APPROACH TO THE PEDIATRIC PATIENT: CENTRAL DIABETES INSIPIDUS

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ABSTRACT

Central diabetes insipidus (CDI) is a complex disorder in which large volumes of dilute urine are excreted due to arginine-vasopressin deficiency, and it is caused by a variety of disorders affecting the hypothalamic-posterior pituitary network. The differential diagnosis is challenging and requires a detailed medical history, physical examination, biochemical approach, imaging studies and, in some cases, histological confirmation. Magnetic resonance imaging is the gold standard method for evaluating congenital or acquired cerebral and pituitary stalk lesions. Pituitary stalk size at presentation could be normal, but it may change over time, depending on the underlying condition, while other brain areas or organs may become involved during follow up. Early diagnosis and treatment are crucial in order to avoid central nervous system damage, germ cell tumor dissemination, and to minimize complications of multiple pituitary hormone defects.

We provide a practical update on the diagnosis and management of patients with CDI and highlight several pitfalls that may complicate the differential diagnosis of conditions presenting with polyuria and polydipsia.

The need for a careful and close follow-up of patients with "apparently" idiopathic CDI is particularly emphasized, because the underlying condition may be recognized over time. The clinical scenario that we outline at the beginning of this article represents the basis for the discussion about how the etiological diagnosis of CDI can be overlooked, and demonstrates how a water intake and urine output improvement can be a sign of progressive damage of both hypothalamus and anterior pituitary gland with associated pituitary hormonal deficiencies.

Key words: diabetes insipidus. Water deprivation test. Copeptin. MRI. Germinoma. LCH.

Overall Learning Objectives are:

1. To discuss clinical signs, symptoms and management of conditions associated with polyuria –polydipsia and endocrine disorders.
2. To raise awareness of the diagnostic pitfalls and gaps in patients with CDI.
3. To highlight the importance of inter-professional care to improve patient outcomes.
4. To provide the most updated evidences supporting early and accurate diagnostic work-up and long-term follow-up of patients with CDI.

Target Audience

Patients with sudden onset of polyuria and polydipsia and clinical signs of diabetes insipidus may be first identified and followed by primary care physician and the short- and long-term outcomes of these patients will depend on the skills of GPs, pediatricians, or specialists (pediatric or adult endocrinologists), and on their awareness of the pitfalls in the diagnosis and management of the underlying condition. Physicians will be involved throughout the process of diagnosis, follow-up, treatment decision-making, and ongoing patient management and monitoring. The availability of skilled multidisciplinary staff is crucial. Diagnosis can include a series of tests. Radiologists/neuroradiologists are involved in early stages of diagnosis and the availability of a skilled radiologist/neuroradiologist is essential for the interpretation of pituitary and pituitary stalk lesions; depending on the underlying disorder, neurosurgeons, oncologists and other specialists could also be involved in the context of a multidisciplinary approach to patient management.

Patient Case

A 14-year- old girl was admitted to our Pediatric ward for a second opinion after 2- year history of central diabetes insipidus (CDI). The blood tests at the time of first evaluation revealed hypernatremia (Na 147 mEq/L), high plasma osmolality (305 mOsm/kg/H_2O), yet low urine osmolality (109 mOsm/Kg/ H_2O) that led to the diagnosis of CDI for which the girl

was treated with Desmopressin. Sixteen months later, decrease of water intake and urine output was observed, although no recent variation of body weight or Desmopressin dose had been reported. Due to the improvement of polyuria, her physician reduced Desmopressin dose progressively, until "normalization" of water output was reported two months later. This led to a diagnosis of reversible CDI and Desmopressin treatment was therefore withdrawn. Two months later (18 months since first diagnosis), she experienced extreme fatigue, nausea, progressive memory loss, up to confusion and lethargy. Patient's mother contacted our centre and the girl was first seen at our department 24 months after the diagnosis of CDI. Clinical examination revealed signs of dehydration, behavior and sensory disturbances and confusion, while laboratory analyses revealed hypernatremia (Na 156 mEq/L), high plasma osmolality (330 mOsm/kg/H_2O), low urine osmolality (84 mOsm/Kg/ H_2O), low morning cortisol (80 nmol/L n.v. 138-635 nmol/L) and adrenocorticotropic hormone levels (0.88 pmol/L, n.v.1.3-16.7 pmol/L) as well as low thyrotropin (0.1 mU/L, n.v. 0.4-4 mU/L) and FT4 values (0.68 ng/dL; n.v. 0.7-1.9 ng/dL). How should this patient be managed?

Background and Etiology of Diabetes Insipidus

Polyuria is characterized by urine volume in excess of 2 L/m^2/24 h or 150 mL/kg/24 h at birth, 100–110 mL/kg/24 h up to 2 years of age and 40–50 mL/kg/24 h in older children and adults (1).

Vasopressin (AVP) is the main regulator of water homeostasis. It is produced in the magnocellular neurons of the hypothalamic paraventricular and supraoptic nuclei and stored within the posterior pituitary (1,2). AVP secretion is controlled by specialized neural osmoreceptors in the anterior hypothalamus. Water homeostasis is also regulated by non-osmotic stimuli, including hypovolemia, hypotension, renin-angiotensin and aldosterone system, cortisol and thyroid hormones (3). Disorders of AVP secretion and of its action in the kidney (nephrogenic diabetes insipidus, NDI) are associated with disrupted water metabolism

leading to polyuria and thirst (1,2); the diagnostic challenge of hypotonic polyuria lies in the distinction between the different causes of diabetes insipidus, and primary polydipsia (PP) (2).

Central diabetes insipidus (CDI) is a heterogeneous condition caused by an inadequate secretion of AVP upon osmotic stimulation and it is commonly acquired from disorders causing a disruption or degeneration of hypothalamic neurons (1-5). Extensive destruction can be due to germinoma, craniopharyngioma, Langerhans-cell histiocytosis (LCH), inflammatory, autoimmune/vascular diseases, brain malformations, trauma and other conditions. In rare cases, genetic defects in AVP synthesis, inherited as autosomal dominant, autosomal recessive or X-linked recessive traits, are the underlying cause (5-8) (Table1).

Arginine vasopressin is transported from the hypothalamus through the neural component of the pituitary stalk and stored in nerve terminals in the posterior pituitary. In normal subjects, the posterior pituitary is hyperintense on sagittal T1-weighted magnetic resonance imaging (MRI), and the frequency of hyperintensity decreases with age (5). In patients with CDI, the damage of posterior pituitary function is associated with the loss of MRI posterior hyperintensity, though this finding is a no specific neuroimaging marker. In contrast, the identification of a thickened infundibulum or pituitary stalk (or both) suggests the presence of an acquired infiltrative disorder (5). The diagnosis of lesions causing pituitary stalk thickening (PST) is challenging, and the identification of the underlying condition may require long-term follow-up (1,5,6). Notably, clinical signs of pulmonary and/or bone LCH became evident after a median follow-up of 10 years in children previously diagnosed with CDI and isolated PST (6).

