

Diabetes Insipidus – Diagnosis and Management

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Key Words

Central diabetes insipidus · Langerhans cell histiocytosis · Pituitary stalk · Vasopressin

Abstract

Central diabetes insipidus (CDI) is the end result of a number of conditions that affect the hypothalamic-neurohypophyseal system. The known causes include germinoma/cranio-pharyngioma, Langerhans cell histiocytosis (LCH), local inflammatory, autoimmune or vascular diseases, trauma resulting from surgery or an accident, sarcoidosis, metastases and midline cerebral and cranial malformations. In rare cases, the underlying cause can be genetic defects in vasopressin synthesis that are inherited as autosomal dominant, autosomal recessive or X-linked recessive traits. The diagnosis of the underlying condition is challenging and raises several concerns for patients and parents as it requires long-term follow-up. Proper etiological diagnosis can be achieved via a series of steps that start with clinical observations and then progress to more sophisticated tools. Specifically, MRI identification of pituitary hyperintensity in the posterior part of the sella, now considered a clear marker of neurohypophyseal functional integrity, together with the careful analysis of pituitary stalk shape and size, have provided the most striking findings contributing to the diagnosis and understand-

ing of some forms of 'idiopathic' CDI. MRI STIR (short-inversion-time inversion recovery sequencing) is a promising technology for the early identification of LCH-dependent CDI.

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Definition/Classification

Diabetes insipidus is a disease in which large volumes of dilute urine (polyuria) are excreted due to vasopressin (AVP) deficiency [central diabetes insipidus (CDI)], AVP resistance [nephrogenic diabetes insipidus (NDI)], or excessive water intake (primary polydipsia). Polyuria is characterized by a urine volume in excess of $2\text{ l/m}^2/24\text{ h}$ or approximately $150\text{ ml/kg}/24\text{ h}$ at birth, $100\text{--}110\text{ ml/kg}/24\text{ h}$ until the age of 2 years and $40\text{--}50\text{ ml/kg}/24\text{ h}$ in the older child and adult.

Etiology

In many patients, CDI is caused by the destruction or degeneration of neurons originating in the supraoptic and paraventricular nuclei. The known causes of these lesions include local inflammatory or autoimmune dis-

eases, vascular diseases, Langerhans cell histiocytosis (LCH), sarcoidosis, germinoma/craniopharyngioma, trauma resulting from surgery or an accident, metastases and midline cerebral and cranial malformations [1]. In rare cases, genetic defects in AVP synthesis, inherited as autosomal dominant, autosomal recessive or X-linked recessive traits, are the underlying cause. X-linked NDI is secondary to AVP receptor 2 (AVPR2) mutations, which results in a loss of function or dysregulation of the renal AVPR2. Abnormalities of the aquaporin 2 (AQP2) water-channel gene, located on chromosome 12 at 12q13 are responsible for familial autosomal recessive and dominant forms of NDI.

Epidemiology

Diabetes insipidus is a rare disease with a nonunivocal reported prevalence of 1:25,000 [2]. Less than 10% of diabetes insipidus can be attributed to hereditary forms [3]. In particular, X-linked NDI (OMIM 304800) represents 90% of cases of congenital NDI and occurs with a frequency of 4–8 per 1 million male live births; autosomal NDI (OMIM 125800) accounts for approximately 10% of the remaining cases [4]. No gender difference has been reported for the other forms. While the prevalence of Wolfram syndrome has been reported as 1–9/1,000,000 (www.orpha.net), the frequency of autosomal dominant CDI is currently unknown.

Pathogenesis and Pathology

Anatomy

The posterior pituitary consists of magnocellular neurons that produce AVP and/or oxytocin. The cell bodies of magnocellular neurons are located in the paraventricular and the supraoptic nuclei, and axons project to the neurohypophysis where the hormones are secreted into the blood stream. These axons store quantities of AVP great enough to sustain basal release for 30–50 days or to allow maximum antidiuresis for 5–10 days [5]. While the blood supply for the anterior pituitary is via the hypothalamic-pituitary portal system from the suprahypophyseal arteries, the vascularization of the posterior pituitary is direct from the inferior hypophyseal arteries.

AVP Biosynthesis

The AVP-neurophysin II gene (*AVP-NPII*) is located distally at the short arm of chromosome 20 (20p13). It cov-

ers 2.5 kb and comprises 3 exons. Exon 1 encodes the signal peptide of 19 amino acid residues, the nonapeptide AVP and the N-terminal region of NPII (9 amino acid residues). Exon 2 encodes the central highly conserved region of the NPII peptide (67 amino acid residues). Exon 3 encodes the C-terminal region of NPII (17 amino acid residues) and a 39 amino acid glycopeptide known as copeptin [6].

The *AVP-NPII* gene product, the AVP prehormone, is cotranslationally targeted to the endoplasmatic reticulum (ER), where the signal is cleaved off by signal peptidase and the copeptide is core glycosylated. AVP and NPII associate after cleavage and then form the tetramer, which increases the binding affinity of AVP for NPII. After the formation of 7 disulphide bonds within NPII and 1 bond within AVP and after glycosylation of the copeptide, the proprecursor is packaged into neurosecretory granules and then cleaved into the product peptides during axonal transport to the posterior pituitary [6]. Neurophysin serves to stabilize the hormone during its transport and storage, while recent data suggest copeptin may play an important role in the correct structural formation of the AVP precursor as a prerequisite for its efficient proteolytic maturation [7]. AVP and its protein carrier NPII are released from the posterior pituitary by calcium-dependent exocytosis when the axon is depolarized by osmoreceptor or baroreceptor stimuli (fig. 1).

Physiology of Water Homeostasis

The maintenance of water balance in healthy humans is achieved principally by three interrelated determinants: thirst, AVP and kidney function.

Recently, apelin – a bioactive peptide – has been isolated from bovine stomach extracts (similar to ghrelin, another stomach-hypothalamus association). It is expressed in the supraoptic and paraventricular nuclei and exerts its action on specific receptors located on vasoressinergic neurons. Apelin acts as a potent diuretic neuropeptide which counteracts AVP actions through inhibition of AVP neuron activity and AVP release. The coexistence of apelin and AVP in magnocellular neurons, along with their converse biological effects and regulation, is likely to play a key role in maintaining body fluids [8].

AVP acts on its major target organ, the kidney, where it increases urine osmolality. It binds to the V₂-receptors in the basolateral membrane of the renal collecting tubular and activates the G_s-adenyl cyclase system, increasing intracellular levels of cyclic 3',5'-adenosine monophosphate (cAMP). The latter activates protein kinase A, which in turn phosphorylates preformed AQP2 water channels localized in intracellular vesicles [9]. Phosphor-

