The Diagnosis of Children with Central Diabetes Insipidus

Stefano Ghirardello¹, Maria-Luisa Garré², Andrea Rossi³ and Mohamad Maghnie⁴

¹Institute of Pediatrics and Neonatology, Fondazione IRCCS “Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena”, University of Milan, Italy and Departments of ²Neuro-Oncology/Hematology Oncology, ³Neuroradiology and ⁴Pediatrics, IRCCS G. Gaslini, University of Genova, Genova, Italy

ABSTRACT

Central diabetes insipidus is the end result of a number of different diseases that affect the hypothalamic-neurohypophysial system. In many patients, especially children and young adults, it is caused by the destruction or degeneration of neurons that originate in the supraoptic and paraventricular nuclei of the hypothalamus. The known causes of these lesions include germinoma or craniopharyngioma; Langerhans cell histiocytosis; local inflammatory, autoimmune or vascular diseases; trauma resulting from surgery or an accident; sarcoidosis; metastases; and midline cerebral and cranial malformations. In rare cases, genetic defects in AVP synthesis that are inherited as autosomal dominant, autosomal recessive or X-linked recessive traits are the underlying cause. Accurate diagnostic differentiation is essential for both safe and effective disease management. Proper etiological diagnosis can be achieved via a series of steps that start with clinical observations and then progress, as needed, to more sophisticated methods. Indeed, magnetic resonance imaging (MRI) represents the examination method of choice for evaluating hypothalamic-pituitary-related endocrine diseases due to its ability to provide strongly-contrasted high-resolution multiplanar and spatial images. Specifically, MRI allows a detailed and precise anatomical study of the pituitary gland by differentiating between the anterior and posterior pituitary lobes. MRI identification of pituitary hyperintensity in the posterior part of the sella, now considered to be a clear marker of neurohypophysial functional integrity, together with careful analysis of pituitary stalk shape and size, have provided the most striking recent findings contributing to the diagnosis and understanding of some forms of 'idiopathic' central diabetes insipidus.

KEY WORDS

central diabetes insipidus, germinoma, vasopressin, MRI, posterior pituitary, anterior pituitary, AVP-II gene, Wolfram syndrome, Langerhans cell histiocytosis

INTRODUCTION

Central diabetes insipidus (CDI) is a heterogeneous condition characterized by the excretion of abnormally large volumes of dilute urine due to a deficiency of arginine vasopressin peptide (AVP). In many patients, especially children and young adults, it is caused by the destruction or degeneration of neurons that originate in the supraoptic and paraventricular nuclei of the hypothalamus. The known causes of these lesions include germinoma or craniopharyngioma; 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, genetic defects in AVP synthesis that are inherited as autosomal dominant, autosomal recessive or X-linked recessive traits are the underlying cause. Although 20-50% of cases are considered idiopathic, the identification of an autoimmune phenomenon involving vasopressin-secreting cells and recent advances in imaging techniques have shed new light on pathophysio-
logical aspects of CDI, making the idiopathic form a very uncommon condition (Table 1).

Genetic diagnosis can identify inherited causes for clinical cases of CDI precisely. Based on current knowledge of protein structure and intracellular processing, the identification of many mutations of the AVP-NPII and Wolframin (WFS1) genes has improved our understanding of the molecular basis of CDI.

GENETIC FORMS OF CENTRAL DIABETES INSIPIDUS

Autosomal dominant form

The AVP-NPII gene is located on chromosome 20p13 and contains three exons; the AVP-NPII gene product is synthesized as a precursor polypeptide, pre-prohormone, which includes the AVP peptide, its carrier protein neurophysin-II (NPII), and the copeptide, a glycopeptide of unknown function. The precursor is cotranslationally targeted to the endoplasmic reticulum (ER), where the signal is cleaved off; subsequently, vasopressin and neurophysin II associate to form the tetramer, and the proprecursor is packaged into neurosecretory granules and transported to the posterior pituitary (PP). To date, more than 50 different mutations resulting in a defective pre-hormone and a deficiency of vasopressin have been identified in familial neurohypophyseal DI; all except a few show an autosomal dominant pattern of inheritance.

Autopsy studies of patients with a familial form of DI show a selective loss of magnocellular neurons in the paraventricular nuclei associated with moderate gliosis and relative preservation of small neurosecretory cells, suggesting that the disorder is due to degeneration of these hypothalamic neurons.