Although CDI with normal neuroimaging findings is classified as “idiopathic CDI”, lesions affecting the anterior pituitary, the posterior pituitary, the pituitary stalk, the suprasellar region, the pineal gland, and/or the brain may appear over time. Therefore, clinical,

biochemical, and neuroimaging follow-up and use of instrumental investigations are mandatory in these patients.

Diagnostic Work-up

1. **Clinical Evaluation**

The primary signs of water homeostasis disturbance are polyuria and polydipsia; young children may have severe dehydration, vomiting, constipation, fever, irritability, nocturia, failure to thrive, and growth retardation. The age at the onset of signs or symptoms, the time lag between their onset and diagnosis, and the pattern of fluid intake may influence subsequent investigation (1-5). A family history or an early onset of polyuria/polydipsia should alert for a genetic form (7,8). In autosomal dominant CDI, the clinical disease onset varies from the first to the sixth year of life, but cases of delayed onset have been reported (7, 8). Neonatal CDI has been reported mainly in patients with brain malformations including optic nerve hypoplasia, septo-optic dysplasia, holoprosencephaly, absence of the internal carotid and in idiopathic conditions (1,9). It is worth to point out that polyuria and polydipsia due to DI may be underestimated in the first two years of life. The major pitfall at this age is represented by an incorrect diagnosis of primary polydipsia, either for the difficult evaluation and interpretation of biochemical/water deprivation tests, or for the underestimation of other signs and symptoms.

Children and adolescents with CDI may exhibit a variety of symptoms such as growth retardation, precocious/delayed puberty or brain involvement including headache and visual defects associated with intracranial tumors; the latter being very rare in children under the age of 6 years (5). Among 70 children with germ cell tumors, those with suprasellar tumors showed endocrine symptoms, while patients with pineal tumors presented with symptoms related to hydrocephalus (10).Common symptoms of intracranial pure germinoma include

headache (69%), nausea and vomiting (50%), polyuria and/or polydipsia (59%), double vision (34%), changes in visual acuity (27%), fatigue (33%), poor growth (17%) and premature puberty (14%) (1,5). Careful attention to other signs such as recurrent otitis media, skin lesions, dyspnea or bone pain/lesions is needed in order to rule out multi-organ involvement by LCH (1,5, 6). Hypothalamic adipsic DI (ADI) is a rare variant of CDI associated with thirst abnormalities, and is usually caused by osmoreceptor damage in the circumventricular region (11-13). Recently, antibodies specifically reactive to the mouse subfornical organ, the hypothalamic animal model of /for the centre of thirst in the mammals (14), were identified in the sera of children with adipsic hypernatremia without apparent hypothalamic-pituitary lesions (15).

The full manifestation of DI can be hampered by the coexistence of adrenal insufficiency (AI) or hypothyroidism. This occurrence is known as masked DI and is unmasked by glucocorticoid replacement in patients with AI (16). This impaired water clearance can be explained by AVP-dependent and AVP-independent mechanisms. Some studies have shown an exaggerated AVP expression in rat models with AI, while others have shown that inhibition of water diuresis can occur independent of AVP mechanism (16-19).

2- First-line Investigations

The first step is to establish polyuria through the evaluation of water balance and volume combined with clinical and blood examination. Normal serum glucose and calcium rule out diabetes mellitus or hypercalcemia-induced NDI. Normal serum potassium excludes hypokalemia-induced NDI and normal blood urea nitrogen makes intrinsic renal disease less likely; 24 h evaluation of water balance is mandatory. The second step would be to assess for urine osmolality with a random morning urine osmolality (UOsm)>700–800 mOsm/kg suggesting appropriate renal response to AVP; nocturnal fasting followed by morning plasma osmolality (POsm) and UOsm evaluation may be indicative but such tests have several

pitfalls, i.e. lack of night adherence in water drinkers/PP, lack of available nurse staff, minimal thirsting time needed, and have never been standardized in children or adolescents. Severe hypernatremia (> 147 mmol/L) with consequent high plasma osmolality (> 300 mOsm/kg H2O), and a resulting urine/POsm ratio <1 is commonly detected in dehydrated DI infants who do not have free access to water (1 ,4, 11). In older subjects with polyuria and polydipsia a high serum sodium (>145-147 mmol/L) and POsm measurements (>295-300mOsm/Kg) associated with UOsm<700–800 mOsm/Kg could be suggestive of partial DI; in contrast, a low or low normal sodium (<135 mmol/L) or low POsm (<295mOsm/kg) could not rule out CDI in water drinkers of different etiology (1,11). A practical algorithm for differential diagnosis of polyuria–polydipsia has been proposed by Christ-Crain et al (Reference 4, Figure 5).

3- Water Deprivation Test: Advantages and Pitfalls

In the absence of a straightforward diagnosis, a water deprivation test (WDT) is indicated (1,4, 11,20). A 7 h- deprivation test or a shorter time is usually appropriate, except in cases of PP when a longer period of fluid deprivation (personal experience) may be required (1, 21, 22). The combination of UOsm< 400 mOsm/kg and POsm> 302mOsm/kg seems to be the best cut-off for the diagnosis of DI as recently reported in a large cohort of mainly adult patients, with a sensitivity of 90% and a specificity of 98% (23). Despite some reports of cases of partial CDI that concentrate above 500 mosm/kg, UOsm values between 300 and 450 mOsm/kg in children lead often to a misdiagnosis of PP instead of partial DI in our experience (personal experience). The WDT can be discontinued as soon as the patient's POsm exceeds the expected cut-off (23).

The administration of Desmopressin following the WDT will help in the differential diagnosis between CDI and NDI (4). In cases where UOsm does not increase by >50% after Desmopressin administration, complete NDI is diagnosed while complete CDI is diagnosed

when the UOsm increases by>50%. However, a reliable diagnosis can be difficult in patients with partial CDI or PP where UOsm can change slightly: indeed, reported increases of UOsm above 9% after Desmopressin administration in partial CDI, and increases below 9% in PP (4, 24) need further validation.

