AN OVERVIEW ABOUT POLYURIA-POLYDIPSIA SYNDROME IN CHILDREN

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Abstract

Background: Diabetes insipidus (DI) belongs to the polyuria polydipsia syndrome and is characterized by a high urinary output of more than 50 mL per kg body weight per 24 h, accompanied by polydipsia of more than 3 L a day. After exclusion of AVP-independent causes (such as hyperglycemia), the differential diagnosis of hypotonic polyuria includes central or nephrogenic DI and primary polydipsia. Differentiation is crucial since treatment varies and wrong treatment can have dangerous consequences. Polyuria polydipsia syndrome is a common problem in clinical practice with the main entities being central or nephrogenic DI and primary polydipsia. Central DI is characterized by an insufficient vasopressin (AVP) secretion from the pituitary, and nephrogenic DI results from an AVP resistance at the level of the kidneys. Both entities lead to hypotonic polyuria with consequent polydipsia. The most common form of central DI occurs mainly due to lesions of the posterior pituitary or the hypothalamic median eminence. A number of acquired disorders (e.g. trauma, neoplastic disease, granulomatous diseases) can lead to central DI. Transsphenoidal surgery can lead to transient central DI in up to 30% of cases and to permanent central DI in 2–10%

Keywords: Polyuria-polydipsia syndrome

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Introduction

Diabetes insipidus (DI) belongs to the polyuria polydipsia syndrome and is characterized by a high urinary output of more than 50 mL per kg body weight per 24 h, accompanied by polydipsia of more than 3 L a day. After exclusion of AVP-independent causes (such as hyperglycemia), the differential diagnosis of hypotonic polyuria includes central or nephrogenic DI and primary polydipsia. Differentiation is crucial since treatment varies and wrong treatment can have dangerous consequences **(1).**

Since decades, the gold standard for differential diagnosis is the classical indirect water deprivation test, which however, has its limitations and has a diagnostic accuracy of only around 70%. To overcome these limitations, the direct test was proposed with measurement of arginine vasopressin (AVP) upon osmotic stimulation. However, despite initial promising results, this test did not enter clinical routine, mainly due to technical limitations of the AVP assay. Novel approaches are therefore urgently needed. This review focuses on new diagnostic approaches in the differential diagnosis of polyuria polydipsia syndrome **(2).**

The polyuria polydipsia syndrome

Polyuria polydipsia syndrome is a common problem in clinical practice with the main entities being central or nephrogenic DI and primary polydipsia **(2).**

Central DI is characterized by an insufficient vasopressin (AVP) secretion from the pituitary, and nephrogenic DI results from an AVP resistance at the level of the kidneys **(3).**

Both entities lead to hypotonic polyuria with consequent polydipsia. The most common form of central DI occurs mainly due to lesions of the posterior pituitary or the hypothalamic median eminence. A number of acquired disorders (e.g. trauma, neoplastic disease, granulomatous diseases) can lead to central DI. Transsphenoidal surgery can lead to transient central DI in up to 30% of cases and to permanent central DI in 2–10% **(2).**

Genetic defects in the AVP synthesis can lead to inherited forms of central DI**(3).**

In most cases thirst mechanisms are intact, which leads to compensatory polydipsia. However, in a variant of central DI called osmoreceptor dysfunction, thirst is also impaired and hypodipsia can result in serious complications associated with hyperosmolality **(4).**

Nephrogenic DI results due to a lack of aquaporin 2 (AQP2)-mediated water reabsorption in the collecting duct. This can either result from mutations in the genes encoding for the key proteins AVPR2 and AQP2 or is secondarily triggered by biochemical disorders or by certain drugs especially lithium **(5).**

Excessive fluid intake over an extended period of time also causes polyuria despite intact AVP secretion and renal response, but the pathomechanism is less clear. In few cases, it can result from an abnormality in thirst mechanisms (sometimes called dipsogenic DI), but more often it is due to psdejeychiatric disorders (referred to as psychogenic polydipsia). Excessive fluid intake results in a decrease in osmolality and suppressed AVP release. Consequently, water is excreted to compensate for the high fluid intake. An analysis of 23 patients with profound hyponatremia due to primary polydipsia revealed an increased prevalence for psychiatric diagnosis such as dependency disorders (43%) and depression (35%) **(2).**