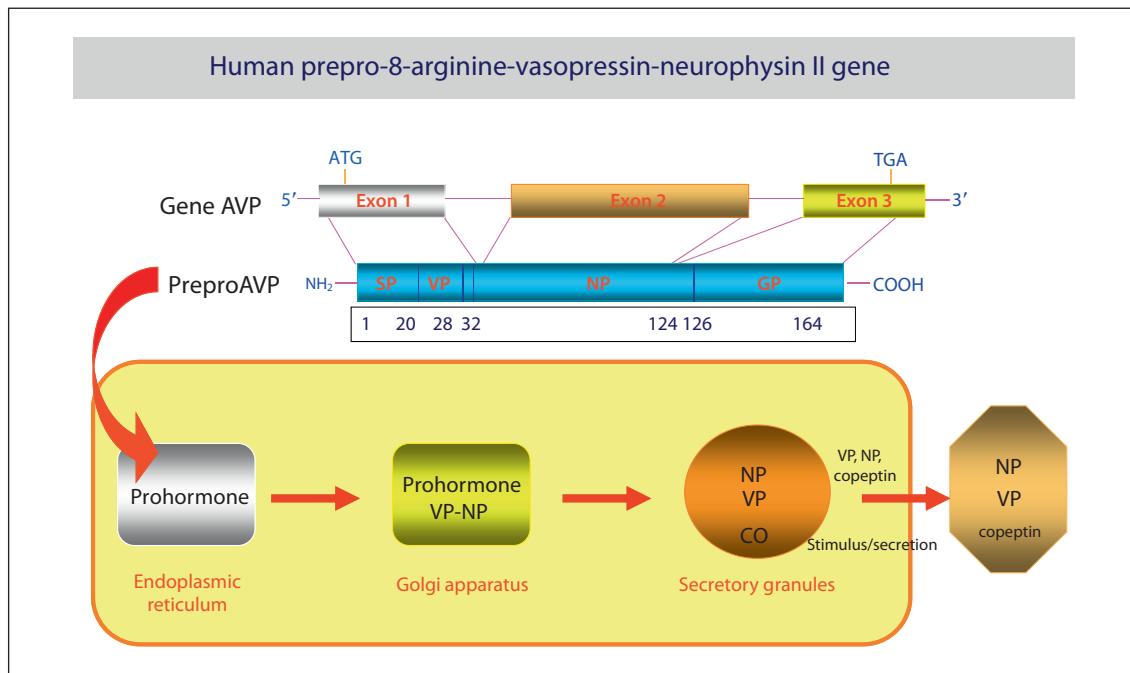


Fig. 1. Schematic representation of AVP biosynthesis. CO = Copeptin; NP = neurophysin.

ylation promotes trafficking to the apical membrane, followed by exocytic insertion of AQP2 vesicles into the cell membrane. The insertion of AQP2 renders the collecting duct water-permeable, allowing the free movement of water from the lumen of the nephron into the cells of the collecting duct along an osmotic gradient, thus concentrating the urine. The synthesis of AQP2 channels, as well as their movement, is regulated by AVP stimulation. Aquaporin 3 and aquaporin 4, responsible for the subsequent passage of water from within the cell into the renal interstitium, are constitutively present in the basolateral membrane [10].

Pathogenesis

An increase in polyuria occurs when more than 80% of the AVP-secreting neurons are damaged. Extensive destruction can be caused by a variety of pathological processes including genetic causes. Autopsy studies after traumatic section of the pituitary stalk (PS) have revealed a loss of large neurosecretory cells in the hypothalamic nuclei. This transpires within 4–6 weeks, with more damage for lesions which occur at the level of infundibulum or above it [11]. Autopsy studies of patients with a familial form of diabetes insipidus show a selective loss of magnocellular neurons in the paraventricular nuclei associated

with moderate gliosis and a relative preservation of small neurosecretory cells [12], suggesting that the disorder is due to degeneration of these hypothalamic neurons.

Genetic Forms of CDI

At present, more than 55 different mutations resulting in a defective prohormone and a deficiency of AVP have been identified in familial neurohypophyseal CDI [6, 13]; all except a few show an autosomal dominant pattern of inheritance. Six patients with homozygous missense mutation in the region encoding the AVP domain show an autosomal recessive pattern of inheritance [14, 15]. Despite some clinical similarities with the dominant form, the symptoms in these cases appear to be secondary to the reduced biological activity of the mutant AVP peptide. This hypothesis is supported by the high circulating level of mutant hormone, the absence of normal AVP hormone in the homozygous state and the absence of clinical or subclinical abnormalities in heterozygous carriers.

Indeed, no mutations in the coding region, the intronic region or the 1.5-kb upstream region from the initial transcription site of the AVP-NPII gene were found in a Chinese family with an autosomal dominant inheritance

pattern of overt CDI [16]. Linkage analysis indicated that the corresponding gene(s) responsible for the autosomal dominant form in this family was/were located in a 7-cM interval defined by two short tandem repeat markers on chromosome 20. This suggests the presence of locus heterogeneity of autosomal dominant CDI and implies a genetic diversity in the cause of CDI.

The autosomal dominant inheritance of this disease can occur through many mechanisms including dominant negative activity by interactions of mutant and wild-type (WT) precursor, accumulation of mutant precursor in the ER leading to stress protein response and autophagy, and cellular toxicity by pathways that are still not completely defined. The study of the trafficking and processing of the mutant AVP prohormone in vitro has demonstrated that the mutation eliminates ER exit and processing of the AVP prohormone, resulting in an aberrant endoplasmic morphology and possible cell dysfunction and death [6]. The presence of cytosolic autophagy suggests nonapoptotic cell death [17–19]; however, programmed cell death cannot be excluded [20].

Mutations that involve the signal peptide decrease its ability to initiate proper processing of the prepro-AVP-NPII [21]; mutant precursors also impair intracellular trafficking of the WT precursor by forming heterodimers, thus reducing the bioavailability of active AVP by means of a ‘nontoxic mechanism’, i.e. a dominant negative effect [19, 22]. The demonstration of two pathways of degradation (via the ER lumen and directly from the cytosol), involving both the WT and the mutant prohormone, suggests that the cytotoxic effect may result from processes that are quantitatively, but not fundamentally, different from those occurring in cells expressing the WT protein [21, 23].

Acquired Forms of CDI

Idiopathic CDI

Although 20–50% of cases are considered ‘idiopathic’, the identification of antibodies against AVP-secreting cells (AVPc-Abs) on the one hand, and recent advances in imaging techniques [24] on the other, have shed new light on the pathophysiological aspects of CDI, making the idiopathic form a very uncommon condition.

Various clinical observations suggest an important role for autoimmunity in the pathogenesis of CDI. Autoimmune polyendocrinopathy and CDI associated with an MRI picture of a thickened PS suggest that patients with CDI and a thickened PS may share a common etiol-

ogy [1, 25, 26]. While there is a temporal relationship between a viral infection (trigger) and the onset of CDI in about a quarter of patients with idiopathic CDI [1], anterior pituitary (AP) involvement in the course of idiopathic CDI is highly suggestive of an autoimmune neurohypophyseal basis and fits well with the bioptic demonstration of the lymphocytic infiltration of the PS [27]. This hypothesis is strengthened by the fact that the pituitary gland is susceptible to CD8 T-cell-mediated autoimmunity, triggered by a cell-specific model autoantigen [28], as well as to the development of autoimmune hypophysitis through the immunization of female SJL/J mice with mouse pituitary extracts [29]. However, the identification of AVPc-Abs in subjects who have either idiopathic CDI, LCH or germinoma indicates that this finding cannot be considered a completely reliable marker of autoimmune CDI [24]. Thus, to ensure a definitive etiological diagnosis, a close clinical and MRI follow-up are needed, as the presence of AVPc-Abs may mask germinoma or LCH.

The underlying process of PS thickening in idiopathic CDI is not completely understood. The term ‘lymphocytic infundibulo-hypophysitis’ has been coined [1] to distinguish between children and adolescents with CDI, pituitary hormone deficiency, reduction of AP size and transient or persistent PS thickening and adult patients with similar PS findings at MRI, but normal AP size and function [30]. The identification by Mirocha et al. [31] of two different potential pathogenetic mechanisms, i.e. one potentially directed against self-antigens (T helper dominance), and the other against non-self-antigens (postinfection), both of which induce primary hypophysitis, adds another piece to the puzzle of this intriguing condition. Patients with autoimmune-driven hypophysitis would benefit from steroids or from other immunosuppression treatment, whereas immunosuppression may exacerbate conditions that are not autoimmune. It is worth pointing out that extrapituitary localizations of LCH including the chest or liver may become evident after the onset of CDI [32]. Rarely, de novo mutations of the AVP-NPII gene are responsible for some idiopathic forms of CDI associated with normal PS size [33, 34].