<p>| TABLE 1 |</p>
<table>
<thead>
<tr>
<th>Etiologies of central diabetes insipidus</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Familial</strong></td>
</tr>
<tr>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>Autosomal recessive</td>
</tr>
<tr>
<td>X-linked</td>
</tr>
<tr>
<td>DIDMOAD syndrome (Wolfram syndrome)</td>
</tr>
<tr>
<td>Unknown genes (?)</td>
</tr>
<tr>
<td><strong>Acquired</strong></td>
</tr>
<tr>
<td>Idiopathic</td>
</tr>
<tr>
<td>Intracranial tumors-germinoma, craniopharyngioma, glioma, metastases, leukemia/lymphoma</td>
</tr>
<tr>
<td>Traumatic</td>
</tr>
<tr>
<td>Langerhans cell histiocytosis</td>
</tr>
<tr>
<td>Infecions</td>
</tr>
<tr>
<td>Familial</td>
</tr>
<tr>
<td>Autoimmune</td>
</tr>
<tr>
<td>Sarcoidosis, others</td>
</tr>
<tr>
<td>Hypoxic-ischemic</td>
</tr>
<tr>
<td><strong>Cerebral malformations</strong></td>
</tr>
<tr>
<td>Midline defects (septo-optic dysplasia, holoprosencephaly)</td>
</tr>
</tbody>
</table>

JOURNAL OF PEDIATRIC ENDOCRINOLOGY & METABOLISM
Autosomal recessive form

One unique homozygous missense mutation in the region encoding the AVP domain shows an autosomal recessive pattern of inheritance\textsuperscript{16}. The recessive mutation does not seem to affect intracellular trafficking, but rather the final processing of the prohormone into neurophysin II and AVP hormone\textsuperscript{27}. Despite some clinical similarities with the autosomal dominant form, the symptoms appear to be secondary to the reduced biological activity of the mutant vasopressin peptide\textsuperscript{16}. 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.

Unknown gene(s)

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 showing an autosomal dominant inheritance pattern of overt CDI\textsuperscript{24}.

Linkage analysis indicated that the corresponding gene(s) responsible for the autosomal dominant CDI in this family was 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.

Pathogenesis

The autosomal dominant mutations identified to date can be expected to dictate the production of an abnormal precursor that fails to fold, self-associate or traffic properly in the ER. This failure can be attributed to one or both of two general mechanisms: mutations that interfere with the binding of the AVP and NPII moieties, and mutations that alter the flexibility, rigidity or disulfide bridging of the folded pro-hormone\textsuperscript{27}.

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 understood. The study of the trafficking and processing of the mutant vasopressin pro-hormone \textit{in vitro} has demonstrated that the mutation abolishes ER exit and processing of the vasopressin pro-hormone, resulting in aberrant endoplasmic morphology and possible cell dysfunction and death\textsuperscript{20}. The presence of cytosolic autophagy suggests non-apoptotic cell death\textsuperscript{27},\textsuperscript{29,30}, however, programmed cell death cannot be excluded\textsuperscript{31}.

Mutations involving the signal peptide decrease its ability to initiate proper processing of the pre-pro-AVP-NPII\textsuperscript{15,32}; mutant precursors also impair intracellular trafficking of the WT precursor by forming heterodimers, thus reducing the bio-availability of active AVP by means of a 'non toxic mechanism', i.e. a dominant negative effect\textsuperscript{29,33}.

Recently, the demonstration of two pathways of degradation (via the ER lumen and directly from the cytosol), involving both the WT and the mutant pro-hormone, 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\textsuperscript{23,34}.

Clinical features

Clinical disease onset typically ranges from the first to the sixth year of age\textsuperscript{20}, but various cases with early or delayed onset have also been reported\textsuperscript{20,24,32}. Usually symptoms worsen with age in patients with 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\textsuperscript{20,35,36}.