Another prospective study with 156 patients with polyuria polydipsia syndrome however showed a similar rate of 27% for psychiatric disorders between patients with primary polydipsia and patients with complete central DI **(6).**

As the chronic polydipsia in patients with primary polydipsia leads to a downregulation of the AQP2 channels in the kidneys, the renal medullary concentration gradient is reduced, making any diagnostic evaluation of the urinary measures difficult **(7).**

Differential diagnosis of the polyuria-polydipsia syndrome

The polyuria-polydipsia syndrome may arise from central DI caused by insufficient secretion of AVP, nephrogenic DI resulting from resistance to AVP action in the kidneys and primary polydipsia, by which excessive water intake leads to physiological suppression of AVP **(4).**

Central DI

Central or neurogenic DI is due to a deficiency of AVP production and/or secretion caused by a variety of acquired or congenital disorders. Clinical manifestations of acquired or congenital central DI are variable and range from mild to severe forms, depending on the degree of neuronal damage. Usually, before patients manifest polyuria or polydipsia, 80–90% of the magnocellular neurons in the hypothalamus need to be destroyed **(8).**

In magnetic resonance imaging, the posterior pituitary shows a hyperintense signal on sagittal T1-weighted imaging in healthy patients (the posterior pituitary ‘bright spot’), and the absence

of this hyperintensity is used as a non-specific hallmark of central DI **(9).**

Etiologies for acquired central DI include pituitary surgery, some types of central nervous system tumours, trauma, hemorrhage and autoimmune and granulomatous disease, whereas genetic mutations of the AVP gene are much less common. The most frequently encountered entity of acquired central DI is after transsphenoidal surgery. Transient central DI is observed in 16–34% of patients recovering from sellar region operations, and 2–10% develop permanent central DI **(9).**

A variety of central nervous system tumors has been shown to be associated with central DI. Tumors involving the hypothalamus (i.e. craniopharyngioma, germ cell tumors) and central nervous system malformations are a common cause of central DI, especially in children and young adults, accounting for approximately one-third of the acquired cases **(10).**

By contrast, although case reports have been published, pituitary adenomas very rarely present with central DI, even when complete anterior pituitary insufficiency is present **(3).**

In about 25% of the patients with central DI, no clinical evidence of a related disease can be linked, and no abnormality is found on neuroimaging (classified as idiopathic central DI) **(10).**

However, in one-third of patients with apparently idiopathic central DI, AVP-secreting cell autoantibodies have been demonstrated, suggesting an underlying autoimmune basis. Autoimmune destruction of the posterior pituitary often presents with pituitary stalk thickening and enlargement of the posterior pituitary in imaging studies **(11).**

Table (1): Etiologies of central and nephrogenic diabetes insipidus **(9).**

Various etiologies of central diabetes insipidus	**Various etiologies of nephrogenic diabetes insipidus**
Acquired: • Pituitary surgery, head trauma (deceleration) • Tumours comprising the hypothalamus or posterior pituitary (e.g. craniopharyngioma, germ cell tumours, metastases, pituitary adenomas), central nervous system malformations (e.g. hydrocephalus, ventricular/suprasellar cyst, Rathke's cleft cyst) • Vascular (i.e. ischaemia, hemorrhage (Sheehan syndrome), thrombosis) • Idiopathic • Autoimmune or inflammatory diseases (i.e. lymphocytic infundibuloneurohypophysitis, lymphocytic hypophysitis), granulomatous (i.e. histiocytosis, sarcoidosis), infectious (i.e. toxoplasmosis, HIV, meningitis, encephalitis)Congenital: • AVP precursor gene mutations • Wolfram Syndrome (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness, DIDMOAD) Gestational diabetes insipidus: • Exacerbation of central or nephrogenic diabetes insipidus • Increased degradation of AVP by placental vasopressinase	Acquired: • Drug-induced (i.e. lithium, amphotericin B, demeclocycline, dexamethasone, dopamine, ifosfamide, ofloxacin, orlistat and cisplatin, etc.) • Kidney disorders (i.e. acute and chronic kidney failure, sarcoidosis, amyloidosis, obstructive nephropathy • Hypercalcemia and hypokalemia Congenital: • AVP- receptor 2 gene mutations (inherited mostly X-linked) • Aquaporin 2 gene mutations (inherited autosomal recessive)

- AVP, arginine vasopressin; HIV, human immunodeficiency virus.