Vascular CDI

CDI may be caused by vascular brain damage, but the pathophysiology of such a mechanism has never been precisely understood. In a group of patients with idiopathic CDI and normal anterior pituitary function, standard MRI showed a normal PS and AP gland size [35]. Indeed, dynamic MRI studies after contrast-medium injection revealed the absence of posterior pituitary lobe enhance-

ment, whereas normal enhancement of the AP was present. The lack of contrast enhancement of the posterior lobe suggests that a selective vascular injury to the inferior hypophyseal arteries could be causally linked to CDI. The mechanism affecting the posterior pituitary blood supply remains largely undefined, but the possibility that a congenital lack/poor development of the posterior pituitary vascular system (without any evidence of macroscopic morphological abnormality of the pituitary gland at MRI or secondary changes of vascular supply due to a local inflammatory process), i.e. vasculitis, cannot be ruled out.

Langerhans Cell Histiocytosis

CDI is the most frequent CNS manifestation of LCH, occurring in 10–50% of all patients [36, 37]. A retrospective multicenter analysis of LCH patients showed that the risk of developing CDI, after diagnosis and specific therapy, was 16% at 5 years of age and 20% at 15 years of age, respectively, and strongly correlates with the presence of a multisystem disease followed by lesions in the craniofacial area [36]. Some patients with CDI and endocrinopathies seem to be at risk for long-term neurodegenerative CNS disease, though brain and pineal involvement can be diagnosed shortly after the onset of CDI. Growth hormone deficiency is the most frequent additional deficit, accounting for 42% of cases with CDI and LCH. The 10-year cumulative incidence of growth hormone deficiency among patients with CDI in the French nationwide LCH survey was approximately 54% [38]. The identification of circulating AVPc-Abs in LCH patients and their tendency toward spontaneous clearance [24, 25] suggest that these autoantibodies might be an LCH-related immune epiphénoménon.

PS thickening can be found in approximately 50–70% of patients with LCH at presentation or at follow-up [1, 39] and may even be present before the onset of CDI. Anterior pituitary size has been found to be normal, reduced, or rarely, enlarged [1, 36, 40]. The search for extracranial lesions (dermatological and bone survey, chest X-ray, ear, nose and throat examination) suggestive of LCH in patients with PS thickening is recommended, and could reduce the need for intracranial biopsy.

Tumors

Germinomas

Intracranial germ tumors comprise 7.8% of primary pediatric brain tumors [41]. MRI findings suggest that suprasellar and neurohypophyseal germinomas arise primarily from the posterior pituitary to the infundibulum [42]. Partial or complete stalk thickening is detectable in

78–100% of cases at presentation and may be the only finding in small germinomas at presentation [42]; its presence increases the risk of malignancy to about 15–17%, while the risk decreases to 3% in patients with a normal-sized stalk.

Serial contrast-enhanced brain MRI in patients affected by CDI with PS thickening (every 3–6 months for the first 2 years) may reduce the amount of time for germinoma diagnosis by as much as 1 year [1]. However, a thickened stalk has been reported up to 5 years after the onset of CDI, preceded by a lymphocytic tissue infiltration as a host reaction to the presence of a germinoma that could mask diagnosis [43]. As an exception, germinoma can mimic multisystemic LCH, with vertebral compression, recurrent ear infections, a thickened PS, an enlarged pineal gland and serum and negative cerebrospinal fluid for germ cell tumor markers, as demonstrated in a 9-year-old female [44].

The role of human chorionic gonadotropin (hCG) and other tumor markers in the early diagnosis of germinoma is not very well understood. A negative result for hCG in the cerebrospinal fluid does not exclude a diagnosis of germinoma [1]. The presence of circulating AVPc-Abs in these patients prior to treatment [24] may also mask the diagnosis of germinoma and thus require further confirmation. PS biopsy is mandatory in the presence of a progressive thickening of the lesion up to more than 6.5–7 mm and/or anterior pituitary enlargement. Growth arrest and multiple pituitary hormone deficiencies are common and early findings in pituitary germinomas (almost 100% of cases at follow-up), but hormone deficiency is not necessarily predictive of its presence.

Craniopharyngioma and Postsurgical CDI

Craniopharyngioma is a benign tumor arising from squamous cell nests in the primitive Rathke's pouch. It constitutes approximately 6–9% of all intracranial tumors in children and is the most frequent suprasellar neoplasm in the pediatric population, i.e. in 54% of cases [41]. Classic presentation includes visual impairment due to chiasmal compression and bilateral optic atrophy; systemic symptoms related to raised intracranial pressure account for 60–75% of cases at presentation. In various large pediatric series, signs and symptoms of AP dysfunction were detected in about 20–70% of cases [41]. CDI and multiple pituitary hormone deficiency are common complications of childhood craniopharyngioma. The frequency of pre-surgery CDI varies from 16–55%, while postsurgical and permanent CDI account for up to 80% of cases; transient CDI is reported in 13% of affected cases [45].

Impairment of hypothalamic posterior pituitary function after complete section of the PS is a common, predictable outcome, characterized by the classic triphasic response of urine volume. The initial phase of CDI (1–4 days) is followed by a second phase of oliguria which may reflect the degeneration and death of neurosecretory neurons with the release of stored AVP into the circulation (4–7 days), and by a third and final phase of permanent CDI. The diagnosis of CDI after surgery is often made within a few hours, although abnormalities of AVP secretion and fluid balance often begin during the intraoperative period [45]. A recent study showed a frequent occurrence of the triphasic response after primary surgery for craniopharyngioma in childhood, which was predicted by a longer duration of surgery [46].

Diagnosis of Diabetes Insipidus

Clinical Manifestations, Symptoms and Signs

Clinical examination may provide important clues to possible underlying diagnoses. The age at which symptoms develop together with the pattern of fluid intake, may influence subsequent investigation of diabetes insipidus. The primary symptoms are persistent polyuria and polydipsia, and young children may have severe dehydration, vomiting, constipation, fever, irritability, sleep disturbance, failure to thrive and growth retardation. Nocturia in children often presents as enuresis. Severe dehydration of early onset in males is highly suggestive of NDI; some mental retardation has been reported, probably caused by repeated and unrecognized dehydration before the diagnosis has been established.

In a large cohort of patients with CDI of different etiologies [1], 40% of the patients had symptoms other than polyuria and polydipsia at presentation; while headache was not discriminatory, visual defect was associated with intracranial tumor. Growth retardation was not significantly more common in patients with CNS tumors, in contrast with previous reports indicating that such delays strongly suggest an intracranial tumor as the cause of CDI. In addition, the patients who did not have an intracranial tumor were significantly younger than those who did, and none of the patients with intracranial tumor was younger than 5 years of age [1].

In autosomal dominant CDI, clinical disease onset typically ranges from the first to the sixth year of life, but various cases of early or delayed onset have also been reported [47]. Usually symptoms worsen with age in pa-

tients with an early onset of mild polyuria and polydipsia, especially before 10 years of age, but it is also possible that complete CDI is expressed from the neonatal period [41]. The wide variability in the age of onset and the severity of the AVP deficiency among patients with the same mutation may be ascribed to individual differences among such patients, like the rate of production of the mutant precursor, the intensity of neurohypophyseal stimulation, individual susceptibility to the toxic effect of the mutant precursor, the capacity to degrade mutant precursors and variations in the secretory reserve capacity or in the development of the gland itself.