The wide variability in the age of onset and the severity of the AVP deficiency among patients with the same mutation may be attributed to individual differences among such patients, such as 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, variations in secretory reserve capacity or the development of the gland itself\textsuperscript{32}. Further studies on the contribution of any of the mechanisms involved in cell dysfunction and/or impaired AVP secretion, together with magnetic resonance imaging (MRI) follow-up, would
help to better understand the disease. The majority of the mutations currently described affect the NPII moiety; only a few mutations have been identified within the signal peptide sequence. No substantial temporal relationship between the type of mutation, the time of disease onset and the degree of severity was found among patients affected by the same missense mutation.\[20\]

Magnetic resonance imaging

The spectrum of MRI findings in patients affected by familial CDI appears to be heterogeneous. The most common feature observed is the presence of the posterior pituitary hyperintense signal (PPHS) in young patients and its progressive disappearance with time or in adulthood.\[20\] Accumulated mutant vasopressin and neurophysin II complexes might explain the persistence of posterior pituitary hyperintensity imaged by MRI in patients with autosomal dominant CDI, as opposed to that observed in patients with an idiopathic form despite the absence of circulating AVP; this phenomenon was first reported by our group.\[4\] Subsequent serological and molecular studies have attempted to explain the pathophysiology of the disease.

Some variation in the posterior pituitary (PP) feature at MRI has been reported, even among affected members of the same family.\[5\] Other studies have described the presence of PPHS in adult patients with early and severe onset of symptoms.\[20,35\] The lack of PPHS in two out of three patients affected by the autosomal recessive form underlines our imperfect knowledge of the phenomenon.

WOLFRAM SYNDROME

Wolfram syndrome (WS) (OMIM 222300), first described by Wolfram and Wagener in 1938, is a rare, autosomal recessive disorder. It is known by the acronym DIDMOAD (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness); an estimated prevalence of 1:770,000 live births and a carrier frequency of 1:354 have been reported.\[39\] The disease phenotype is caused by mutations in WFS1, a nuclear gene mapped to chromosome 4p16.1 that encodes the 100 kDa protein wolframin.\[30,41\] Since he discovery of the WFS1 gene, several mutations have been identified in patients with WS, most likely resulting in a loss of wolframin function.\[42,43\] Moreover, heterozygous missense mutations in WFS1 have been reported to be involved in autosomal dominant low frequency sensorineural hearing impairment.\[44\]

The function of wolframin is unknown but biochemical studies suggest that it is an endoglycosidase membrane glycoprotein, predominantly localized in the ER.\[45,46\] Indeed, wolframin appears to be involved in membrane trafficking, protein processing, regulation of Ca\(^{2+}\) homeostasis and \(\beta\)-cell proliferation.\[46\] Interestingly, abnormal processing of vasopressin precursor in the supraoptic and paraventricular nuclei has been reported in WS, as well as in the autosomal dominant form of CDI\[42\]; WFS1 likely functions to maintain certain populations of neuronal and endocrine cells.\[46\] A recent study provides evidence that WFS1 mutations lead to loss of normal function by rapid degradation and cellular depletion of wolframin. Autopsy studies and MRI findings suggest that the decrease in AVP secretion might be due to a secondary progressive AVP-neuron cell depletion, and that WFS1 mutation(s) might be involved in the pathogenesis of isolated forms of idiopathic CDI.

Clinical features of Wolfram syndrome

Diabetes mellitus has been reported to be the usual first symptom to present at a median age of 6 years, followed by onset of optic atrophy at a median age of 11 years.\[39\] The phenotype-genotype correlations in a series of nine families with WS show an average age at onset of diabetes mellitus of 8.4 years, in agreement with other studies.\[51-55\] The development of polyuria and/or enuresis can indicate diabetes insipidus; the time of onset varies considerably, and DI does not generally appear until the second or third decade.\[26,39,54,56\] CDI may initially be partial. The frequency of CDI varies between reports, ranging from 48% to 78%.\[55,57,58\] A wide spectrum of abnormalities affects the endocrine glands and the central nervous system (CNS), including anosmia, ataxia, seizures, nystagmus, gaze palsies, dysarthria, dysphagia, psychiatric abnormalities, cognitive deficits, hypoxia or areflexia and neurogenic bladder, central sleep apnea, neurogenic upper airway collapse, myoclonus, Parinaud's
syndrome, hypothyroidism, hypogonadism and adrenocorticotropic deficiency\textsuperscript{39,51}. Treatment with desmopressin (DDAVP) can be very successful\textsuperscript{56}.

**Magnetic resonance imaging in Wolfram syndrome**

MRI findings include atrophy of the cerebellum, brainstem, and cerebral hemispheres, with a dilated ventricular system, prominent cortical sulci and abnormal signal\textsuperscript{39,59,60}. Specific abnormalities, such as atrophy of the optic pathways, thinning of the hypothalamus and infundibulum, and absence of posterior pituitary hyperintensity are also described\textsuperscript{39,58-60}. There is a direct correlation between the frequency and severity of neurological manifestations, MRI abnormalities, and patient age\textsuperscript{45}.

