Case Report

Infundibuloneurohypophysitis in Children
A Report of 2 Cases

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Key Words
Diabetes insipidus · Infundibuloneurohypophysitis · Chronic inflammatory infiltrate · Infundibulum · Histiocytosis · Germinoma

Abstract
Two children with diabetes insipidus secondary to a chronic inflammatory infiltrate of the infundibulum – infundibuloneurohypophysitis – are presented. Features unique to these cases are contrasted with prior case reports. The differential diagnoses of diabetes insipidus and inflammatory pituitary disorders are discussed. Recommendations for diagnosis and treatment are proposed.

Introduction
The term infundibuloneurohypophysitis has been used to describe a disorder characterized by idiopathic diabetes insipidus, an abnormal MRI of the neurohypophysial system and a chronic inflammatory infiltrate pathologically [1, 2]. Its pathogenesis is poorly understood. Current thinking is that this disorder may be the result of an autoimmune response to the hypothalamic neurohypophysial axis. Indeed, autoantibodies to the vasopressin-secreting cells of the hypothalamus have previously been demonstrated [3, 4]. Case reports in adults are few, in children even fewer [1, 2, 4–6]. We present 2 cases and discuss the approach to diagnosis and treatment of this disorder.

Case Reports

Case 1
A 9-year-old boy presented with excessive thirst in August 1988. Endocrine work-up confirmed diabetes insipidus and suggested a growth hormone deficiency. Other endocrine function, development and neurologic exam were normal. An MRI was obtained which was normal (fig. 1a, b). Over a 12-month period, however, a 30-lb weight gain was noted prompting repeat neuroimaging in February 1991 (fig. 1c, d). This demonstrated a 1-cm, enhancing, ovoid mass in the infundibulum not present on his prior study. Additional work-up included a skeletal survey, CSF beta-HCG and AFP, and neuropsychological testing, all of which were unremarkable. In May 1991, the child underwent a right frontotemporal craniotomy and biopsy of a grossly firm and fibrous mass arising from the infundibulum. Postoperatively, he awoke with a mild third nerve palsy and bitemporal visual field deficit which eventually resolved. The postoperative course was generally smooth, and the child was discharged on postoperative day 11. Final pathology revealed reactive gliosis with a chronic inflammatory infiltrate (fig. 2a, b). On follow-up in June 1991, his neurologic exam was back to normal. Over the next several years, the child required growth hormone, testosterone, thyroid replacement and cortisol at times of stress. Yearly MRIs (fig. 1e, f) demonstrated a fading residual hypothalamic abnormality. At the time of last follow-up, this 18-year-old was a senior in high school with a 4.0 grade point average.
Case 2

A 4-year-old boy was brought to medical attention in 1992. His parents related a history of excessive thirst. He would drink anything, including warm water. There was also a 6-lb weight loss in recent months. The child was neurologically and developmentally normal. Other tests of endocrine function were within normal limits. The diagnosis of diabetes insipidus was made and an MRI performed (fig. 3a, b). A 1-cm, enhancing lesion in the infundibulum of the hypothalamus was identified. A skeletal survey and CSF beta-HCG and AFP were negative. Because of our prior experience with case No. 1, the treatment options were discussed with the patient’s family and the decision made to follow the child clinically and with periodic neuroimaging. Although the child became hypothyroid and required replacement, development and neurologic function otherwise remained normal. At the age of 8 and a half years, the child was making As and Bs in school and was released to return as needed. MRIs from 1993 through 1996 (fig. 3c, d) demonstrated a fading residual enhancing abnormality.

Fig. 1. Case 1: Initial T1-weighted MRI without enhancement is within normal limits (a, b). T1-weighted MRI with enhancement 1 year later shows a 1-cm enhancing ovoid infundibular mass (c, d). MRI 2 (e) and four (f) years later demonstrates regression of the residual enhancing abnormality.
**Discussion**

Our literature review yielded 3 other reported cases in children. Mootha et al. [6] reported 8 children with diabetes insipidus and enhancing abnormalities of the infundibulum. Six cases had biopsy-proven germinoma. One child with a thickened, enhancing stalk underwent biopsy which showed a monocytic inflammatory infiltrate. Some regression was demonstrated at 3 months follow-up. Another child was followed and had some regression of his lesion without intervention at 9 months. Hoshimaru et al. [5] reported 7 patients with diabetes insipidus and an abnormal MRI of the posterior pituitary or stalk. Three patients underwent biopsy and were found to have a chronic inflammatory infiltrate. One was a child 6 years of age. At an unspecified length of follow-up, all had some regression of the lesion.