In Wolfram syndrome, diabetes mellitus has been reported to be the usual first symptom to present at a median age of 6 years, followed by the onset of optic atrophy at a median age of 11 years [48]. The phenotype-genotype correlations in a series of 9 Wolfram syndrome families show an average age at onset of diabetes mellitus of 8.4 years, in agreement with other studies [49, 50]. The development of polyuria and/or enuresis can indicate diabetes insipidus and the time of onset varies considerably, generally not appearing until the second or third decade [39, 46]; CDI may initially be partial. The frequency of CDI varies between reports ranging from 48 to 78% [51].

Measurement of Osmolality

While the tonicity and osmolality of sodium and other electrolytes are identical, urea and glucose show great variation between the osmotic pressure ascertained by freezing-point depression and the effective osmolality in vivo. The accuracy of the measurement of plasma osmolality by routine hospital laboratories and by freezing-point depression is usually not high enough to fulfill the quality criteria required (coefficient of variation of 1% or less at 290 mosm/kg H₂O), especially when osmolality is determined in serum or frozen plasma.

Indeed, extracellular and plasma osmolality can be reasonably considered to correspond to sodium salts. Thus, plasma osmolality is estimated well by 2 × plasma sodium concentration. However, the contributions of two other solutes, glucose and urea, should be included to more closely approximate plasma osmolality: plasma osm = 2 [Na⁺] + [blood glucose] + [urea].

The molecular weight of glucose is 180, and that of the two nitrogens in urea is 28. The plasma contents of both are usually expressed as mg/dl (instead of mg/l), so molecular weights must be divided by 10. Thus, glucose can be estimated by the plasma glucose content (in mg/dl)/18 and urea can be estimated by the blood urea nitrogen (BUN; in mg/dl)/2.8. It is mandatory that laboratories us-

ing SI units do not need to make the above-described calculations.

Finally, a good estimate of plasma osmolality, usually accurate to within 1–3% (i.e. 9 mosm/kg H₂O) of what is determined directly by osmometry [11], can be obtained with the following formula:

$$P = 2[\text{Na}^+] + \frac{\text{glucose}}{18} + \frac{\text{BUN}}{2.8}.$$

Deprivation Test and Desmopressin Challenge

It is essential that 24-hour urine volume is completed and polyuria confirmed. A range of baseline investigations including plasma electrolytes, random plasma osmolality and urine osmolality, as well as an assessment of kidney function, may assist in a correct diagnosis. In the absence of an immediate diagnosis, the child's fluid intake and output should be studied in greater detail. The ability of the CNS to produce AVP and of the kidney to respond to it should be established by means of a formal water deprivation test and a desmopressin (DDAVP) trial [52].

A 7-hour (or less) deprivation test is usually sufficient for diagnosis, except in cases of primary polydipsia, where a longer dehydration period is sometimes required. The test must be discontinued if weight loss exceeds 5% of the starting weight and/or plasma Na⁺ is found to be higher than 143 mEq/l and/or plasma osmolality is higher than 295 mosm/kg H₂O and/or urine osmolality increases to normal (table 1). It is important to get the results quickly, so close collaboration about feedback from the laboratory is needed.

Diagnosis of CDI is based on the demonstration of plasma hyperosmolality (>300 mosm/l) associated with urine hypoosmolality (<300 mosm/l or urine/plasma osmolality ratio <1) and polyuria (urinary volume >4–5 ml/kg/h for 2 h (consecutively) after surgery). Adrenocorticotropin deficiency may mask the signs of partial CDI and polyuria may become manifest after corticosteroid replacement therapy [45]. The administration of DDAVP will help to make a differential diagnosis between CDI and NDI. Recently, copeptin and AQP2 have also been used in the differential diagnosis of CDI versus NDI [53, 54]. Aquaporin is synthesized in the kidney and excreted in urine in response to AVP. Patients with CDI show no increase in AQP2 with dehydration, but their excretion increases in response to DDAVP, suggesting that AQP2 expression persists in patients with CDI. Thus, the main value of AQP2 in the differential diagnosis of diabetes insipidus would be to indicate a diagnosis of NDI when there is no increase in AQP2 excretion following DDAVP administration.

Table 1. Interpretation of the water deprivation test and DDAVP test

Urine osmolality, mosm/kg		Diagnosis
after fluid deprivation	after DDAVP	
<300	>750	CDI
<300	<300	NDI
>750	—	PP
300–750	<750	? Partial CDI ? Partial NDI ? PP

PP = Primary polydipsia.

Imaging

Once the diagnosis of CDI has been established, other investigations are mandatory, including tumor markers, skeletal survey (in LCH, the skull is involved in as many as 85% of cases), and especially brain neuroimaging [13]. In an MRI, the posterior pituitary can be seen as a hyperintense signal on sagittal T1-weighted imaging under basal conditions (fig. 2). A lack of posterior pituitary hyperintensity (although not specific), is a hallmark of hypothalamic-posterior pituitary disorders and may signify the early stage of occult local tumors (fig. 3). In autosomal dominant CDI, the identification of posterior pituitary hyperintensity does not necessarily indicate that the functional integrity of the hypothalamic-neurohypophyseal axis is preserved [1, 13, 39, 55]. When initially present, the signal disappears on a regular basis at follow-up.

Thickening of the PS or infundibulum, defined as exceeding 3 mm, although not specific (sometimes the proximal part of the stalk is less than 3-mm thick compared to the distal part), is observed in approximately one third of children with CDI (fig. 4). PS size at presentation is variable and can change over time (fig. 5). In two large pediatric series of idiopathic CDI patients, PS thickening was found in approximately 50–60% of subjects [1, 40]. Spontaneous evolution of a thick PS was similar in both reports from unchanged (30%), to reduction (30–50%) or further enlargement (10–20%) of stalk size. Among patients with idiopathic CDI and a thick PS, 90–94% developed anterior pituitary hormone deficits with isolated growth hormone deficiency accounting for 60% of cases. Multiple pituitary hormone deficits were present in 30–50% of patients with a widened PS while only 10% of the 19 patients with normal PS had an additional hormonal deficit [1]. Brain examination in order to rule out CNS

