4 Central Diabetes Insipidus with Pituitary Stalk Thickening

Ahsan Uddin and Shabana Kalladi Puthanpurayil

Case Description

A 7-year-old female was evaluated by her pediatrician for complaints of intermittent headaches, polydipsia, polyuria, and new onset nocturnal enuresis. Her symptoms persisted despite bedtime water restriction. Workup initiated by her pediatrician showed a serum sodium of 147 mmol/L and they were referred to pediatric endocrinology. At repeat evaluation, studies showed sodium of

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A. Uddin
Department of Internal Medicine and Pediatrics, William Beaumont Hospital, Royal Oak, MI, USA
e-mail: Ahsan.Uddin@beaumont.org

S. Kalladi Puthanpurayil (✉)
Department of Pediatrics, Beaumont Children's Hospital, Royal Oak, MI, USA

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147 mmol/L, creatinine of 0.65 mg/dl, serum osmolality of 291 mOsm/kg, and urine osmolality of 137 mOsm/kg. Antidiuretic hormone (ADH) level was undetectable. An inpatient water deprivation test was recommended to rule out diabetes insipidus.

Water deprivation testing was conducted approximately 4 weeks following onset of symptoms. The study confirmed central diabetes insipidus (CDI), with doubling of urine osmolality in response to desmopressin administration, and the patient was started on treatment with 0.05 mg of desmopressin twice daily by mouth. Magnetic resonance imaging (MRI) of brain with and without gadolinium was performed to evaluate for an underlying cause of CDI. The study showed markedly thickened and homogeneously enhancing pituitary stalk (17 mm × 10 mm) (Fig. 4.1a) suggestive of Langerhans cell histiocytosis (LCH). This prompted scheduling of a pituitary stalk biopsy and skin biopsy. The skin biopsy report was normal. During the endoscopic procedure for pituitary stalk biopsy, which was performed 7 weeks after the initial MRI, direct visualization of the pituitary stalk did not show any abnormalities and therefore no tissue sample was taken. A repeat brain MRI performed at this time (i.e., 7 weeks after the initial MRI) showed complete resolution of the previously demonstrated pituitary stalk thickening (PST). Follow-up MRIs at 5

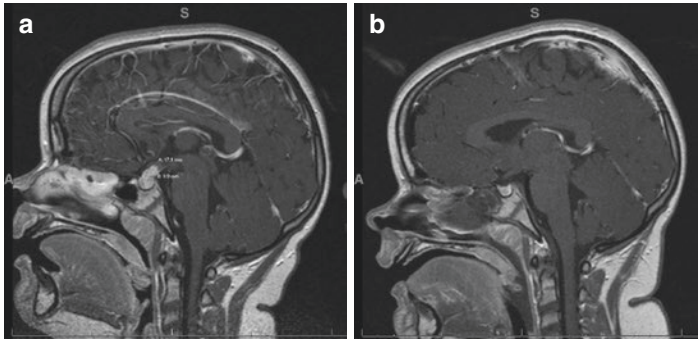

Fig. 4.1 (**a**) MRI of the pituitary with gadolinium contrast demonstrating marked thickening of the pituitary stalk. (**b**) MRI of the pituitary in the same patient 7 weeks later showing complete resolution of previously demonstrated pituitary stalk thickening

and 15 months after initial diagnosis continued to demonstrate complete resolution of the infundibular mass (Fig. 4.1b) suggesting transient inflammation as the likely cause. Alpha-fetoprotein (AFP) and beta human chorionic gonadotropin (hCG) were normal in blood and cerebrospinal fluid (CSF), and CSF cytology was also negative.

At a follow-up visit in clinic 1 year later, she presented with new papular, scaly appearing skin lesions on left thumb, forearm, and fourth digit of right hand. Given these new findings, she was referred to dermatology for a repeat skin biopsy and to oncology for re-evaluation of possible histiocytic disease. A repeat MRI of the pituitary gland performed 28 months after initial diagnosis continued to demonstrate absence of the posterior pituitary bright spot with no other structural abnormalities.