**ACQUIRED FORMS OF CENTRAL DIABETES INSIPIDUS**

**Idiopathic CDI**

In recent years, various studies have suggested that autoimmune phenomena could be involved in the pathophysiology of idiopathic CDI\textsuperscript{1,61-64}. The assessment of vasopressin-cell autoantibodies (AVPc-Ab’s) in patients affected by autoimmune polyendocrinopathies and CDI, together with standard and dynamic MRI techniques which allow a better definition of morphology and vascularization of the hypothalamic-pituitary region, have improved our knowledge of the underlying processes that affect the neurohypophyseal system of patients with ‘idiopathic’ CDI.

The most common MRI findings in idiopathic CDI include lack of PPHS in the great majority of patients at presentation; when present, the signal disappears on a regular basis at follow-up (Figs. 1, 2). Pituitary stalk (PS) size at presentation is variable and can change over time (Figs. 1, 2). In two large pediatric series of patients with idiopathic CDI, pituitary stalk thickening (PST) was found in approximately 50-60% of the children\textsuperscript{1}. Spontaneous evolution of thick PS was similar in both reports from unchanged (30%), to a regression or reduction (30-50%) or further enlargement (10-20%) of stalk size. Among patients with idiopathic CDI and PST, 90-94% developed anterior pituitary (AP) hormone deficits, with isolated growth hormone deficiency (GHD) accounting for 60% of cases. Multiple pituitary hormone deficits were present in 30-50% of patients with PST, while only 10% of the 19 patients with normal pituitary stalk had an additional hormonal deficit\textsuperscript{1}.

The underlying process of pituitary stalk thickening in ‘idiopathic’ CDI is not completely understood. Recent reports of a thickened pituitary

![Fig. 1: Sagittal T1-weighted MRI in normal subjects showing posterior pituitary hyperintensity (arrowhead), normal anterior pituitary size (double arrows) and normal pituitary stalk (arrow). The shape of the anterior pituitary gland in a is different from that in b.](image-url)
Fig. 2: Sagittal (a-c) and coronal (d-f) T1-weighted MRI before (a, c, d, f) and after (b, e) gadolinium injection in a patient with central diabetes insipidus. Posterior pituitary hyperintensity is absent (a, c; arrowhead); anterior pituitary gland size is normal (double arrows); and pituitary stalk is thick (a, b, d, e; arrow). Spontaneous normalization of pituitary stalk size is evident in c and f.
stalk in association with autoimmune or inflammatory disease, termed ‘lymphocytic hypophysitis’ \(^{65,66}\), ‘necrotizing infundibulo-hypophysitis’ \(^{67}\), or ‘lymphocytic infundibulo-neurohypophysitis’ \(^{68}\), focus on adults with histological features of lymphocyte and plasma cell infiltration, fibrosis and necrosis (Table 2). Hence, lymphocytic hypophysitis is a rare chronic inflammatory process that affects the pituitary gland variably. It is worthwhile pointing out that clear-cut criteria for diagnosis of lymphocytic hypophysitis in children and adolescents are still lacking and that CDI is manifest in only about 20-25% of cases. An autoimmune pathogenesis is strongly supported by diverse clinical, histopathological and laboratory findings \(^{66}\) (Table 2).

The term ‘lymphocytic infundibulo-hypophysitis’ has been coined \(^{1}\) to distinguish children and adolescents with CDI, anterior pituitary hormone deficiency, reduction of AP size and transient or persistent PS thickening from adult patients with similar PP and PS findings at MRI, but normal AP size and function; according to recent diagnostic criteria, GHD was defined in adult patients as GH response after pharmacological stimulation tests lower than 10 rather than 3 μg/l \(^{1,6,20}\). In adult patients such as those described, the term ‘lymphocytic infundibulo-neurohypophysitis’ is more appropriate \(^{5}\).