DI occurring during pregnancy is often transient and develops due to accelerated degradation of AVP by increased activity of placental vasopressinase **(11).**

Congenital forms of central DI are uncommon, mostly inherited in an autosomal-dominant fashion, and account for 1–5% of all causes of central DI. So far, several different mutations located in the coding region of the AVP precursor gene have been reported. These mutations lead to an abnormal precursor protein, which accumulates within the neuron. It appears that the slow progressive cell apoptosis causes the AVP deficiency **(12).**

Hence, congenital central DI typically develops months to years after birth. Central DI is rarely inherited in an autosomal recessive manner and is caused by mutations in the WSF1 gene encoding wolframin. The protein wolframin is involved in pancreatic beta cell proliferation, intracellular protein processing and calcium homeostasis. Its deficiency produces a wide spectrum of endocrine and central nervous system disorders, such as central DI, diabetes mellitus, optic atrophy and deafness (DIDMOAD) **(13).**

Nephrogenic DI

In patients with nephrogenic DI, the renal action of AVP is decreased because of an acquired or genetic defect. The clinical presentation is similar to central DI except that basal plasma AVP is elevated, similar to other endocrine syndromes of hormone resistance. Where nephrogenic DI is present, up to 95% of adults have the acquired form, with lithium treatment being the principal cause. Acquired nephrogenic DI can also be due to other drugs, such as antifungal agents (amphotericin B), antibiotics (ofloxacin, demeclocycline), dexamethasone, dopamine, ifosfamide, orlistat and cisplatin. Typically transient nephrogenic DI can occur in patients with acute or chronic renal failure, hypokalaemia, hypercalcaemia and after relief of obstructive nephropathy **(14).**

Congenital nephrogenic DI is less common, and in about 90% of cases, congenital nephrogenic DI is due to mutations in the AVP-receptor 2 gene and is mostly inherited in an X-linked recessive manner. In a few cases, autosomal recessive or dominant mutations in the aquaporin-2 gene have been described. Consequently, most of these patients are male, and the clinical presentation includes hypernatraemic dehydration combined with dilute urine as well as failure to thrive **(15).**

Primary polydipsia

Primary polydipsia is caused by excessive fluid intake, which results in a decrease in serum osmolality and, consequently, in an inhibition of AVP and hypotonic polyuria. Primary polydipsia was first described in patients with schizophrenia and was therefore named psychogenic polydipsia. However, psychiatric diseases other than schizophrenia, such as anxiety disorders, depression and addictive disorders, have been linked with this disease **(16).**

Another form of primary polydipsia is dipsogenic polydipsia, which occurs mostly in healthy people. This might be explained by a disturbed thirst sensation and a lower osmotic limit of thirst sensitivity below the osmotic threshold for AVP secretion **(17).**

Clinical manifestations

Patients with DI, especially those with osmoreceptor defect syndromes, can manifest with dehydration and hyperosmolality, if water loss cannot be compensated by fluid intake. Manifestations may range from non-specific symptoms such as irritability and cognitive dysfunction to more severe manifestations such as disorientation, reduced consciousness, seizure, coma, focal neurologic deficits and cerebral infarction. However, most patients have an intact thirst perception and water availability. In these patients the characteristic clinical symptom is polyuria and polydipsia which does not differ in manifestation between central or nephrogenic DI or primary polydipsia **(2).**

Patients with central DI are reported to have more often nocturia and a sudden onset of symptoms, resulting from the fact that urinary concentration can be maintained until the residual capacity of the hypothalamus to synthesize AVP falls below 10–15% of normal, after which urine output increases significantly. In addition, historically, it has been reported that patients with DI in contrast to patients with primary polydipsia prefer cold water as best quenching beverage and have a more sustained and less fluctuating course of symptoms **(2).**