Assessment and Diagnosis

Diabetes insipidus usually presents with a combination of polydipsia and polyuria along with decreased urine osmolality and increased serum osmolality. Diabetes insipidus may be classified as central or peripheral, caused by ADH deficiency or resistance, respectively. They can be differentiated based on response to administration of ADH at the end of a water deprivation study (see Chap. 2 for making the diagnosis of central diabetes insipidus). Once the diagnosis of central diabetes insipidus (CDI) has been established, it is important to identify the underlying etiology, which in children can be due to infectious, neoplastic, traumatic, or genetic processes that disrupt the hypothalamus or pituitary stalk. In particular, identifying neoplasia is critical to determine the best approach to therapy, with germinoma (or other germ cell tumors), craniopharyngioma, and Langerhans cell histiocytosis all being important causes of CDI. Other infiltrative lesions such as lymphoma, although rare, should also be considered [1]. These should ideally be identified early to avoid the pitfall of empiric treatment of presumed hypophysitis (See Chap. 5).

MRI with gadolinium contrast is indispensable in the evaluation of these children as imaging with CT is unable to identify

many pituitary abnormalities [2] leading to incorrect classification of many cases as "idiopathic". Some patients with CDI may present with obvious lesions such as tumors or midline malformations that explain the development of CDI and suggest the underlying diagnosis. One of the most common, albeit non-specific, findings on MRI is absence of the normal pituitary bright spot on T1-weighted imaging [3]. Thus, the absence of the posterior pituitary bright spot is consistent with CDI, but gives no information regarding its underlying etiology. One-third of children with CDI present with pituitary stalk thickening (PST) on initial evaluation with MRI. The normal size of the pituitary stalk is dependent on age. Therefore, the definition of pituitary stalk thickening also changes with the age of the patient. Some authors define stalk thickening in children to be >2.5 mm [2, 4, 5], in the largest cross-section on imaging while most use >3 mm [6]. In patients older than 8 years, the adult definition of >3.5 mm [4] may be used. The thickening may be seen in the proximal, middle, or distal portion of the stalk and this location may have an impact on management as thickening closer to the optic chiasm may warrant more aggressive intervention [7] given the higher likelihood of visual impairment. Given the size changes under consideration, consultation with a neuroradiologist for optimal MRI parameters, including slice thickness, is recommended where the resources are available. Previous studies have shown that the degree of PST is variable depending on the underlying etiology [8] and a significant number of cases are associated with neoplasm of which CDI may be the initial presentation. Furthermore, regression of PST has been observed in many cases of CDI with PST which is attributed to idiopathic or autoimmune process.

In addition to focused MRI examination of the pituitary gland, patients with thickened stalk should have MRI imaging of the brain and spinal cord to seek other abnormalities. Other imaging findings can include abnormal size of the anterior pituitary gland and lesions in the pineal gland, the presence of which may be more suggestive of infiltrative/neoplastic diagnoses such as germ cell tumor (GCT) or less commonly LCH.

MRI findings with CDI are dynamic and it is important to serially follow these patients for changes. Most authors recommend

following patients with CDI with MRI every 3–6 months for at least 2–3 years to identify changes suggestive of neoplasm [9, 10]. In particular it has been demonstrated that frequent neuroimaging follow up can reduce time delay in diagnosis of germinoma from 2.5 years to 1 year [11]. The optimal timing may vary based on patient factors with some authors advocating for more frequent scans [2]; conversely, it may be reasonable to have less frequent follow up in individuals with normal initial imaging or stable imaging beyond the first 2 years. Increasing stalk size is more frequently associated with eventual diagnosis of neoplastic process and may be an indication for pituitary stalk biopsy whereas decreasing size is more suggestive of transient inflammatory process. In cases where stable or resolving PST is noted, routine neuroimaging follow up may be discontinued after 3–5 years. For those patients with persistent or progressive PST, at least annual neuroimaging may be recommended along with consideration of biopsy and investigation of extracranial sites with suspicion of underlying LCH [9].