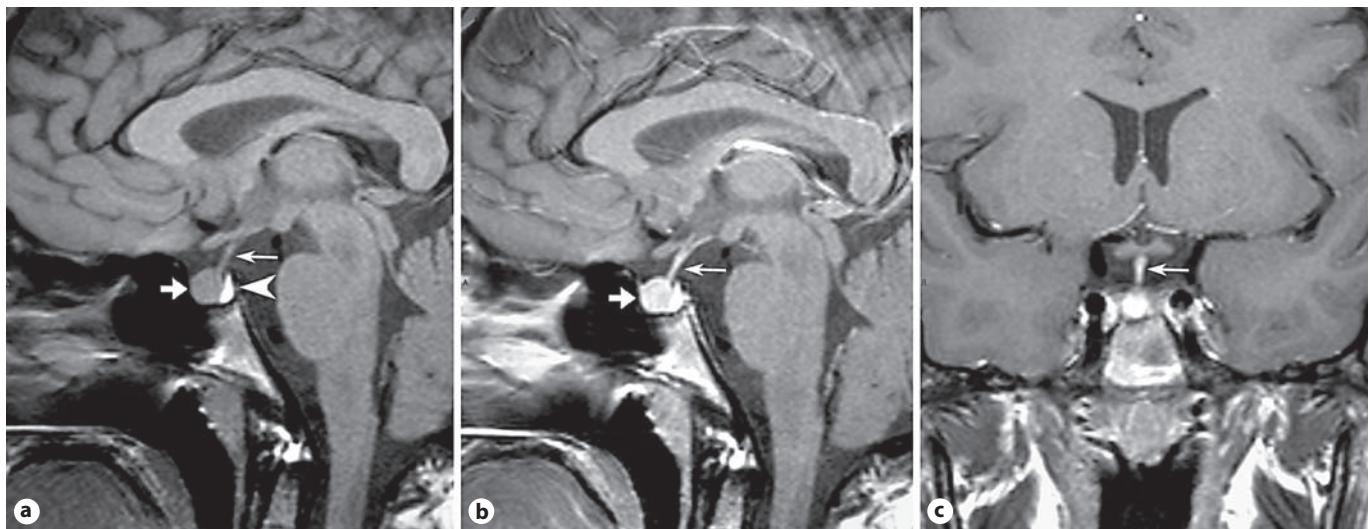


Fig. 2. Normal MRI findings. **a** Sagittal T1-weighted image shows normal anterior pituitary (thick arrow), typical posterior pituitary hyperintensity known as 'bright spot' (arrowhead), and normal PS (thin arrow). Postcontrast sagittal (**b**) and coronal (**c**) T1-

weighted images show normal enhancement of the PS (thin arrows) whose thickness does not exceed 3 mm on both planes. The anterior pituitary also enhances (thick arrow, **b**).

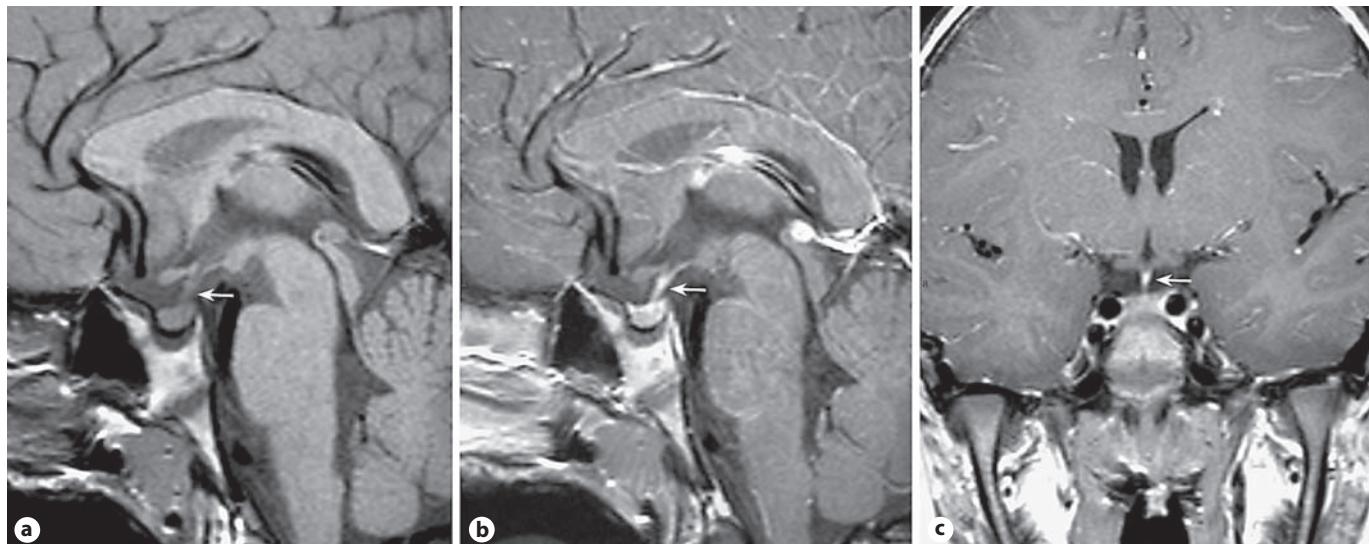


Fig. 3. CDI. **a** Sagittal T1-weighted image shows absent posterior pituitary hyperintensity, normal anterior pituitary and normal PS size (arrow). Postcontrast sagittal (**b**) and coronal (**c**) T1-weighted

images show normal thickness of the enhancing PS (arrows). The pituitary gland is also enhancing.

localizations, as well as careful attention to other signs such as recurrent otitis media or dyspnea, is mandatory in order to rule out multiorgan involvement (fig. 6).

Clinical, radiological and endocrine studies are needed during follow-up. In particular, MRI follow-up is rec-

ommended for all patients with a widened PS (every 3–6 months) and PS biopsy is recommended if the MRI reveals enlargement of the PS lesion (>6.5 mm) or of the AP gland (AP size is age-dependent) or third ventricle involvement (fig. 7, table 2) [1, 13, 27, 40–42, 56, 57]. Dy-

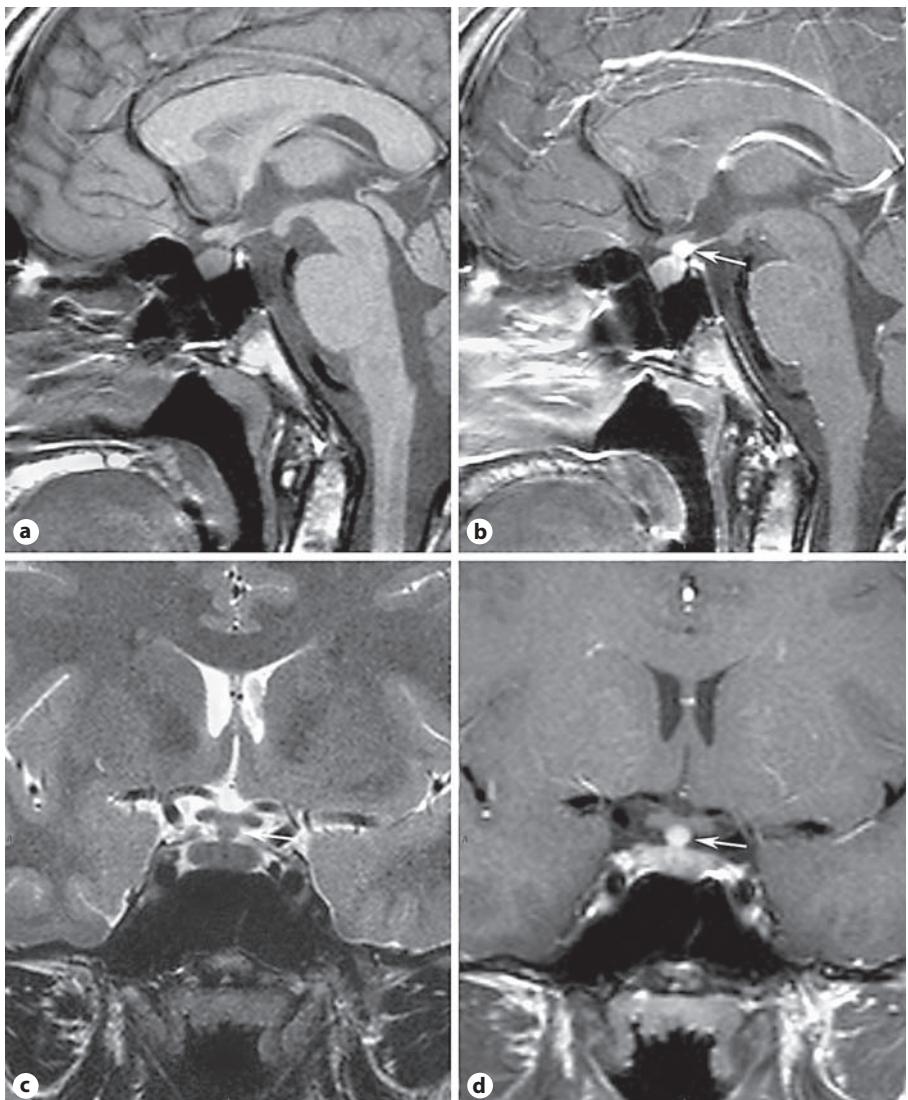


Fig. 4. CDI with thickened stalk. **a** Sagittal T1-weighted image shows absent posterior pituitary hyperintensity and normal anterior pituitary. **b** Postcontrast sagittal T1-weighted image shows thickened, enhancing PS (arrow). Coronal T2-weighted (**c**) and T1-weighted (**d**) images confirm thickening of the PS (arrows).

namic MRI can help identify cases of CDI and normal PS size associated with abnormal blood supply to the posterior pituitary [33, 58]. Diagnostic flowcharts for polyuria, polydipsia and CDI are reported in figures 8 and 9.

