Diabetes insipidus due to Hypophysitis

Key Words
Diabetes insipidus
Autoimmune disease
Hypophysitis
Magnetic resonance imaging
Desmopressin acetate

Abstract
Central diabetes insipidus is a chronic disorder which in most patients occurs secondary to tumor, infection, trauma or other lesions. In about 20–30% of patients etiology is unclear, however a destructive autoimmune process in the hypophysis may play a role. We report the case of an 18-year-old girl with central diabetes insipidus. Vasopressin levels were typically decreased. Examinations performed 1.5 years after manifestation showed no pathologic changes on MRI and no additional endocrine disorder. MRI was repeated 1.5 years later wherea a thickening of the pituitary stalk as a typical sign of hypophysitis was apparent. No other reasons could be found for the vasopressin deficiency. The finding of hypophysitis in our patient 3 years after disease manifestation suggests that the characteristic MRI changes may take as long as 3 years to become apparent.

Case Report
Diabetes insipidus is a chronic disorder characterized by polyuria and polydipsia with either a renal or central etiology. Central diabetes insipidus may be familial, secondary to hypothalamic or pituitary disorders or idiopathic. It is caused by a failure of the neurohypophysial system to release sufficient vasopressin to maintain water balance.

We report the case of an 18-year-old girl with central diabetes insipidus. At the age of 15 years she started to drink large quantities of water (8 litres of water/day). One year later she underwent an appendectomy, directly after which she presented in an acute hyperosmolar coma (sodium 194 mmol/l; serum osmolarity 367 mosm/l). Central diabetes insipidus was suspected and immediate intravenous therapy with 2 mg desmopressin acetate (DDAVP)/day was started. Under this regime there was a rapid increase in urine osmolality (576 mosm/l). Urine excretion was reduced. Cranial CT and MRI, both with and without gadolinium contrast, showed no pathological findings.

At this time, LH (<0.1 mU/ml) and FSH (0.9 mU/ml) levels were decreased. Serum levels of estradiol (51 pg/ml), T₃ (1.4 ng/ml), T₄ (9.6 µg/dl), TSH (2.3 µU/ml), cortisol (16.1 µg/dl) and ACTH (44 pg/ml) were normal. The tumor markers AFP and β-HCG were not increased. No insulin, pancreatic islet cells, vasopressin, arginine vasopressin (AVP) cells, hypothalamus, adrenal, thyroid, antinuclear, anti-smooth muscle and antimitochondrial autoantibodies were found.

This girl showed an initial bone age retardation of 3 years (according to Greulich and Pyle) and a partial deficiency of growth hormone in the provocation test with arginine hydrochloride (maximum peak 6.6 ng/ml). She reached her target height by the age of 18 years.

MRI with gadolinium contrast was repeated 1.5 years later. This time there was a thickening of the pituitary stalk.
Central diabetes insipidus is caused by a hypothalamic lesion in ca. 50% of patients [1], mainly of secondary origin, caused by tumor, infection, trauma or other processes.

About 20–30% of patients will remain without a specific etiological diagnosis. In these patients diabetes insipidus might be part of a polyendocrine autoimmune syndrome in which the disease shows an association with other autoimmune diseases such as Graves' disease, adrenali-tis, hypophysitis and insulin-dependent diabetes mellitus. In these patients the anterior pituitary is the principal site of inflammation. In our case, insulin, pancreatic islet cells, adrenal, vasopressin and AVP cell antibodies were not increased.

Scherbaum and Bottazzo [2] reported the examinations of 62 patients with diabetes insipidus. There were 9 cases with idiopathic diabetes insipidus and associated organ-specific autoimmune disease. Only 6 of these patients were positive for AVP cell antibodies. There are no published follow-up studies on these patients, therefore there exists no information about changes in antibody levels as described in other autoimmune diseases. In 3 of these patients the onset of diabetes insipidus was before the age of 16. There are only a few reports about autoantibodies to AVP cells in children with diabetes insipidus. Scherbaum et al. [3] studied 13 patients with idiopathic diabetes insipidus occurring in childhood. In 6 of them (46.1%) they found autoantibodies to AVP cells. Growth hormone deficiency accompanied diabetes insipidus in 3 patients, although antibodies to the somatotrophins of the anterior pituitary gland were not detectable [3]. The association of idiopathic diabetes insipidus with autoimmune diseases in children is less frequent than in adults. Only 1 patient with long-standing diabetes insipidus and positive AVP cell antibodies developed associated autoimmune disease.

Autoantibodies have also been found in patients with histiocytosis X. Scherbaum and Bottazzo [2] studied 13 cases of diabetes insipidus secondary to histiocytosis X, and 7 patients showed antibodies to vasopressin-secreting cells. Only 2 of 68 sera of patients with secondary diabetes insipidus reacted with AVP cells. These findings were interpreted as a reflection of hypothalamic infiltration by histiocytosis X cells. Two years after manifestation of disease, antibodies to vasopressin-secreting cells were not detectable in our patient.