Although the WDT is still the standard test for the differential diagnosis of DI, it has a diagnostic accuracy of only around 70% and it is cumbersome for children and for their families because of the long time interval of thirsting that may be required in partial CDI (25), and for the need for hospitalization, the presence of trained staff throughout the whole test, and patient adherence. The reported diagnostic accuracy of the WDT is shown in table 2.

Copeptin versus AVP: Strengths and Limitations

To improve the differential diagnosis of polyuria polydipsia, Robertson et al developed a radioimmunoassay for direct plasma AVP measurement in order to increase the sensitivity of WDT (26). However, the complex pre-analytical requirements, and the lack of readily available and fast assays limited the AVP use as a clinical routine marker (25,27). By contrast, copeptin, the C-terminal segment of the AVP precursor peptide, has been recently proved to be an attractive new surrogate marker for the diagnosis of DI. Processed from the same precursor peptide, the release of plasma copeptin and plasma AVP into the circulation is regulated by the same physiological stimuli, which is a relative increase in systemic osmolality and a relative decrease in arterial blood volume and pressure. The main advantages of measuring copeptin compared to AVP are that it requires only a small sample volume (50 μL of serum or plasma), no extraction step, or other pre-analytical procedures, and that the results are normally available in < 2 h. In addition, copeptin is much more stable in plasma or serum ex vivo with <20% loss of recovery for at least 7 days at room temperature and at 14 days at 4 °C, making the handling of patient blood samples less complicated. Two assays are currently available and validated: the original manual sandwich

immunoluminometric assay (LIA) and the automated immunofluorescent successor (on the KRYPTOR platform) (25-28).

A baseline copeptin level higher than 21.4 pmol/L without prior thirsting has been reported to unequivocally identify NDI, making additional water deprivation unnecessary (29, 30). It is worth to point out that the diagnosis of X-linked NDI in children does not usually require dehydration test because of severe associated- dehydration and chronic hypernatremia, while NDI caused by acquaporin-2 gene mutations maybe variably severe and very rare. On the other hand, for the more challenging differentiation between children with primary PP and CDI, osmotically stimulated copeptin values are needed, because baseline levels show a large overlap in the two patient groups (25,29,30). The use of osmotically stimulated copeptin levels has recently been confirmed in the so far largest study including 156 patients with DI or PP (31). Osmotic stimulation was achieved using hypertonic saline infusion aimed at a plasma sodium level of 150 mmol/L or greater, at which time copeptin was measured. In a head to-head comparison with the classical WDT, osmotically stimulated copeptin at a cut-off level greater than 4.9 pmol/L showed a diagnostic accuracy of 97% vs 77% in distinguishing patients with primary polydipsia from patients with CDI (31). However, the hypertonic saline infusion test is based on the induction of hypernatremia and therefore has several caveats including the adverse effects associated with an increase in sodium and is contraindicated in patients with heart failure or epilepsy (31, 32). In 2019, Winzeler et al. demonstrated that a copeptin cutoff of 3.8 pmol/L after arginine infusion had an accuracy of 93% in differentiating between DI and PP, with a sensitivity of 93% and a specificity of 92%(32). Compared to hypertonic saline stimulation, the tolerability profile appears clearly more attractive, especially for children. However, copeptin assays are not routinely available in all healthcare settings and additional studies are required (25). It should be emphasized that the pathophysiological role of copeptin in children with disturbances of

water homeostasis, including hyponatremia [Syndrome of inappropriate antidiuretic hormone (SIADH), cerebral salt-wasting syndrome (CSW)], requires elucidation and that robust d**ata on the value of copeptin measurement in different pediatric age groups with normal weight, overweight or obese are needed (33, 34).**

Tumor Markers and Hypothalamic–Pituitary Antibodies

Once the diagnosis of CDI has been established, germ cell tumor markers including serum and cerebrospinal fluid (CSF) human chorionic gonadotropin (β-HCG), placental alkaline phosphatase and alpha-fetoprotein (AFP) are commonly evaluated. Indeed, a negative result in CSF does not exclude germinoma (1,5) and they may be negative at presentation in patients with CDI and pituitary stalk involvement; they may also develop over different time periods (1,5). Among the 70 patients treated for intracranial pure germinoma and non germinomatous GCTs (NGGCT) at Massachusetts General Hospital between 1998 and 2012, serum and CSF markers were initially normal in 10 out of 11 patients presenting with CDI and PST, and became positive in two patients with progressive pituitary stalk enlargement diagnosed with germinomas; one patient with pure germinoma developed elevated serum AFP (491 ng/mL) and CSF AFP (663 ng/mL) shortly before chemotherapy and was re-classified as NGGCT (10). In a recent study, 13 (14%) among 94 patients with germinoma received a diagnosis based on classical radiologic findings or tumor markers; 6 of these 13 patients had β-HCG elevation, with a median serum β-HCG of 24 IU/L (range, 3–38) and a median CSF β-HCG of 32 IU/L (range, 14–44). Overall 12 patients (13%) had a high serum β-HCG and 8 (9%) a high CSF β-HCG (35).

Brain tumors can be associated with the development of hypothalamic–pituitary antibodies; the presence of lymphocytic hypophysitis or infundibulo-neurohypophysitis may represent the first sign of a host reaction to an occult germinoma (36). Thus, the correct interpretation

of hypothalamic–pituitary antibodies is essential to avoid a misdiagnosis of an autoimmune pituitary involvement in patients with brain tumors, including germinoma (36).

Imaging in Central Diabetes Insipidus

Brain MRI is essential for the identification of the underlying condition causing CDI; imaging of brain or hypothalamic-pituitary involvement may be negative at disease onset, but additional findings may appear over time. Therefore, appropriate MRI and other imaging investigations during follow-up are mandatory.

Imaging protocol

MRI is the primary imaging method for evaluating sellar/suprasellar region in pediatric patients with CDI, because of its high soft-tissue contrast resolution and lack of invasiveness (37). MRI of the sellar/suprasellar region is performed on 1.5 T or 3 T MR scanners with thin slice: T1, T2, and gadolinium-enhanced T1-weighted sequences of both the sagittal and the coronal planes are the most advantageous in evaluating this region. In addition, an isotropic high-resolution, sub-millimetric, sagittal heavily T2-weighted sequence [i.e. driven equilibrium (DRIVE)], which allows a very detailed representation of the pituitary stalk and suprasellar compartment, is recommended (38, 39). Evaluation of the whole brain should always be performed in case of CDI to assess the presence of additional abnormalities that may better reveal an underlying condition (1,40).