However, we have only recently prospectively evaluated clinical signs and symptoms: Although the majority of patients with DI indeed reported a sudden onset of symptoms, still more than one-third experienced a slow process. Moreover, also more than 60% of patients with primary polydipsia reported nightly drinking, the majority of them preferred cold beverages, and nearly 80% indicated a sustained character of symptoms. Interestingly and in contrast with the described high prevalence of psychiatric diseases in primary polydipsia, less than 30% of patients with primary polydipsia had been psychiatrically diagnosed, which was the same prevalence as found in patients with complete central DI. Taken together, clinical signs and symptoms are not specific and sensitive enough to differentiate between the various entities of the polyuria polydipsia syndrome **(18).**

Radiological findings

Unenhanced brain MRI via assessment of the posterior pituitary and the pituitary stalk has been reported to provide important information in the differential diagnosis of DI. Specifically, an area of hyperintensivity, referred to as the pituitary 'bright spot', is normally observed in the posterior part of the sella turcica in sagittal views on T1-weighted images and is thought to result from the T1-shortening effects AVP which is stored in neurosecretory granules of the posterior lobe of the pituitary **(19).**

However, although earlier small studies demonstrated the absence of the bright spot in patients with central DI, other larger studies showed that an age-related absence of a the bright spot is observed in up to 52–100% of normal subjects. In addition, a loss of the bright spot has also been observed in nephrogenic DI patients bearing AVPR2 mutations **(1).**

Conversely, individual cases with persistent bright spot despite the presence of central DI have also been reported. Similarly, we recently showed in a prospective large-scale evaluation that the bright spot was persistent in 36% of patients with central DI, whereas it was missing in 36% of patients diagnosed with primary polydipsia. Consequently, the presence or absence of the bright spot on MRI appears not sensitive and specific enough as a diagnostic test in patients with DI **(20).**

Tests for differential diagnosis

For decades the standard diagnostic test for the evaluation of polyuria polydipsia syndrome was the indirect water deprivation test. Here insufficient AVP secretion or effect is diagnosed upon insufficient renal concentration capacity over a prolonged period of water deprivation and its

response to exogenous AVP administration. Interpretation of the test results is based on recommendations from Miller et al. according to the results of 29 patients with central DI (including 11 patients with partial DI), 2 patients with nephrogenic DI and five patients with primary polydipsia. Patients showing a urinary osmolality below 300 mosm/kg during the water deprivation test are classified as complete central DI if the urinary osmolality increased >50% after exogenous AVP injection. Patients staying below this cut-off are diagnosed as having nephrogenic DI. Patients with partial central DI and primary polydipsia are expected to have a urinary osmolality between 300 and 800 mosm/kg upon thirsting. Urinary osmolality after AVP administration then differentiates patients with partial central DI from patients with primary polydipsia: Patients with partial central DI have an increase in urinary osmolality >9%, whereas patients with primary polydipsia remain below 9%. However, the proposed cut-off levels were post hoc derived on a small patient cohort, showed a wide overlap in urinary osmolalities and were never prospectively validated **(21).**

Consequently, recent evaluations in patients with the polyuria polydipsia syndrome resulted in a diagnostic accuracy of only around 70%, with an especially low accuracy in patients with primary polydipsia **(6).**

To overcome these limitations, in 1981, Zerbe et al. proposed the 'direct' test, with direct measurement of plasma AVP upon osmotic stimulation. Thereby, AVP levels were evaluated in relation to the area of normality describing the physiological relationship between AVP release and plasma osmolality. Plasma AVP levels above the area of normality were defined as nephrogenic DI, levels below as central DI and levels in the normal range were defined as primary polydipsia **(22).**

The results clearly showed that direct measurement of plasma AVP had a superior diagnostic accuracy compared to the classical water deprivation test. However, despite these promising first results disappointing test results derived from recent investigations showing that AVP measurements, especially when using commercially available assays, pointed toward a correct diagnosis in only 38% of patients and were especially bad for differentiation between partial central DI and primary polydipsia **(21).**

Possible reasons are that an accurate definition of the normal physiological relationship describing plasma AVP as a function of osmotic activity has long been missed. The precise definition of this normal area, however, is a fundamental prerequisite for the use of direct AVP measurement. Secondly, the AVP assay per se is subject to several technical limitations, resulting in a high preanalytical instability. In addition, the few available reliable assay are not commercially available. Therefore, measurement of AVP never entered every day's clinical practice **(2).**

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