Prior reports have demonstrated loss of the normal hyperintense signal on T1-weighted MRI, thickening and enhancement of the pituitary stalk, or enlargement of the neurohypophysis in children and adults presenting with diabetes insipidus [7–9]. Several of the biopsied cases...
have revealed a chronic inflammatory infiltrate [1, 4, 5]. Our 2 cases demonstrate that this process can produce a sizable, spherical, enhancing mass in the region of the infundibulum suggestive of a small germinoma or hypothalamic glioma. Also unique to our case reports is the extended length of follow-up confirming the indolent natural history of this entity. At 9 years for the first case and 4 and a half years for the second, continued regression of the enhancing abnormality on MRI was documented. Both patients were left with permanent diabetes insipidus and significant anterior pituitary dysfunction. We speculate that the latter is related to interruption of normal production or transit of hypothalamic releasing factors. Anterior pituitary deficiency accompanying diabetes insipidus has been reported in other cases [4–6].

Two large series of children with diabetes insipidus accumulated prior to 1984 found intracranial tumor to be responsible for nearly half the cases followed by ‘idiopathic’ cases in 12–29%. Other etiologies included postinfectious, intracranial defects, histiocytosis and trauma [10]. With the advent of MRI, the incidence of idiopathic diabetes insipidus is on the decline, and even in cases in which the etiology is not yet known, signal abnormalities of the hypothalamic-pituitary axis are being demonstrated [9]. Also, with modern imaging, inflammatory disorders of the pituitary and hypothalamus have been increasingly recognized. Lymphocytic hypophysitis was first described by Goudie and Pinkerton in 1962 and is now a well established syndrome in pregnant or postpartum women resulting from lymphocytic infiltration of the anterior pituitary [11–16]. Inflammatory lesions more commonly affecting the posterior pituitary and producing diabetes insipidus include granulomatous hypophysitis, histiocytosis and the more recently recognized infundibuloneurohypophysitis [17–20].

The differential diagnosis of suprasellar lesions in children and adults is exhaustive (table 1). With MRI, however, the differential diagnosis of lesions similar in pre-
sentation and appearance to our cases will commonly include histiocytosis, germinoma, and hypothalamic/optic glioma. Therefore, the work-up should include a skeletal survey and skull series, and CSF beta-HCG and AFP [6]. Children with histiocytosis will usually have systematic manifestations. In the 1989 review of Dunger et al. [17], 14 of 15 children with diabetes insipidus secondary to histiocytosis had at least skull involvement by the disease. Although most germinomas will present with larger mass lesions, in smaller lesions CSF may still be positive. In the series of Mootha et al. [6], 50% of the children with supra-sellar germinoma had CSF positive for beta-HCG [6]. Hypothalamic glioma generally involves the optic chiasm on neuroimaging with little or heterogeneous enhancement. Although children may present with a diencephalic syndrome and diabetes insipids, visual complaints and optic nerve pallor are distinctly commoner [23–25].

MRI should be performed on all children presenting with diabetes insipids. If the etiology remains undetermined, MRI should be repeated at an appropriate length of time or with the appearance of any new symptoms [8]. In one of our cases and in other reported cases, a child’s scan has been initially normal only to reveal a mass lesion at a later date [26]. Once an abnormality is identified, optimal management depends on imaging findings, results of CSF markers, and patient and family preferences. We recommend observation with frequent follow-up neuroimaging for lesions 1 cm or less with an appearance similar to those presented here. The recognition of this entity should not lead to complacency. Since germinomas can grow rapidly and disseminate through the CSF pathways, the first follow-up MRI should be performed by 4–6 weeks, and families should be aware of this possibility when conservative management is chosen. We do not believe there is a role for a ‘trial of irradiation’ for supra-sellar mass lesions, and all children should have tissue diagnosis prior to initiating therapy.

References

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