Various clinical observations suggest an important role for autoimmunity in the pathogenesis of CDI. Indeed, autoimmune polyendocrinopath and CDI associated with an MRI picture of thickened pituitary stalk suggests that patients with CDI and thickened pituitary stalk may share a common etiology \(^{1,63}\). Circulating AVPc-Abs have been reported in a large series of adult patients with CDI and autoimmune diseases and similar neuroradiological findings \(^{64}\). In a recent study, AVPc-Abs were found in 75% of children and young adults with idiopathic CDI, suggesting that hypothalamic-neurohypophyseal autoimmune involvement is more common in children and young adults with idiopathic CDI than has generally been thought \(^{62}\); the higher frequency of AVPc-Abs in pediatric patients, compared to the one-third found in adult patients with identical disease duration \(^{61,63}\), underlines the fact that an autoimmune cause in idiopathic CDI is quite frequent. In addition, AVPc-Abs were found in approximately 77% of patients with combined posterior and anterior pituitary dysfunction, a finding that goes well beyond the reported association of anterior pituitary hormone defects in as many as 23% of patients with isolated vasopressin deficiency \(^{68,69}\). This indicates that AP involvement in the course of idiopathic CDI is highly suggestive of an autoimmune neurohypophyseal basis and fits well with biopptic demonstration of lymphocytic infiltration of the PS in a patient with evolving pituitary stalk lesion and pituitary hormone deficiencies \(^{70}\). The total absence of AVPc-Abs in healthy children compared to patients with CDI underlines the specificity of these autoantibodies. The role of viral infections in the etiology of CDI is rather intriguing \(^{1}\). In about one-fourth of patients with idiopathic CDI, there is a temporal relationship between a viral infection (trigger) and the onset of CDI \(^{7}\). 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 \(^{71}\).

The identification of AVPc-Abs in patients who could have either idiopathic CDI or LCH or germinoma, however, indicates that this finding cannot be considered a completely reliable marker of autoimmune CDI. Thus, to ensure a definitive etiological diagnosis, close clinical and MRI follow-up are needed because AVPc-Abs may mask germinoma or LCH.

**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 normal PS and AP gland size \(^{8}\). Indeed, dynamic MRI studies after contrast medium injection demonstrated the absence of posterior pituitary lobe enhancement 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 posterior pituitary blood supply remains largely undefined, but the possibility that a congenital lack/poor development of the posterior pituitary...
<table>
<thead>
<tr>
<th>Disease</th>
<th>F/M</th>
<th>Age at presentation</th>
<th>CDI %</th>
<th>AP deficiency</th>
<th>Signs/symptoms other than polyuria</th>
<th>MRI</th>
<th>Autoimmunity</th>
<th>Histology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphocytic hypophysitis&lt;sup&gt;66&lt;/sup&gt;</td>
<td>F &gt; M</td>
<td>&gt;28 yr</td>
<td>100%</td>
<td>High PRL</td>
<td>Papilledema (1 case)</td>
<td></td>
<td></td>
<td>DM, Graves' disease; antinuclear</td>
</tr>
<tr>
<td>Lymphocytic infundibulo-neurohypophysitis&lt;sup&gt;6&lt;/sup&gt;</td>
<td>F = M</td>
<td>0.1-16 yr</td>
<td>100%</td>
<td>GHD 80%</td>
<td>Growth retardation, headache, fatigue</td>
<td></td>
<td></td>
<td>Organ-specific Abs 80% (including AVPc-Abs (75%))</td>
</tr>
<tr>
<td>Autoimmune CDI&lt;sup&gt;21&lt;/sup&gt;</td>
<td>F &gt; M</td>
<td>Adulthood</td>
<td>100%</td>
<td>Absent</td>
<td>Signs/symptoms related to eventual autoimmune diseases</td>
<td></td>
<td></td>
<td>Autoimmune diseases*; organ-specific Abs; AVPc-Abs (50-80%)</td>
</tr>
<tr>
<td>Idiopathic CDI&lt;sup&gt;21&lt;/sup&gt;</td>
<td>F &gt; M</td>
<td>1.8-13.1</td>
<td>100%</td>
<td>GHD (75%)</td>
<td>Transient or persistent thick PS (75%); absent PPHS (100%)</td>
<td></td>
<td>AVPc-Abs (75%) other auto-Ab (83%)</td>
<td></td>
</tr>
</tbody>
</table>

AP = anterior pituitary; PPHS = posterior pituitary hyperintense signal; PS = pituitary stalk; DM = diabetes mellitus; AVPc-Abs = vasopressin cell autoantibodies; GHD = growth hormone deficiency; MPHD = multiple pituitary hormone deficiencies; PRL = prolactin.

* Hashimoto’s/Graves’ disease, diabetes mellitus, vitiligo, atrophic gastritis, Addison’s disease, celiac disease, premature ovarian failure, autoimmune polyendocrinopathies.
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 [vasculitis?]) cannot be ruled out.