Typical neuroimaging findings of CDI include absence of the posterior pituitary hyperintensity and normal or PST encompassing the proximal (>3 mm), distal (>2 mm) or the entire stalk. Indeed, this finding is not specific since a PST may be the early manifestation of germ cell tumor, LCH, lymphocytic infundibulo-hypophysitis and other inflammatory/autoimmune conditions; in addition, it can be present in idiopathic cases (40). Hence, the diagnosis of lesions causing PST is challenging and may require a long-term follow-up (5,40); concomitant volumetric increase in the size of the stalk and of anterior

pituitary supports the diagnosis of infiltrative/neoplastic disorders, particularly neurohypophyseal germinoma. On the other hand, the association of anterior pituitary hormone deficiency with MRI evidence of progressive reduction in size of the anterior pituitary is suggestive of an inflammatory/autoimmune condition, although it does not rule out a germinoma infiltrating the hypothalamus and/or the third ventricle. The evolution of PST and its relationship with pattern of contrast-enhancement has been recently evaluated in children with CDI (41). In the latter study, serial MRIs in patients with CDI of different etiology provide new information by identifying the "mismatch pattern" (defined as discrepancy between PS thickness in T2-DRIVE and post-contrast T1-weighted images) affecting the pituitary stalk anatomy, and pituitary function; it appears that the mismatch pattern is very likely generated as the result of chronic local inflammation of the proximal pituitary stalk and represents a marker of anatomical stabilization of pituitary stalk lesion, which is significantly associated with anterior pituitary defects. It remains to be confirmed if the appearance of mismatch pattern in patients with CDI may allow to identify patients with idiopathic forms, thus excluding the presence of LCH or other specific conditions.

Spine MRI, as well as a radiological skeletal survey, chest X-ray and the more recent whole-body MRI [short-tau inversion-recovery (STIR) and spin echo T1-weighted images], that allows the evaluation of the entire body in a single examination without radiation exposure, can be required in the diagnostic work-up of CDI (1, 40).

A diagnostic imaging algorithm in subjects with PST is shown in Figure 1. Between 2014 and 2019, a multidisciplinary, expert national guideline development group in the UK reported a management flowchart and clinical practice guidelines to inform specialist care and improve outcomes in children and young people with idiopathic PST (42).The main recommendations are summarized in the following key points: 1) to consider a pituitary stalk as thickened, cutoffs of 4 mm or more at the optic chiasm or 3 mm or more at pituitary insertion are

suggested. However, without pediatric norms, size alone cannot distinguish physiological from pathological variants; 2) minimally invasive first-line investigations are strongly recommended in all cases including: a. serum β-hCG and AFP to detect secreting germ-cell tumor; b. chest x-ray, abdominal ultrasonography and skeletal survey to detect signs of LCH and possible sites for diagnostic biopsy; c. evaluation of anterior and posterior pituitary function to detect occult growth hormone and adrenocorticotropin deficiency; d. optometry (visual acuity and field assessment), especially if PST encroaches on the optic chiasm; 3) CSF tumor markers (β-hCG and AFP) and whole-body imaging are second-line investigations recommended in cases where stalks are large (>6.5–7mm), enlarging, pituitary or visual dysfunction is evolving, or a combination of all three; 4) pituitary stalk biopsy should only be done in specialist multidisciplinary centers in selected patients with endocrine or visual symptoms whose second-line investigations have been negative, and whose stalk thickening is sufficient (>6.5–7 mm) to yield a diagnostic biopsy without further visual or endocrine harm.

Genetic Testing for CDI

Genetic evaluation of patients with suspected inherited CDI should be considered in those with a positive family history of DI or with early-onset "idiopathic forms of CDI" who might carry a *de novo* mutation of AVP-NPII or Wolfram gene mutations (1,7,8, 43). More than 80 variants resulting in AVP deficiency have been described (1,7,8,43, 44, 45). All but a few have an autosomal dominant pattern of inheritance and are in the 2.5 kb AVP-NPII gene, which is located on chromosome 20p13 (1,7,8,44,45). In subjects with genetic CDI, posterior pituitary hyperintensity may be recognized as normal or as a "small hypointense signal" (8, 43). Indeed, its identification by neuroradiologists represents a potential imaging pitfall that leads specialists to erroneously diagnose a primary polydipsia, rather than favoring the suspicion of genetic forms of CDI (8, 43); a loss of the hyperintense signal over time is also

predictable. Thus, molecular analysis of AVP-NPII gene and counseling should be provided in selected young cases to avoid unnecessary investigations and to ensure an early and adequate treatment.

Management of CDI

The mainstay of treatment for CDI is free access to water associated with a pharmacologic agent. Both vasopressin and Desmopressin act by stimulating V2 receptor in renal collecting duct principal cells, but Desmopressin has a longer half-life and lacks vasopressor effects (45). Desmopressin is therefore the first-choice drug in patients with CDI and it is available in a variety of formulations; the route and timing (fixed or on-demand) of administration depend on the clinical setting (1,11,44,46) (Table 3). Personalized fixed dose of Desmopressin 2 to 3 times/day is orally administered in children followed by a subsequent dose when polyuria recurs (> 5 ml/kg/hour) (47).

Pituitary stalk injury – both surgical and traumatic – may be followed by biphasic or triphasic response in sodium and fluid balance. Triphasic response is observed in up to 22.5% of patients after surgery, when pituitary stalk damage is complete, with polyuria/polydipsia in the immediate post-operative days, followed by SIADH a few days later (2-8 days), and eventually by permanent CDI. The first phase is attributed to the shock of initial injury, followed by the release of AVP that had been previously stored in posterior pituitary cells, and finally by permanent AVP deficiency; hence the need for rapid switches in fluid replacement volumes and Desmopressin therapy, in order to avoid steep changes in serum sodium (48). A temporarily reduced need for Desmopressin in the postoperative period has been reported also in patients with a pre-existing CDI diagnosis who undergo pituitary surgery.

In case of partial damage, only first phase or first two phases may be observed, with subsequent *restitution ad integrum*. Furthermore, in acute setting, in order to manage CDI

effectively, confounding causes for polyuria should be ruled out, such as steroid-induced hyperglycemia, mannitol, or other diuretic therapy, CSW, as well as confounding factors for hyper- or hyponatremia such as carbamazepine or other anticonvulsant therapy, CSW, kidney or liver disease, heart failure, adrenal insufficiency (AI), hypothyroidism, insufficient or excessive iv fluid replacement, impaired thirst due to altered level of consciousness (49).