Our suggested algorithm, based on available literature, for evaluation of a child with central diabetes insipidus and PST, has been outlined in Fig. 4.2. In cases where CDI is present without PST, we recommend following MRIs every 6 months for one year and then annually thereafter. In those where PST is present, follow-up MRI every 3–6 months during the first year, 6–12 months during the second year, then annually up to 5 years is suggested.

In addition to deficiency of ADH, some patients may have associated abnormalities of other pituitary hormones. Anterior pituitary hormone deficits (APDs) can present at any point through the course of CDI associated with structural pituitary abnormalities. There may be a single deficit or multiple deficits. Overall, the most common hormone affected tends to be growth hormone (GH) (60%) followed by thyrotropin (TSH), then adrenocorticotropin (ACTH), luteinizing hormone (LH), and follicle-stimulating hormone (FSH). When PST is present, nearly all cases may demonstrate an associated APD at some point during the disease. The number and rate at which APDs develop may also be predictive of underlying malignancy. Most APDs develop within the first 24 months of diagnosis, particularly GH deficiency. However,

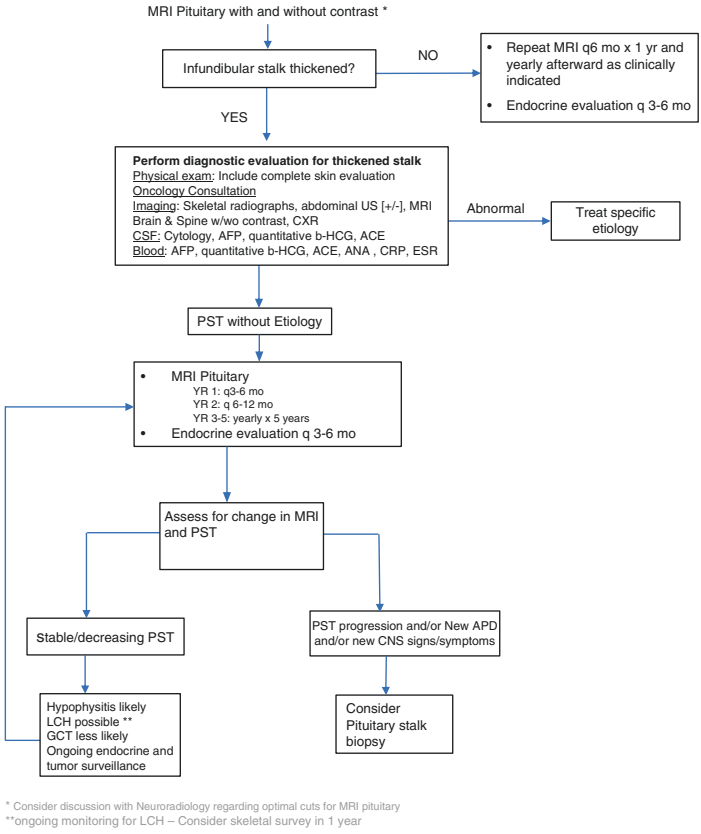

Fig. 4.2 Suggested algorithm for evaluation and follow up of a child with central diabetes insipidus

TSH and ACTH deficiency may develop up to 12 years after initial diagnosis. Therefore, it would be prudent to monitor pituitary function clinically and biochemically every 3–6 months during the initial 2–3 years and annually thereafter [12]. Identification of APDs would warrant appropriate treatment by the endocrinologist. Some authors advise caution when approaching patients with CDI and associated GH deficiency as some evidence has suggested that treatment with GH replacement may cause progression

of the underlying infiltrative disease due to its mitogenic properties [1].