CDI and Thirst Abnormalities

Adipsic disorders are characterized by an inappropriate lack of thirst, with a consequent failure to drink to correct hyperosmolality. The incidence of postoperative CDI and thirst abnormalities has recently been reported as about 1/3 of patients with craniopharyngiomas [59].

Adipsic CDI is characterized by abnormally low thirst scores and no thirst response to marked plasma hypertonicity during hypertonic saline infusion.

Patients with craniopharyngioma who develop an adipsic syndrome and postoperative CDI fail to increase serum AVP in response to drug-induced hypotension; moreover, they do not express thirst sensation after either a fall in blood pressure or hypertonic saline infusion, indicating that both osmotic and nonosmotic pathways are involved [45]. A failure to secrete AVP in response to hypotension or hypovolemia may increase the risk of dehydration and life-threatening hypernatremia. In adipsic patients, a fixed daily fluid intake should be established, appropriate for a weight at which the patient is known to

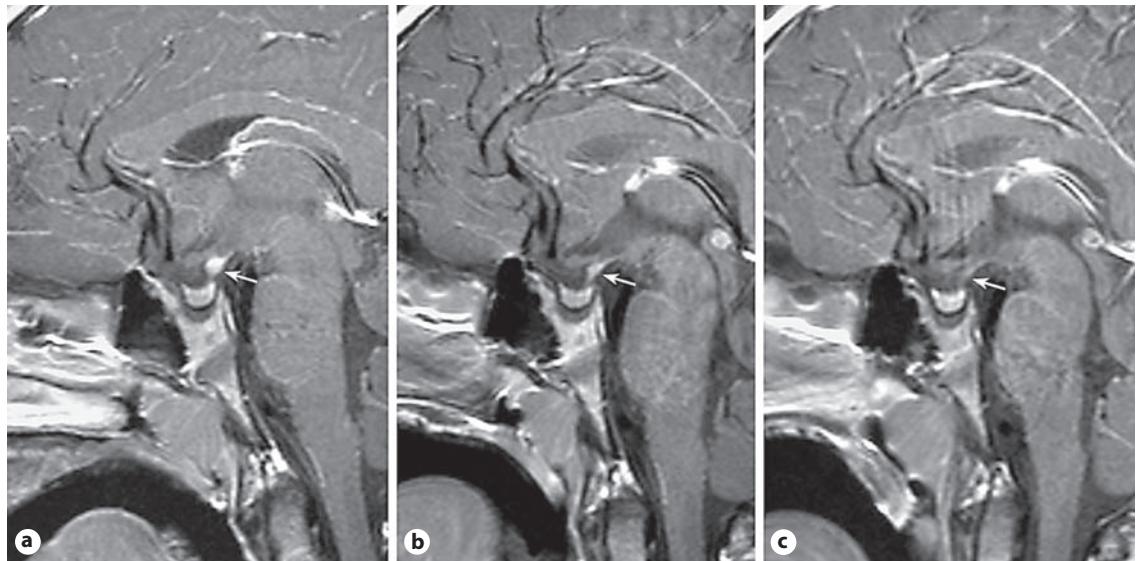


Fig. 5. CDI: evolution of findings. **a** Postcontrast sagittal T1-weighted image shows thickened PS (arrow). Post-contrast sagittal T1-weighted images obtained after 6 (**b**) and 12 (**c**) months show progressive reduction in size (arrows).

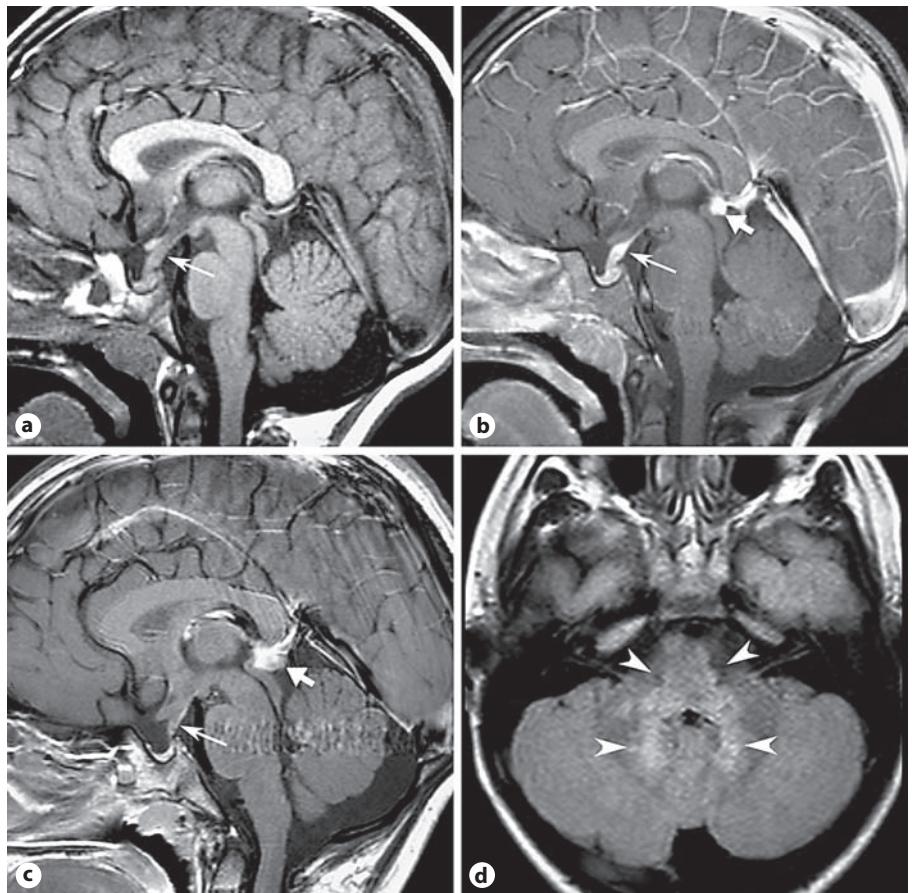


Fig. 6. LCH with CNS involvement. **a** Sagittal T1-weighted image shows small anterior pituitary, absent posterior pituitary and thickened PS (arrow). **b** Postcontrast sagittal T1-weighted image shows enhancement of the thickened PS (thin arrow). Notice normal pineal gland (thick arrow). **c** Postcontrast sagittal T1-weighted image obtained after 1 year shows normalized size of the PS (thin arrow). The pineal gland has increased in size (thick arrow). **d** Axial FLAIR image shows ill-defined hyperintensities involving the brainstem and deep cerebellar white matter (arrowheads).