In infants with CDI, limited literature supports the use of thiazide diuretics as a safer alternative to Desmopressin because they are dependent on liquid for nutrition and lack free access to fluids (1, 9,11, 45). Indeed, Desmopressin is generally safe with limited adverse effects, although it is very important that treated patients are carefully monitored to prevent the risk of hyponatremia particularly in those using multi-drug for associated conditions (11,47,50). In order to prevent hyponatremia, patients should be instructed to avoid drinking a greater amount of fluids than what is necessary to extinguish thirst. Inter-patient differences in drug-response require individualized titration of Desmopressin while minimizing electrolyte disturbances (1,11). In adults, hyponatremia could be avoided by different strategies including intermittent delay or withdrawal of one or more doses of Desmopressin (51).

In the presence of adipsia or hypodipsia, CDI presents a difficult challenge due to wide swings in plasma sodium, and therefore CDI with hypo/adipsia is initially best managed by adjusting the Desmopressin dosage and fluid intake in a hospital setting. The patient should be instructed to maintain continuous Desmopressin use and regular and periodic water ingestion. A fixed, appropriate for body-weight daily fluid intake should be established in order to maintain a personalized value of natremia at which the patient is known to be “eunatremic” and “euvolemic” (11), in particular in patients with adipsia. Desmopressin is then administered at a dose and frequency able to establish an appropriate urine output and neutral fluid balance, allowing for insensible losses; regular weighing and checking of serum

sodium levels are mandatory. Intravenous hydration or nasogastric tube could be used when the patient is unable to drink (11,52,53).

Back to our patient with Germinoma -*First do no harm*

In our patient, the misleading interpretation of "reversible" CDI after 18 months from diagnosis, the onset of clinical symptoms such as fatigue, nausea, vomiting and the results of blood testing suggestive of serum hypernatremia and high plasma osmolality, represent signs and markers most likely compatible with central AI and hypothyroidism in the context of a "permanent" CDI secondary to a progressive hypothalamic-pituitary involvement. Indeed, the clinical signs of dehydration and the appearance of central nervous system symptoms such as memory loss, behavior and sensory disturbances, confusion and lethargy were highly indicative of brain/hypothalamus and thirst center involvement (hypodipsia/ adipsia).

In this case, polyuria and polydipsia started at age 12 years, and the correct diagnosis of CDI was followed by treatment with Desmopressin. MRI performed at the time of diagnosis showed normal anterior pituitary and pituitary stalk size, with absence of posterior pituitary hyperintensity or other brain abnormalities. However, the 18-24 month patient's course led to a misdiagnosis of a reversible form of CDI and to the discontinuation of Desmopressin treatment, suggesting a lack of adequate work-up, including a second MRI, and an inaccurate follow-up.

We also believe that the patient's physician was possibly relieved by the progressive disappearance of polyuria and polydipsia, which were interpreted as an improvement of underlying disease, leading to gradual Desmopressin tapering until withdrawal. Furthermore, the "interpretation" of the absence of brain lesions at MRI (Figure 2 A-B) may have falsely reassured healthcare workers about a possible "reversible idiopathic form of CDI". Indeed, the "normalization" of water intake and urine output can be explained both by the damage of hypothalamic-pituitary function, including of ACTH and TSH deficiencies, and of patient's

thirst center as confirmed by the presence of a huge mass invading the hypothalamus and the third ventricle compatible with a germinoma and leptomeningeal metastases (Figure 2 C-D).

Why are brain tumors diagnosis still missed? The differential diagnosis of acquired CDI is challenging and a significant proportion of patients with germinoma have been reported to experience a delay in time to diagnosis up to 72 months (10). Among 54% of 70 pediatric patients who had a delayed diagnosis, 49% were evaluated by a general pediatrician, and 66% by pediatric subspecialists. Patients with delayed diagnosis saw a greater number of physicians before diagnosis, 63% were seen by 2 or more physicians, and 40% by 2 or more subspecialists. In our experience, the diagnosis of germinoma was made in the great majority of patients and based on the time of referral- within the first 2 years after the diagnosis of CDI avoiding disseminated disease (6).

This case highlights the key role of an adequate work-up in patients presenting with polyuria and polydipsia and of clinical, endocrine and neuroimaging follow-up for the early and correct diagnosis and prognosis of patients with “apparently” idiopathic CDI; delay and inaccuracy in both initial work-up and subsequent follow up increase the risk of metastases. It also shows that signs of apparent improved water balance in CDI patients should alert and not relieve physicians, because it could be the late manifestation of multiple pituitary hormone deficiencies and of thirst center damage caused by the development of an undiagnosed "occult" brain mass. Attention should be paid, moreover, to the single first MRI result of isolated absence of posterior pituitary hyperintensity in patients with CDI as a “safe” marker: this cannot be considered as a reliable indicator of "normal brain imaging", and further neuroimaging follow up is needed; it has been reported that the second MRI investigation after 6 months is essential and should not be missed (6).

Key Points

1. The age of onset of polyuria and polydipsia, the time lag between the onset of symptoms and the diagnosis, and the pattern of fluid intake may help in the differential diagnosis of DI.
2. Brain MRI is crucial for etiological diagnosis; neuroimaging may be not suggestive of sellar/suprasellar or pineal lesions at disease onset, but pathological findings can appear over time.
3. Early etiological diagnosis of conditions presenting with polyuria and polydipsia is possible in the great majority of patients with CDI within the first 2 years. MRI examination every 6 months for 2 years is essential and the second MRI is extremely helpful.
4. Acquired CDI is not reversible but could be masked by adrenal and/or thyroid insufficiency or the development of thirst abnormalities.
5. Clinical, biochemical, endocrine and neuroimaging studies are needed during follow-up of patients with apparently idiopathic CDI; the appearance of additional clinical signs and the need of a multidisciplinary approach should not be underestimated.

Areas of Uncertainty and Research

1. Optimization of strategies to improve the management and outcomes.
2. Definition of the diagnostic accuracy of copeptin in healthy and in children with water disturbances.
3. Identification of new serum and CSF markers helpful in the differential diagnosis of conditions associated with CDI
4. Establishment of normative MRI criteria for pituitary stalk size in children and adolescents.

5. Address research gaps and priorities in order to identify the role of novel imaging techniques in securing an early diagnosis without the use of brain biopsy.
6. Create machine-learning algorithms within a systems framework for the identification of patients with different level of risks, and for targeted interventions improving long-term outcomes.
7. Provide support to coordinate actions among families, specialists and researchers, in both the early phase of diagnosis and during follow-up.

Data Availability Statement: Data supporting the findings of this study are available within the article. Additional information can be required to the corresponding author.

