measured again after the glucose infusion to monitor sodium levels. Throughout the test, vital parameters, blood pressure, and pulse are monitored [12, 13]. Copeptin values after stimulation with hypertonic saline infusion <4.9 pmol/L indicate central DI, while values ≥4.9 pmol/L point to primary polydipsia [6,12].

Conclusion

During fluid restriction in primary polydipsia, urine osmolality increases, as observed in our patient. Basal copeptin measurement excluded nephrogenic DI, and copeptin measurement after the infusion test excluded central DI. Based on the test results, the diagnosis of primary polydipsia was established.

Table 1. Values before hospitalization

INTAKE 5.5 L/24h
DIURESIS 4.5 L/24h
Na 138 mmol/L
Na-ureza 38 mmol/24h
K 4.1 mmol/L
K-ureza 42 mmol/24h

Table 2. Values during hospitalization

INTAKE 4.5 L/24h
DIURESIS 4.1 L/24h
Na 135 mmol/L
Na-ureza 153 mmol/24h

K 4 mmol/L
K-ureza 42 mmol/24h
Serum osmolality 292...285...280 mOsm/kg
Urine osmolality 223...126...488 mOsm/L
Urine specific gravity 1.012...1.012...1.015

References

1. Robinson AG VJ. Posterior pituitary. Williams Textbook of Endocrinology, ed. 13; 2015: 300–3322015.
2. Fenske W, Allolio B. Clinical review: Current state and future perspectives in the diagnosis of diabetes insipidus: a clinical review. J Clin Endocrinol Metab. 2012; 97(10): 3426–37.
3. Garrahy A, Moran C, Thompson CJ. Diagnosis and management of central diabetes insipidus in adults. Clin Endocrinol (Oxf). 2019; 90(1): 23–30.
4. Bichet D. Diagnosis of polyuria and diabetes insipidus. UpToDate, Waltham MA (Accessed on March 25, 2015). 2009.
5. Weir MR, Januszewicz A, Gilbert RE, Vijapurkar U, Kline I, Fung A, et al. Effect of canagliflozin on blood pressure and adverse events related to osmotic diuresis and reduced intravascular volume in patients with type 2 diabetes mellitus. J Clin Hypertens (Greenwich). 2014; 16(12): 875–82.
6. Timper K, Fenske W, Kühn F, Frech N, Arici B, Rutishauser J, et al. Diagnostic Accuracy of Copeptin in the Differential Diagnosis of the Polyuria-polydipsia Syndrome: A Prospective Multicenter Study. J Clin Endocrinol Metab. 2015; 100(6): 2268–74.
7. Christ-Crain M, Fenske W. Copeptin in the diagnosis of vasopressin-dependent disorders of fluid homeostasis. Nat Rev Endocrinol. 2016; 12(3): 168–76.
8. Verbalis JG, Goldsmith SR, Greenberg A, Korzelius C, Schrier RW, Sterns RH, et al. Diagnosis, evaluation, and treatment of hyponatremia: expert panel recommendations. Am J Med. 2013; 126(10) Suppl 1: S1–42.
9. Morgenthaler NG, Struck J, Alonso C, Bergmann A. Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin Chem. 2006; 52(1): 112–9.
10. Fenske W, Quinkler M, Lorenz D, Zopf K, Haagen U, Papassotiriou J, et al. Copeptin in the differential diagnosis of the polydipsia-polyuria syndrome-revisiting the direct and indirect water deprivation tests. J Clin Endocrinol Metab. 2011; 96(5): 1506–15.
11. Christ-Crain M, Fenske W. Copeptin in the diagnosis of vasopressin-dependent disorders of fluid homeostasis. Nat Rev Endocrinol. 2016; 12(3): 168–76.

12. Fenske W, Refardt J, Chifu I, Schnyder I, Winzeler B, Drummond J, et al. A Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus. N Engl J Med. 2018; 379(5): 428–39.
13. Fenske WK, Schnyder I, Koch G, Walti C, Pfister M, Kopp P, et al. Release and Decay Kinetics of Copeptin vs AVP in Response to Osmotic Alterations in Healthy Volunteers. J Clin Endocrinol Metab. 2018; 103(2): 505–13.