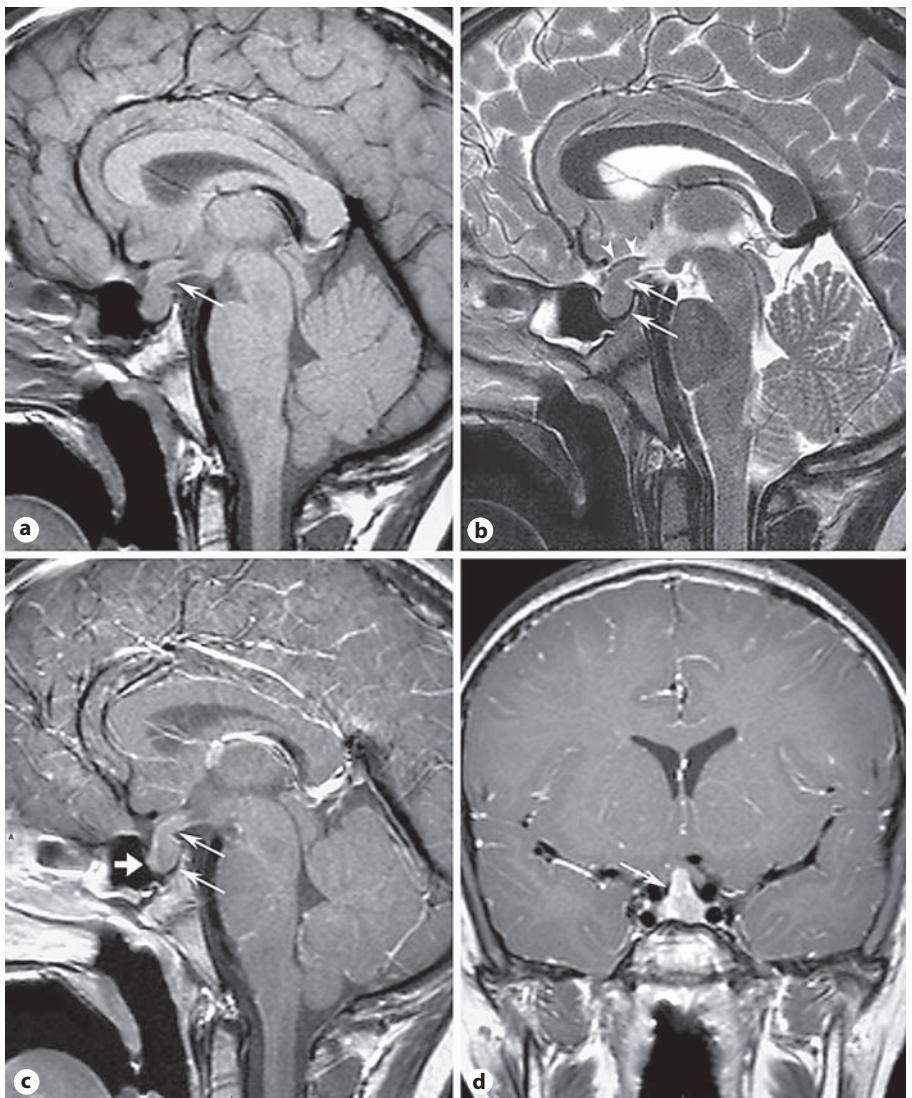
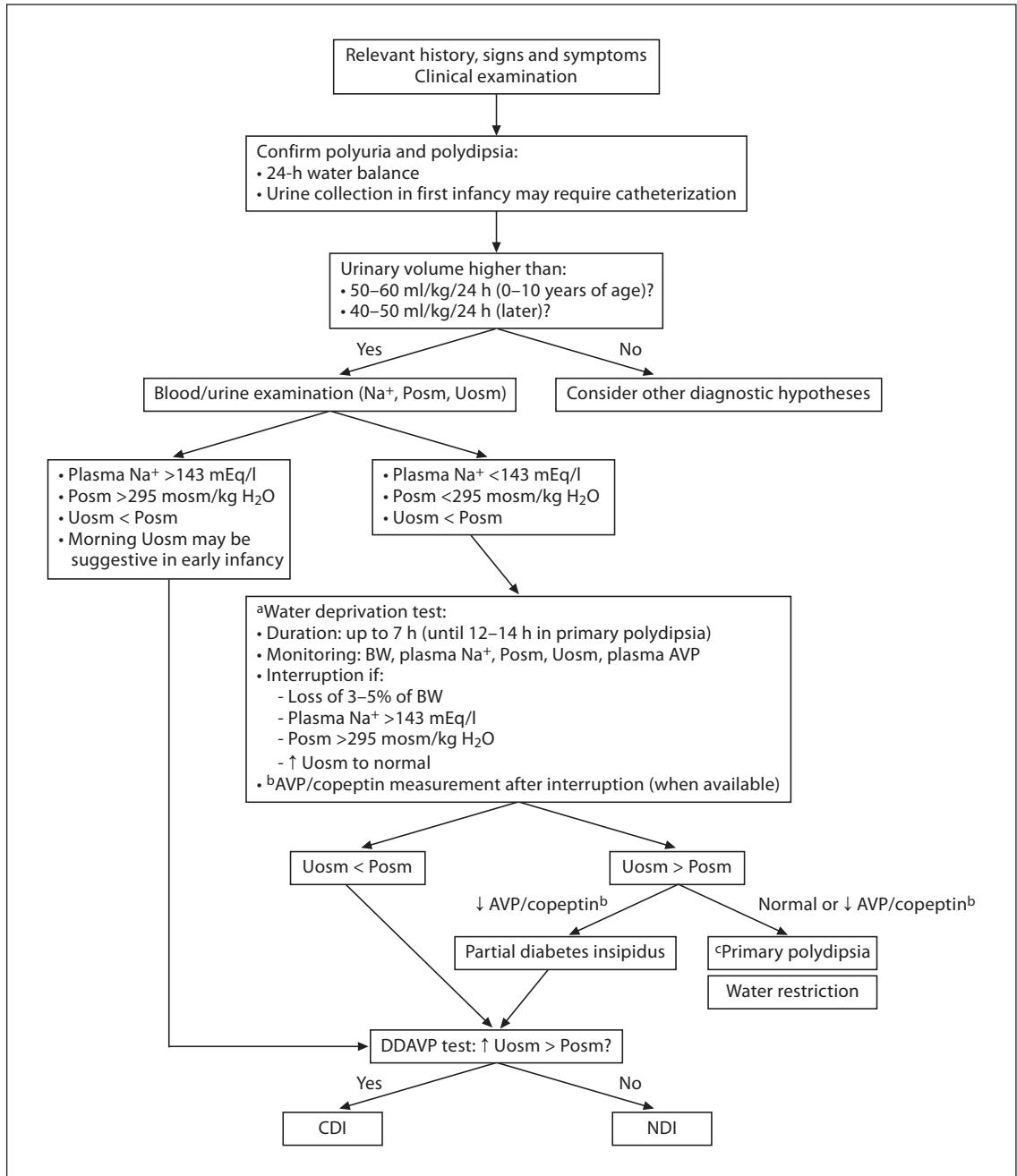


Fig. 7. Germinoma. Sagittal T1-weighted (a) and T2-weighted (b) images show thickened stalk and pituitary gland (arrows). The posterior bright spot is not visible. The optic chiasm is compressed and displaced superiorly (arrowheads, b). c Postcontrast sagittal T1-weighted image shows the pathological tissue extends to the posterior pituitary lobe (arrowheads). The anterior lobe is displaced anteriorly in the pituitary fossa and is visible as an area of more marked enhancement (thick arrow). d Postcontrast coronal T1-weighted image confirms pathological tissue (arrow) causing thickening of the stalk and invading the pituitary fossa.