References

1. Patti G, Ibba A, Morana G, et al. Central diabetes insipidus in children: Diagnosis and management. Best Pract Res Clin Endocrinol Metab 2020;34(5): 101440.
2. Refardt J, Winzeler B, Christ-Crain M. Diabetes Insipidus: An Update. Endocrinol Metab Clin North Am. 2020;49(3):517-31.
3. Di Iorgi N, Napoli F, Morana G, Maghnie M. Disorders of Water Balance. Brook's Clinical Pediatric Endocrinology.7th edition. Wiley 2020: 553-76.
4. Christ-Crain M, Bichet DG, Fenske WK, et al. Diabetes insipidus. Nat Rev Dis Primers 2019;5(1):54
5. Maghnie M, Cosi G, Genovese E, et al. Central diabetes insipidus in children and young adults. N Engl J Med 2000;343(14):998-1007
6. Di Iorgi N, Allegri AE, Napoli F, et al. Central diabetes insipidus in children and young adults: etiological diagnosis and long-term outcome of idiopathic cases. J Clin Endocrinol Metab 2014;99(4):1264-72.
7. Babey M, Kopp P, Robertson GL. Familial forms of diabetes insipidus: Clinical and molecular characteristics. Nat Rev Endocrinol 2011;7(12):701-14
8. Patti G, Scianguetta S, Roberti D, et al. Familial neurohypophyseal diabetes insipidus in 13 kindreds and 2 novel mutations in the vasopressin gene. Eur J Endocrinol 2019;181(3):233-44
9. Djermane A, ElmalehM, Simon D et al. **Central diabetes insipidus in infancy with or without hypothalamic adipsic hypernatremia syndrome: early identification and outcome.** J Clin Endocrinol Metab 2016;101(2):635-43.
10. Sethi R V, Marino R, Niemierko A, Tarbell NJ, Yock TI, MacDonald SM. Delayed diagnosis in children with intracranial germ cell tumors. J Pediatr 2013;163(5):1448-53

11. Di Iorgi N, Morana G, Napoli F, et al. Management of diabetes insipidus and adipsia in the child. Best Pract Res Clin Endocrinol Metab 2015;29:415–36
12. Dalan R, Chin H, Hoe J, et al. Adipsic Diabetes Insipidus-The Challenging Combination of Polyuria and Adipsia: A Case Report and Review of Literature. Front Endocrinol (Lausanne) 2019;10:630
13. Tuli G, Matarazzo P, de Sanctis L. Clinical Approach to Sodium Homeostasis Disorders in Children with Pituitary-Suprasellar Tumors. Neuroendocrinology 2020;110(3-4):161-71.
14. Oka Y, Ye M, Zuker CS. Thirst driving and suppressing signals encoded by distinct neural populations in the brain. Nature 2015;520(7547):349-52.
15. Hiyama TY, Utsunomiya AN, Matsumoto M, et al. Adipsic hypernatremia without hypothalamic lesions accompanied by autoantibodies to subfornical organ. Brain Pathol. 2017;27(3):323-31.
16. Non L,Brito D, AnastasopoulouC. Neurosarcoidosis-associated central diabetes insipidus masked by adrenal insufficiency. BMJ Case Rep.2015:bcr2014206390
17. Ahmed AB, George BC, Gonzalez-Auvert C, Dingman JF. Increased plasma arginine vasopressin in clinical adrenocortical insufficiency and its inhibition by glucosteroids. J Clin Invest 1967;46(1):111-23.
18. Saito T, Saito T, Kasono K, et al. Vasopressin-dependent upregulation of aquaporin-2 gene expression in aged rats with glucocorticoid deficiency. Acta Physiol (Oxf). 2009;196(2):239-47
19. Green HH, Harrington AR, Valtin H. On the role of antidiuretic hormone in theinhibition of acute water diuresis in adrenal insufficiency and the effects of gluco and mineralocorticoids in reversing the inhibition. J Clin Invest 1970;49:1724–36

20. de Fost M, Oussaada SM, Endert E et al. The water deprivation test and a potential role for the arginine vasopressin precursor copeptin to differentiate diabetes insipidus from primary polydipsia. Endocr Connect 2015;4(2):86-91
21. Fenske W, Allolio B. Current state and future perspectives in the diagnosis of diabetes insipidus: A clinical review. J Clin Endocrinol Metab 2012;97(10):3426-37.
22. Pedrosa, W, Drummond JB, Soares BS, Ribeiro-Oliveira Jr A. A Combined Outpatient And Inpatient Overnight Water Deprivation Test Is Effective And Safe In Diagnosing Patients With Polyuria-Polydipsia Syndrome. Endocr Pract 2018;24(11):963-72.
23. Sjöström A, Bartuseviciene I, Höybye C. Simplified and improved fluid deprivation test for diagnosing diabetes insipidus. Eur J Endocrinol 2021;184(1):123-31
24. Miller M, Dalakos T, Moses AM, et al. Recognition of partial defects in antidiuretic hormone secretion. Ann Intern Med 1970;73(5):721-9.
25. Christ-Crain M. Diabetes Insipidus: New concepts for diagnosis. Neuroendocrinology 2020;110(9-10):859-67
26. Robertson GL, Mahr EA, Athar S, et al. Development and Clinical Application of a New Method for the Radioimmunoassay of Arginine Vasopressin in Human Plasma. J Clin Invest 1973;52:2340-52.
27. Dobsa L, Edozien KC. Copeptin and its potential role in diagnosis and prognosis of various diseases. Biochem Med (Zagreb) 2013;23:172-90
28. Christ-Crain M, Fenske W. Copeptin in the diagnosis of vasopressin-dependent disorders of fluid homeostasis. Nat Rev Endocrinol 2016;12:168-76
29. FenskeW, Quinkler M, Lorenz D, 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

30. Timper K, Fenske W, Kühn F, 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.
31. Fenske W, Refardt J, Chifu I, et al. A Copeptin-Based Approach in the Diagnosis of Diabetes Insipidus. N Engl J Med 2018;379(5):428-39
32. Winzeler B, Cesana-Nigro N, Refardt J, et al. Arginine-stimulated copeptin measurements in the differential diagnosis of diabetes insipidus: a prospective diagnostic study. Lancet 2019; 394(10198):587-95.
33. Grandone A, Marzuillo P, Patti G, Perrotta S, Maghnie M. Changing the diagnostic approach to diabetes insipidus: role of copeptin. Ann Transl Med. 2019;7(Suppl 8):S285.
34. Tuli G, Munarin J, Tessaris D, Einaudi S, Matarazzo P, de Sanctis L. Distribution of plasma copeptin levels and influence of obesity in children and adolescents. Eur J Pediatr 2021;180(1):119-26.
35. Lo AC, Hodgson D, Dang J, *et al.* **Intracranial germ cell tumors in adolescents and young adults: a 40-year multi-institutional review of outcomes.** Int J Radiat Oncol Biol Phys 2020;106(2):269-78
36. Patti G, Calandra E, De Bellis A, et al. Antibodies Against Hypothalamus and Pituitary Gland in Childhood-Onset Brain Tumors and Pituitary Dysfunction. Front Endocrinol (Lausanne) 2020;11:16.
37. Di Iorgi N, Morana G, Allegri AE, et al. Classical and non-classical causes of GH deficiency in the paediatric age. Best Pract Res Clin Endocrinol Metab 2016;30(6):705-36.