ADH deficiency in idiopathic diabetes insipidus may be associated with another pituitary dysfunction. Czerni-chow et al. [1] found a growth hormone deficiency in 6 of 17 patients with idiopathic diabetes insipidus occurring in childhood. In 3 patients the deficiency was transitory. These findings indicate that a destructive process disturbing the vasopressin-synthesizing cells may also involve other parts of the hypophysis. Our patient showed initially a partial growth hormone deficiency as demonstrated by an in vivo function test, but we found no evidence of any other endocrine disorders. ACTH and basal cortisol levels were in the normal range. Thyroid function parameters both before and after TRH stimulation were normal. At the age of 17 years our patient had a regular menstrual cycle. Thus there were no clinical signs of a panhypopituitarism.

The major pathologic finding as a cause of diabetes insipidus in our patient was the result of the MRI (fig. 1). As a typical sign of diabetes insipidus there was an absence of the hyperintensive signal of the normal neurohypophysis [4]. There were no other pathologic changes such as signs of tumor or inflammation especially of the pituitary stalk in the initial examination, which was done 1.5 years after clinical manifestation of her disease. Three years after the onset of the disease we repeated the MRI (fig. 2). This time it showed a significant thickening of the pituitary stalk, that was interpreted as a typical sign of hypophysitis.

Development of diabetes insipidus associated with a thickening of the pituitary stalk may be caused by histio-cytosis X or a suprasellar tumor. Gudinchet et al. [5] described a size or signal modification of the pituitary stalk controlled by MRI in 3 of 5 children with diabetes insipidus secondary to suprasellar tumor. In our patient there were no signs of a suprasellar or cerebral tumor in MRI 3 years after manifestation of disease, nevertheless, she is continuously monitored at short intervals to exclude any tumor development. Up to now we found no increase in tumor markers and no evidence of other endocrine disorders of the adeno-hypophysis. In 4 of 20 children with diabetes insipidus of different origin studied by Maghnne et al. [6] an enlargement of the pituitary stalk was seen; in 1 of 2 patients with idiopathic diabetes insipidus and in 3 of 5 patients with Langerhans cell histiocytosis. Tien et al. [7] even found that 3 of 4 patients with Langerhans cell histiocytosis had a symmetrically thickened pituitary stalk that demonstrated homogeneous signal enhancement following contrast administration. MR alteration studied in 14 patients with Langerhans cell histiocytosis showed a thickening of the pituitary stalk in 50% of the patients [8]. Three of these 7 children suffered from diabetes insipidus. In our patient, X-ray of the chest and cranial CT revealed no signs of histiocytosis.
Similar to our case are the results of Imura et al. [9]. They reported a lymphocytic infundibulo-neurohypophysitis as a cause of central diabetes insipidus in 17 patients. All patients showed an absence of the hyperintensive signal of the normal neurohypophysis in T1-weighted images on MRI. Four of the patients were male. Nine of 11 patients had impaired secretory responses of growth hormone to insulin-induced hypoglycemia. Nine of the 17 patients had thickening of the pituitary stalk, enlargement of the neurohypophysis or both. Biopsies of the pituitary stalk or neurohypophysis in 2 of these patients demonstrated lymphatic inflammation. All of these patients had had diabetes insipidus for less than 2 years. These abnormalities disappeared during follow-up suggesting a self-limiting process. This was reported to be compatible with an autoimmune etiology [9]. The youngest patient in the study of Imura et al. [9] was a man of 28 years whose disease started at the age of 20 years. His MRI was normal except the absence of the hyperintensive signal of the neurohypophysis.

In contrast to other reports, none of the patients had anterior pituitary hormone deficiency at the time of admission. In none of them symptoms or signs of hypopituitarism or hypothalamic disturbances other than diabetes insipidus developed. Tests for antipituitary, antineuronal and antivasopressin antibodies were not performed [9]. This isolated hypophysitis of the neurohypophysis seems to be very rare, especially in children. The infundibulo-neurohypophysitis does not seem to be a variant of lymphocytic hypophysitis.

These findings indicate that many of the patients with the diagnosis idiopathic diabetes insipidus have a lymphocytic infundibulo-neurohypophysitis. This diagnosis seems to be extremely difficult to attain because the MRI has to be done at the right time. As in our case, initial examination might not reveal pathologic changes. It should be borne in mind that these changes are either not yet apparent or that they have already regressed, maybe because of a self-limiting process.

Although autoantibodies were not detectable, an autoimmune disorder cannot be generally excluded. For the diagnosis of patients with idiopathic diabetes insipidus, the examination of autoantibodies together with neuroradiological evidence of an enlarged pituitary stalk should be mandatory.
References


Congress Calendar

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02.05.–04.05.1997
Berlin
Germany

Adolescent Endocrinology (46th Annual Meeting of the North German Society for Paediatrics)

03.05.–06.05.1997
Washington, D.C.
USA

Pediatric Academic Societies (PAS) Annual Meeting

06.05.–08.05.1997
Lübeck
Germany

41st Symposium of the German Society for Endocrinology

18.05.–21.05.1997
Copenhagen
Denmark

4th Copenhagen Workshop on Carcinoma in situ and Testicular Cancer: Molecular and Endocrine Aspects

25.05.–29.05.1997
Salzburg
Austria

VI International Congress of Andrology

21.06.–24.06.1997
Boston, Mass.
USA

American Diabetes Association 57th Annual Meeting

22.06.–25.06.1997
Edinburgh
Scotland

European Society of Human Reproduction and Embryology Meeting

22.06.–26.06.1997
Stockholm
Sweden

5th Joint Meeting of the ESPE and the LWPEs in association with APEG, JSPE and SLEEP

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