Specific testing to help establish an underlying etiology must be undertaken at the time of CDI diagnosis. This typically involves obtaining cytology and tumor markers, including quantitative beta hCG and AFP, in both serum and cerebrospinal fluid. If these are non-diagnostic initially, the presence of abnormalities on MRI may warrant a biopsy to establish a tissue diagnosis (Fig. 4.2). Negative initial GCT workup in combination with progressive MRI findings may necessitate repeating these assessments at a later point in the patients' clinical course. Another common cause of CDI with imaging abnormalities is LCH which warrants specific testing including anti-nuclear antibodies, C-reactive protein, erythrocyte sedimentation rate (ESR), and serum and CSF angiotensin-converting enzyme (ACE) (See Chap. 14). Extracranial imaging (skeletal radiographs looking for lytic lesions, abdominal ultrasound looking for organomegaly, and chest radiography) and detailed skin examination [7] are also useful in the workup of potential LCH. It is recommended to collaborate with an oncologist (or neuro-oncologist) when the initial findings are suggestive of neoplastic etiology.

Tissue diagnosis remains the gold standard to identify the underlying etiology for CDI with PST. Where abnormalities of the pituitary stalk exist, pituitary stalk biopsy often has the greatest likelihood of establishing the diagnosis. Due to the invasive nature of pituitary stalk biopsies, particularly through craniotomy, previous authors have advocated for a more conservative approach, recommending to biopsy only if there is a large (>7 mm) degree of thickening [2, 6], demonstration of progressive lesion growth [11], or development of new APDs. Significant change on serial MRI may be defined as a change in dimension of 15% [13], 20% [5], or 25% [7]. We advise discussion with neuroradiology on the threshold of change depending on available resolution at your institution. Conversely, some patients with initial PST can show spontaneous regression and even complete resolution. Most authors advise against biopsy should this be the case [2, 11] given the higher likelihood of transient inflammation being the cause. There is limited data on the safety of performing pituitary stalk

biopsy in pediatric patients. A 2020 study with a limited cohort of 9 patients comments on the safety of endoscopic trans-sphenoidal biopsy compared with open craniotomy [14]. They report a diagnostic yield of 77% despite presence of compelling radiographic evidence suggestive of underlying GCT. In the case of LCH the first choice for biopsy may be an extracranial site particularly in cases where systemic symptoms are suggestive of the diagnosis. A retrospective review of 54 patients with CDI found to be due to LCH had diagnosis made on extracranial biopsy in 91% of the patients [15].

One case describes a 9-year-old girl in which after diagnosis of CDI and PST, LCH was highly suspected from history and empiric therapy was started. However, biopsy of the pituitary lesion itself confirmed diagnosis of germinoma [16]. These examples underscore the importance of histologic confirmation of diagnosis prior to initiation of empiric therapy. Despite best practice, the diagnosis of intracranial GCT can be missed in up to 60% of cases as initial biopsies can show inflammatory changes consistent with hypophysitis, which itself may be secondary to GCT. GCT should remain part of the differential despite initial imaging and tumor marker results and is one of the reasons that serial MRIs are indicated in patients with CDI.

Germ cell tumor (GCT) is a significantly concerning etiology associated with CDI and PST, which is why the evaluation of these patients is designed around early identification of this potential diagnosis. The prevalence of GCT in cases of CDI with PST has been reported to range from 15% [2] to 60% [17]. Initial evaluation with tumor markers from serum and CSF are helpful when positive but too insensitive to be able to exclude the diagnosis when negative [11]. Multiple MRI findings are predictive of GCT including bifocal disease involving the pituitary gland and pineal gland [7], decreased size of adenohypophysis, presence of PST >6.5 mm at any point, and progressive increase in PST on serial imaging [2, 10, 18]. Biochemically, there is correlation between the presence of multiple and early presenting APDs and the eventual diagnosis of GCT [2, 19]; however, this association is strongly demonstrated with degree of PST as well [12]. Therefore, the association between germinoma and multiple APDs may be

modified by PST rather than being an independent association. The absence of the above predictive factors does not rule out germinoma and it should always be considered in the differential, particularly if there is a lack of response to initial therapy [19].