38. Godano E, Morana G, Di Iorgi N, et al. Role of MRI T2-DRIVE in the assessment of pituitary stalk abnormalities without gadolinium in pituitary diseases. Eur J Endocrinol 2018;178(6):613-22.
39. Morana G, Alves CA, Tortora D, et al. T2*-based MR imaging (gradient echo or susceptibility-weighted imaging) in midline and off-midline intracranial germ cell tumors: a pilot study. Neuroradiology 2018;60(1):89-99.
40. Di Iorgi N, Morana G, Maghnie M. Pituitary stalk thickening on MRI: when is the best time to re-scan and how long should we continue re-scanning for? Clin Endocrinol (Oxf) 2015;83(4):449-55
41. Bianco D, Napoli F, Morana G, et al. Endocrine Outcomes In Central Diabetes Insipidus: the Predictive Value of Neuroimaging "Mismatch Pattern". J Clin Endocrinol Metab 2020; 105(11):1-13
42. Cerbone M, Visser J, Bulwer C, et al. Management of children and young people with idiopathic pituitary stalk thickening, central diabetes insipidus, or both: a national clinical practice consensus guideline. Lancet Child Adolesc Health 2021;S2352-4642(21)00088-2.
43. Perrotta S, Di Iorgi N, Ragione FD, et al . Early-onset central diabetes insipidus is associated with de novo arginine vasopressin-neurophysin II or Wolfram syndrome 1 gene mutations. Eur J Endocrinol 2015;172(4):461-72.
44. Feldkamp LLI, Kaminsky E, Kienitz T, Quinkler M. Central Diabetes Insipidus Caused by Arginine Vasopressin Gene Mutation: Report of a Novel Mutation and Review of Literature. Horm Metab Res. 2020;52(11):796-802.
45. García-Castaño A, Madariaga L, Pérez de Nanclares G, et al. Forty-One Individuals With Mutations in the AVP-NPII Gene Associated With Familial Neurohypophyseal Diabetes Insipidus. J Clin Endocrinol Metab 2020;105(4):1112–18

46. OisoY, Robertson GL, Nørgaard JP, Juul KV. Treatment of neurohypophyseal diabetes insipidus. J Clin Endocrinol Metab 2013 ;98(10):3958-67
47. Kim RJ, Malattia C, Allen M, et al. Vasopressin and desmopressin in central diabetes insipidus: adverse effects and clinical considerations. Pediatr Endocrinol Rev 2004;2 Suppl 1:115-23.
48. Kruis RWJ, Schouten-van Meeteren AYN, Finken MJJ, et al. Management and consequences of postoperative fluctuations in plasma sodium concentration after pediatric brain tumor surgery in the sellar region: a national cohort analysis. Pituitary 2018;21(4):384-92.
49. Hannon MJ, Finucane FM, Sherlock M. Clinical review: Disorders of water homeostasis in neurosurgical patients. J Clin Endocrinol Metab 2012 ;97(5):1423-33
50. Garrahy A, Thompson CJ. Management of central diabetes insipidus. Best Pract Res Clin Endocrinol Metab 2020; 34(5):101385
51. Garrahy A, Moran C, Thompson CJ. Diagnosis and management of central diabetes insipidus in adults. Clin Endocrinol (Oxf) 2019;90(1):23-30
52. Baldeweg SE, Ball S, Brooke A, et al. Society for Endocrinology endocrine emergency guidance. Inpatient management of cranial diabetes insipidus. Endocr Connect 2018;7:G8-11.
53. Feld LG, Neuspiel DR, Foster BA, et al. Subcommittee on fluid and electrolyte therapy. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. Pediatrics 2018;142(6):e20183083.

Figure Legends

Figure 1. Diagnostic imaging algorithm in subjects with pituitary stalk thickening.

*Susceptibility-weighted imaging or T2 gradient echo features in germ cell tumors.

**Tumor markers in the cerebrospinal fluid in selected cases based on the neuroimaging findings (Anterior pituitary size, Pituitary stalk size and progression, third ventricle involvement, pineal gland involvement).

***MRI may be repeated after 2-3 months in selected cases with high suspicion of specific conditions based on the previous MRI findings.

**** chronic cough or dyspnea, intense bone pain or swelling, chronic skin manifestations, chronic otorrhea, signs or symptoms of liver or other organ dysfunction.

Abbreviation: LCH=Langerhans Cells Histiocytosis.

Figure 2. A 14-year-old girl with a history of polyuria/polydipsia and central diabetes insipidus (CDI). First MRI was performed at the time of diagnosis of CDI and was not repeated for 2 years.

First MRI sagittal (A) and coronal (B) T1–weighted images at CDI onset showed normal anterior pituitary size (double white arrows) and pituitary stalk (white arrow), absence of posterior pituitary hyperintensity (white arrowhead) with no other brain lesions.

Second MRI sagittal (C) and coronal (D) T1-weighted images performed after 2 years showed a 4.8 cm mass (white star) suggestive of germinoma associated with leptomeningeal metastases.

Table 1. Etiologies of Central Diabetes Insipidus

Congenital	• Associated with ectopic posterior pituitary, anterior pituitary hypoplasia and congenital hypopituitarism • Midline brain developmental defects septo-optic dysplasia
Genetic	• Autosomal dominant / recessive AVP mutation • X-linked • Congenital hypopituitarism with central diabetes insipidus • Wolfram syndrome, wolframin mutation • NFKB2 mutation/DAVID Syndrome • PCSK1 • TFAP2B/Char Syndrome
Acquired	• Idiopathic • Intracranial tumors: germinoma, craniopharyngioma, Rathke's cleft cyst, glioma • Langerhans cell histiocytosis • Autoimmune • Granulomatosis (tuberculosis, sarcoidosis, granulomatosis with polyangiitis) • Prenatal/postnatal infections • Central Nervous system surgery • Traumatic brain injury • Vascular impairment / Hypoxic-ischemic • Metastases

Table 2. Diagnostic Accuracy of Water Deprivation Test in Studies including at least 40 Subjects between 2011-2021.