**Langerhans cell histiocytosis**

CDI is the most frequent CNS manifestation of LCH, occurring in 10–50% of all patients\(^2\). A retrospective multicenter analysis of patients with LCH\(^3\) showed that the risk of developing CDI, after diagnosis and specific therapy, was 16% at 5 years and 20% at 15 years, respectively, and strongly correlates with the presence of a multisystem disease followed by lesions in the craniofacial area\(^2\). Some patients with CDI and endocrinopathies seem to be at risk for neurodegenerative CNS disease\(^3\). GHD is the most frequent additional deficit, accounting for 42% of cases with CDI and LCH\(^3\). The 10-year cumulative incidence of GHD in the French nationwide LCH survey was approximately 54% among patients with CDI\(^1\). The identification of circulating AVPc-Abs in patients with LCH and their tendency toward spontaneous clearance\(^4\) suggest that these autoantibodies might be an LCH-related immune epiphenomenon.

Pituitary stalk thickening can be found in approximately 50–70% of patients with LCH at presentation or at follow-up\(^1,4,74\) and may even be present before CDI onset. Anterior pituitary size has been found to be normal, reduced or, rarely, enlarged\(^1,7,75\). The search for extracranial lesions (dermatological and bone survey, chest X-ray, ear, nose and throat examination) suggestive of LCH in patients with PST is recommended and could reduce the need for intracranial biopsies\(^74\).

**Tumors**

**Germinomas**

Intracranial germ cell tumors comprise 7.8% of primary pediatric brain tumors\(^20\). MRI findings suggest that suprasellar and neurohypophyseal germinomas primarily arise from the posterior pituitary to the infundibulum\(^2,76\). Partial or complete pituitary stalk thickening is detectable in 78–100% of cases at presentation and may be the only finding at presentation in small germinomas\(^2,77\); its presence increases the risk of malignancy to about 15–17%, while the risk decreases to 3% in patients with a normally sized pituitary stalk\(^77\).

Serial contrast-enhanced brain MRI in patients affected by CDI with PST (every 3–6 months for the first 2 years) may reduce by 1 year the amount of time for diagnosis of germinoma\(^1\). However, a thickened pituitary stalk has been reported up to 5 years after the onset of CDI and preceded by lymphocytic tissue infiltration as a host reaction to the presence of a germinoma that could mask diagnosis\(^78\). Exceptionally, a germinoma can mimic multisystemic LCH, with vertebral compression, recurrent ear infections, thickened PS, enlarged pineal gland, negative serum and cerebrospinal fluid for germ cell tumor markers, as demonstrated in a 9-year-old female\(^79\).

The role of 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\(^21\) could also mask the diagnosis of germinoma and needs further confirmation. Pituitary stalk 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 early findings in pituitary germinomas (almost 100% of cases at follow-up), but hormone deficiency is not predictive of the presence of a germinoma.

**Cranioopharyngioma and post-surgical CDI**

Cranioopharyngioma 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, 54% of cases\(^20\). Classical 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\(^20\). CDI and multiple pituitary hormone
deficiencies are common complications of childhood craniopharyngioma. The frequency of presurgery CDI varies from 16-55%, while postsurgical and permanent CDI accounts for up to 80% of cases; transient CDI is reported in 13% of affected patients.

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 degeneration and death of neurosecretory neurons, with 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 intra-operative period. The transsphenoidal approach is now widely used for both intrapituitary and some suprasellar tumors, and is associated with a lower incidence of postoperative CDI. CDI after a transfrontal approach has been reported in association with high plasma AVP immunoreactivity, but the plasma showed no antidiuretic bioactivity; moreover, antidiuretic response to standard AVP was greatly attenuated, suggesting the presence of a circulating vasopressin antagonist affecting the renal action of endogenous and exogenous AVP. This finding has never been confirmed by other studies.

**Metastasis**

Metastasis to the posterior pituitary is a well-known event in systemic cancer due to the direct arterial vascularization of the posterior pituitary lobe. The incidence of pituitary metastases varies from 0.14-28.1% of all brain metastases and is higher in adult autopsy series. They most frequently originate from lung carcinoma, breast cancer, gastrointestinal carcinomas and leukemia/lymphoma, with symptoms seen particularly in terminal stages. About 20% of these metastases to the pituitary-hypothalamic axis are diagnosed clinically, and CDI is the main presenting symptom. A review of the literature showed that CDI has been reported in association with leukemia in 39 of 5,778 children (0.6%), four of whom were under 10 years of age.