Langerhans cell histiocytosis (LCH) is a common cause of CDI with prevalence reported from 7% [20] to 19% [2] and CDI, usually with PST, is often the first presentation of the disease [7]. Diagnosis of LCH is challenging both because of similarity in presentation with GCT and due to its prolonged and unpredictable course. Initial imaging findings can include PST (70%) which may be moderate or large and can increase or decrease in size on follow up [6, 7]. The presence of symmetry and unifocality on MRI are more suggestive of the LCH diagnosis [7] but in many cases the diagnosis relies on identification of extracranial manifestations such as bone, skin, or lung lesions which are present at CDI diagnosis in 18% of patients and may present in another 51% within 1 year follow up [15]. APDs are uncommon on initial presentation and less likely to develop early; however, extended follow up shows a higher likelihood (~80%) of patients with LCH having at least one APD develop within 8 years compared with "idiopathic" CDI cases [11, 20]. LCH must be kept in the differential long-term as the diagnosis may only be apparent 8 or more years after CDI diagnosis.

Not all cases of CDI with PST have an independent disease process. These cases are considered to be "idiopathic". Previously the prevalence of "idiopathic" CDI was reported as 30–50% [11] but this has recently been challenged as an underlying diagnosis is more commonly found, particularly in those patients with abnormal imaging, and so the prevalence of idiopathic cases in recent series is lowered to 12% [8]. Nevertheless, cases of idiopathic CDI with PST do occur, though generally the degree of PST is small or moderate and tends to remain stable (30%) or regress (30–50%) in most individuals [2, 11]. Due to this response, pituitary biopsy is usually not indicated and the diagnosis of presumed transient lymphocytic inflammation is extrapolated from adult studies [6]. Along with PST, these patients may also demonstrate decreased anterior pituitary size along with a single APD (usually GH) [12]. Development of multiple APDs is less common. Some

patients may have the finding of specific antibodies directed against vasopressin cells [21]. In adult series, other factors that may suggest idiopathic inflammation are personal or family history of autoimmune conditions and female sex. However, the same risk factors have not been seen in pediatric patients with lymphocytic neurohypophysitis [5].

Management

Most patients with CDI and associated PST continue to require long-term ADH replacement therapy regardless of underlying diagnosis or resolution of imaging findings. Those who are found to have GCT, LCH, or other infiltrative processes should be managed in cooperation with an oncologist to determine additional disease treatments and surveillance. As mentioned above, a significant proportion of patients with CDI and PST will develop an additional APD on follow up that may warrant replacement therapy. The consideration of treatment of isolated GH deficiency remains controversial due to the theoretical risk of promoting CNS lymphoma in the long term.

Clinical Pearls and Pitfalls

- Diabetes insipidus diagnosed in infancy or childhood can be due to infectious, neoplastic, traumatic, or genetic processes that disrupt the hypothalamus or pituitary stalk.
- Recognizing and understanding the underlying cause of the patient's presentation is critical to treating the patient effectively.
- A histopathological diagnosis may pose a challenge, given lack of data on safety of pituitary stalk biopsy in pediatric population.
- Germ cell tumors and LCH should remain on the differential and warrant surveillance regardless of initial findings.

Outcome

A definitive underlying diagnosis for why this patient had CDI with a high degree of PST has not been established. With recent development of a scaly skin rash, it was recommended that the family have a dermatology consultation for a skin biopsy, to evaluate for LCH. Based on the biopsy report, the skin lesions were diagnosed as verruca vulgaris (common warts).

With disappearance of pituitary stalk thickening, a histopathologic diagnosis via pituitary stalk biopsy could not be achieved. She was initiated on treatment with oral desmopressin for management of CDI. Her other pituitary hormones are being serially monitored and have thus far remained normal. Follow-up MRI scans at 1 year and 28 months after initial presentation have not demonstrated recurrence of PST, although the pituitary bright spot remains absent. Given that PST has completely resolved without recurrence on subsequent MRIs, and surrounding structures are normal, we will repeat MRI in 1 year, sooner if clinically indicated (development of new APDs, new central nervous system signs or symptoms).

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