Authors	**Year**	**Patients n**	**Age (years)**	**Method**	**Fluid-restriction (hours)**	**Results**
Sjostrom et al [23]	2021	153* (30 DI; 123 no DI)	median 47.5 range 12-81 (2 children)	indirect	12 h fasting(range: 12-21 h)	Se 90%; Sp 98%; Cut-off: POsm>302 mOsm/kg and UOsm<400 mOsm/kg
Fenske et al. [31]	2018	144 (36 CDI; 23 PCDI; 3 NDI; 82 PP)	≥ 16	indirect	17 h	DgA73.3% 95% CI (63.9 to 81.2); Cut-off: CDI UOsm< 300 mOsm/kg; PCDI UOsm 300-800 mOsm/kg
De Fost et al. [20]	2015	40 (12 CDI;1 NDI; 27 no DI)	adults	indirect	7 h (range 1-18 h)	a. Se 96%; Sp 100%: Cut-Off: UOsm: 800 mOsm/kg; b. Se 100%; Sp 100% Cut-off: UOsm: 680 mOsm/kg
Fenske et al. [29]	2011	50 (9 CDI; 17 PCDI; 2 NDI) 20 controls	adults	indirect/ direct**	16 h	DgA70% by indirect WDT DgA46% by direct WDT Cut-off: UOsm< 300 mOsm/kg

Abbreviation: CDI= central diabetes insipidus; NDI= nephrogenic diabetes insipidus; PCDI= partial central diabetes insipidus; PP = polyuria polydipsia; POsm=plasma osmolality; UOsm= urine osmolality; DgA= diagnostic accuracy; WDT= water deprivation test; Se = sensitivity; Sp = specificity

* outpatients; **with AVP or copeptin measurement

Table 3. Main Medications Used in the Treatment of Central Diabetes Insipidus

Drug	**Route**	**Dose**	**Disadvantages**
Desmopressin tablets	Oral	100-1200 µg/day in 3 doses	3 doses (versus 2 doses of Desmopressin nasal spray) Variable bioavailability if taken at mealtime
Desmopressin Lyophilisate (melt)	sl	1-5 µg/kg/day in 2-3 doses	inaccurate splitting of tablets 3 doses (versus 2 doses of DDAVP nasal spray)
Desmopressin spray	Nasal	5-30 µg/day in 1-2 doses	difficult dose titration variable absorption risk of hyponatremia need of refrigeration possible side effects (dizziness, rhinitis or epistaxis)
Desmopressin aqueous solution	nasal via rhinyl tube	10-40 µg/day in 1-3 doses	possible side effects (rhinitis, epistaxis, nasal edema)
Desmopressin parenteral	im or sc	0.1-1 µg/day	difficult route of administration

Abbreviation: im= intramuscular; sc=subcutaneous; sl= sublingual

Figure 1

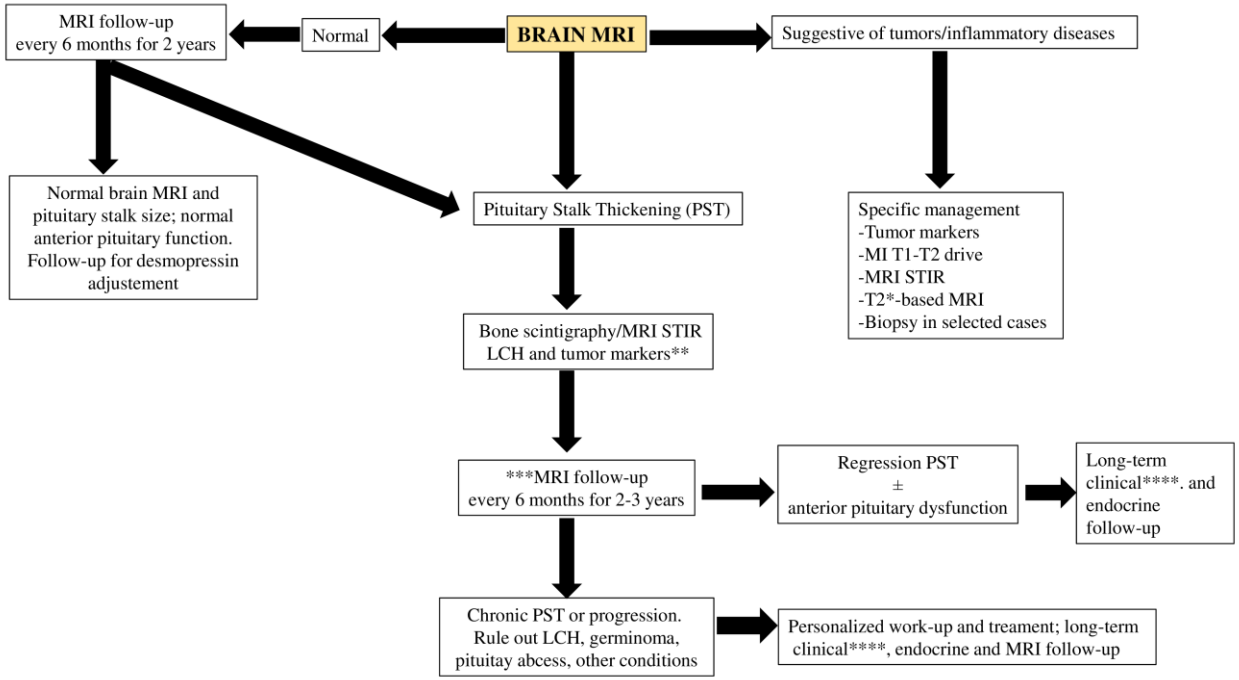
BRAIN MRI
Normal
MRI follow-up
every 6 months for 2 years
Suggestive of tumors/inflammatory diseases
Normal brain MRI and
pituitary stalk size; normal
anterior pituitary function.
Follow-up for desmopressin
adjustement
Pituitary Stalk Thickening (PST)
Specific management
-Tumor markers
-MI T1-T2 drive
-MRI STIR
-T2*-based MRI
-Biopsy in selected cases
Bone scintigraphy/MRI STIR
LCH and tumor markers**
***MRI follow-up
every 6 months for 2-3 years
Regression PST
±
anterior pituitary dysfunction
Long-term
clinical****. and
endocrine
follow-up
Chronic PST or progression.
Rule out LCH, germinoma,
pituitay abcess, other conditions
Personalized work-up and treament; long-term
clinical****, endocrine and MRI follow-up

Figure 2