At MRI, a destructive and inhomogeneously enhancing intrasellar and suprasellar lesion and involvement of adjacent structures can be observed in cases of metastasis; the pituitary stalk can be involved and appears entirely or partially thickened. Progressive thickening of the PS has been the presenting symptom in various pediatric cases of primary lymphoma of the CNS or of myelogenous leukemia. CDI and multiple AP hormone deficiencies can precede the diagnosis of malignancy by one or more years.

**Sarcoidosis**

Sarcoidosis is a multisystemic disease of unknown etiology; the involvement of the CNS occurs in approximately 5-15% of patients and precedes additional symptoms in 25-30% of cases. Autopsy studies have demonstrated that sarcoid granulomas have a predilection for the hypothalamus and less commonly involve the PS or the pituitary gland. Thus, patients with neuroendocrine sarcoidosis commonly have hypothalamic dysfunction and often exhibit hypothalamic disturbances and AP hormone deficiencies. Endocrinopathy is relatively rare, polyuria-polydipsia being the most common symptom, reported in 25-33% of adult patients affected by neurosarcoidosis. In pediatric patients, hypophysial dysfunction was present in 21% of patients, 66% of whom were affected by CDI. Children with neurosarcoid present differently from adults and are more likely to have seizures and less likely to have cranial nerve palsies; eye diseases, such as uveitis, may occur in younger children.

Brain MRI studies showed heterogeneous features, including periventricular white matter foci, leptomeningeal enhancement, hydrocephalus and enlargement of the PS, the latter entity was described in four of the five patients reported by Bullmann et al. To our knowledge, only a few pediatric cases of CDI secondary to neurosarcoidosis have been described.
DIAGNOSIS OF CENTRAL DIABETES INSIPIDUS

Other entities

CDI has been reported in Wegener granulomatosis, a disease characterized by necrotizing vasculitis and granulomatous inflammation of the upper and lower respiratory tract, together with glomerulonephritis; MRI showed an isointense suprasellar mass and enlargement of the infundibulum. Two months after corticosteroid treatment, MRI showed nearly complete resolution of pituitary lesions and dramatic clinical improvement.

Transient CDI associated with CNS tuberculosis is a well-known entity. Tuberculosis of the CNS is the most serious complication in children, accounting for about 3-4% of untreated tuberculosis infections in developed countries. It usually arises from a 'metastatic' caseous lesion in the cerebral cortex or meninges that develops during the lymphohematogenous dissemination of the primary infection. A few pediatric reports refer to tuberculous meningitis followed by acute onset of CDI, variably associated with seizures and/or communicating hydrocephalus; in these cases, MRI showed pituitary stalk thickening.

Acute post-traumatic CDI was reported in 22 of 85 patients who suffered a moderate to severe traumatic brain injury (TBI); five of these patients had persistent abnormal water deprivation test at a median time of 17 months from TBI and expression of permanent partial CDI; the remaining patients showed complete recovery of PP function. In this study, permanent CDI correlated with lower Glasgow coma scale but not with age, gender, basal skull fracture or operative mass evacuation.

Post-traumatic DI may result from inflammatory edema around the hypothalamic or posterior pituitary, with resolution as the swelling resolves. It can also result from direct damage to the paraventricular and supraoptic hypothalamic neurons, the pituitary stalk, or axon terminals in the posterior pituitary.

CENTRAL DIABETES INSIPIDUS AND THIRST ABNORMALITIES

Adipsic disorders are characterized by inappropriate lack of thirst, with consequent failure to drink to correct hyperosmolality. The incidence of postoperative CDI and thirst abnormalities has recently been reported as about one-third of patients with craniopharyngiomas. Adipsic CDI is characterized by abnormally low thirst scores and no thirst response to marked plasma hypertonicity during hypertonic saline infusion.

Patients with craniopharyngioma developing an adipsic syndrome and post-operative 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 non-osmotic pathways are involved. Failure to secrete AVP in response to hypotension or hypovolemia may increase the risk of dehydration and life-threatening hypermotremia. In adipsic patients, a fixed daily fluid intake appropriate for a weight at which the patient is known to be euhydrated and euvoletic should be established. Desmopressin is then administered at a dose and frequency capable of establishing an appropriate urine output and neutral fluid balance, allowing for sensible losses; regular weighing and checking of serum sodium levels are mandatory.