Table 2. Biopsy criteria of thickened PS

First author	Year	PST and CSF-hCG	PST	PST	Additional findings
Mootha [42]	1997	+	increase		
Leger [40]	1999	+	increase	7 mm	
Maghnie [1, 13]	2000/2007	+/-	increase	>6.5 mm	increased AP pineal calcifications third ventricle involvement
Al-Agha [56]	2001	+	increase		
Alter [57]	2002	+	increase		

PST = Pituitary stalk thickening.



be eunatremic and euvolemic. DDAVP is then administered at a dose and frequency capable of establishing an appropriate urine output and neutral fluid balance, allowing for insensible losses; regular weighing and checking of serum sodium levels are mandatory.

Although little is known about how the brain orchestrates systemic osmoregulation, recent advances have been made in our understanding of the molecular, cellular and network mechanisms that mediate the central control of osmotic homeostasis in mammals [60]. Despite

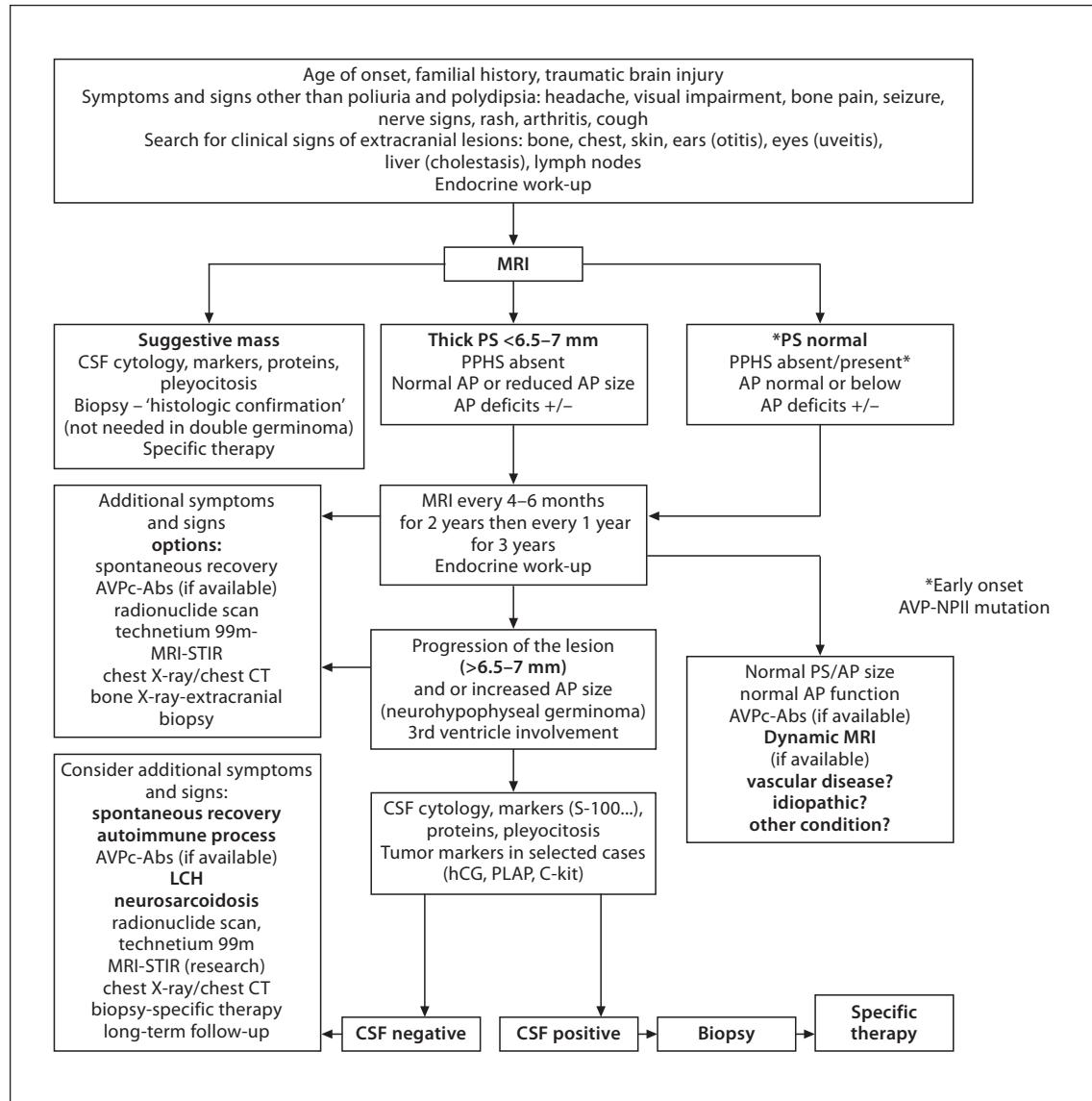


Fig. 9. Diagnostic flowchart for CDI. PLAP = Placental alkaline phosphatase; PPHS = posterior pituitary hyperintense signal.

the fact that cerebral osmoreceptors have a determinant role in the control of osmoregulatory responses, peripheral osmoreceptors also contribute to fluid balance. Indeed, patients with complex midline CNS abnormalities such as septo-optic dysplasia mainly have defective AVP osmoregulation rather than frank CDI [61], which suggests that the disruption of osmoreceptor mechanisms contributes significantly to the etiology of this homeostatic disorder.

Management

Treatment of CDI

The drug of choice for the treatment of diabetes insipidus is DDAVP, a synthetic analog of the endogenous hormone arginine AVP, but with a 2,000- to 3,000-fold lower vasopressor effect. DDAVP may be administered orally, intranasally or parenterally. Given intranasally or orally, maximum plasma concentrations are reached in 40–55 min. The drug's half-life is 3.5 h. Generally, urine output will decrease 1 or 2 h after administration and the

duration of action will range from 6 to 18 h. There is broad individual variation in the dosage required to control diuresis. Daily dosages for oral preparations (20-fold less potent than the intranasal form) vary from 100 to 1,200 µg in three divided doses, for the intranasal preparation approximately 2–40 µg (once or twice a day), and for the parenteral 0.1–1 µg. A low dose should be used initially and increased as necessary.

In early infancy, fluids alone can be a management strategy. When infants are treated with DDAVP, low doses of diluted preparation are also often administered. It is a safe practice to allow a short time of diuresis between two doses. Because DDAVP stability is reduced by dilution, these preparations should not be used for more than one week.

In older children, the intranasal spray and oral form are the current choice for CDI (5–20 µg once or twice daily). Oral DDAVP has been shown to be particularly helpful in childhood. Its positive characteristics include better absorption, fewer complications, and, due to the easy route of administration, good compliance among children and adolescents. Symptomatic dilutional hypo-

natremia is the only potential hazard if DDAVP is administered in excess over a long period of time. Symptoms of hyponatremia include headache, nausea, vomiting and seizure. Untreated, these symptoms can lead to coma and death. However, asymptomatic hyponatremia may also occur. Particular attention is required in cases of multi-drug therapy because of the risk of extrapontine myelinolysis [62].

Rare side effects with intranasal delivery of DDAVP include eye irritation, headache, dizziness, rhinitis or epistaxis, coughing, flushing, nausea, vomiting, abdominal pain, chest pain, palpitations and tachycardia [63]. Evidence to date indicates that the use of DDAVP during pregnancy is safe and is not related to adverse effects on the mother or fetus/child [64].

In the presence of adipsia or hypodipsia, diabetes insipidus presents a difficult challenge and initially is best managed by adjusting the DDAVP dosage and fluid intake in a hospital setting. Daily weight can be used as an index of fluid balance, but regular monitoring of electrolytes is also required.

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