DIAGNOSIS OF CENTRAL DIABETES INSIPIDUS

The age at which CDI symptoms develop, together with the patient's pattern of fluid intake, may influence subsequent investigation. Young children may have severe dehydration, vomiting, constipation, fever, irritability, failure to thrive and growth retardation. Clinical examination may provide important clues to possible underlying diagnoses. It is essential, when possible, that 24 h urine volume be documented and polyuria confirmed. A range of baseline investigations, including plasma electrolytes, morning plasma osmolality and urine osmolality, as well as kidney function at the time of first assessment, may assist in the correct diagnosis. In the absence of an immediate diagnosis, the child's fluid intake and output should be studied in greater detail.

Diagnosis of CDI is based on the demonstration of plasma hyperosmolality (>300 mOsm/l) associated with urine hypo-osmolality (<300 mOsm/l or urine/plasma osmolality ratio <1) and polyuria (urinary volume >4-5 ml/kg/h for two consecutive
Fig. 3: Diagnostic flowchart for central diabetes insipidus.

JOURNAL OF PEDIATRIC ENDOCRINOLOGY & METABOLISM
TABLE 3
Biopsy criteria of thick pituitary stalk

<table>
<thead>
<tr>
<th>Reference</th>
<th>PST + CSF-hCG</th>
<th>PST</th>
<th>PST</th>
<th>Additional findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mootha et al.²</td>
<td>+</td>
<td></td>
<td></td>
<td>Increase</td>
</tr>
<tr>
<td>Leger et al.²</td>
<td>+</td>
<td></td>
<td></td>
<td>Increase 7 mm</td>
</tr>
<tr>
<td>Maghnie⁶⁶</td>
<td>+/-</td>
<td></td>
<td></td>
<td>&gt; 6.5 mm Increased AP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pineal calcifications</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Third ventricle involvement</td>
</tr>
<tr>
<td>Al-Agha et al.⁹⁷</td>
<td>+</td>
<td></td>
<td></td>
<td>Increase</td>
</tr>
<tr>
<td>Alter &amp; Bilaniuk⁷⁷</td>
<td>+</td>
<td></td>
<td></td>
<td>Increase</td>
</tr>
</tbody>
</table>

PST = pituitary stalk thickening; AP = anterior pituitary.

hours). Adrenocorticotropic deficiency may mask signs of partial CDI, and polyuria may become manifest after corticosteroid replacement therapy.⁸⁰

The ability of the CNS to produce and of the kidney to respond to vasopressin should be established by means of a formal water deprivation test. A 7-hour (or less) deprivation test is usually sufficient for making a diagnosis, except in cases of primary polydipsia when a longer dehydration period is sometimes required. The test must be discontinued if weight loss exceeds 5% of starting weight or if thirst becomes intolerable. The administration of DDAVP will help to make a differential diagnosis between central and nephrogenic DI.

Aquaporin-2 has recently been used in the differential diagnosis of central versus nephrogenic DI. Aquaporin is both synthesized in the kidney and excreted in urine in response to vasopressin. Patients with CDI show no increase in aquaporin-2 with dehydration, but their excretion increases in response to desmopressin, suggesting that aquaporin-2 expression persists in patients with CDI. Thus, the main value of aquaporin-2 in the differential diagnosis of DI would be to specify the diagnosis of nephrogenic DI when there is no increase in aquaporin excretion following desmopressin administration.²⁰

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 patients) and especially brain MRI (Fig. 3).

A lack of PPHS is a hallmark of hypothalamic-posterior pituitary disorders, and may represent the early stage of occult local tumors, although evidence of PP hyperintensity does not necessarily indicate that the functional integrity of the hypothalamic-neurohypophyseal axis is preserved.¹²⁶

Clinical, radiological and endocrine studies are needed during follow-up. In particular, MRI follow-up is recommended for all patients with PST (every 3-6 months); enlargement of the pituitary stalk lesion (>6.5 mm) or of the AP gland (AP size is age-dependent) or third ventricle involvement are all indications for PS biopsy (Fig. 3, Table 3). Dynamic MRI, in particular, could help to identify cases of CDI and normal PS size associated with abnormal blood supply to the posterior pituitary (Fig. 3).

REFERENCES


JOURNAL OF PEDIATRIC ENDOCRINOLOGY & METABOLISM


