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Management of diabetes insipidus and adipsia in the child

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Central diabetes insipidus (CDI) is a complex and heterogeneous clinical syndrome affecting the hypothalamic-neurohypophyseal network and water balance. A recent national surveillance in Denmark showed a prevalence rate of twenty-three CDI patients per 100 000 inhabitants in five years. The differential diagnosis between several presenting conditions with polyuria and polydipsia is puzzling, and the etiological diagnosis of CDI remains a challenge before the identification of an underlying cause.

For clinical practice, a timely diagnosis for initiating specific treatment in order to avoid central nervous system damage, additional pituitary defects and the risk of dissemination of germ cell tumor is advisable. Proper etiological diagnosis can be achieved via a series of steps that start with careful clinical observation of several signs and endocrine symptoms and then progress to more sophisticated imaging tools. This review summarizes the best practice and approach for the diagnosis and treatment of patients with CDI.

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Introduction

Diabetes insipidus is a rare disease with a non-univocal reported prevalence of 1:25 000 [1] and less than 10% can be attributed to hereditary forms [2]. In particular, X-linked nephrogenic diabetes insipidus (NDI, OMIM 304800) secondary to vasopressin (AVP) receptor-2 mutations, represents 90% of cases of congenital NDI and occurs with a frequency of 4–8 per 1 million male live births. Autosomal NDI (OMIM 125800) accounts for approximately 10% of the remaining cases [2] and abnormalities of the aquaporin-2 (AQP2) water channel gene, located on chromosome 12 at 12q13 are responsible for familial autosomal recessive and dominant forms of NDI.

While the prevalence of Wolfram syndrome (**D**iabetes **I**nsipidus, **D**iabetes **M**ellitus, **O**ptic **A**trophy, and **D**eafness) has been reported as 1–9/1 000 000 (www.orpha.net), the frequency of autosomal dominant central diabetes insipidus (CDI) due to AVP-neurophysin II (AVP-NPII) gene mutation is currently unknown and in rare cases genetic defects in AVP synthesis is inherited as autosomal recessive or X-linked recessive traits [3,4]. A recent National Surveillance of Central Diabetes Insipidus (CDI) in Denmark from 5 year registration desmopressin prescriptions to 1285 CDI patients showed a prevalence rate of 23 CDI patients per 100 000 inhabitants, with a higher prevalence in children and older adults [5]. The yearly incidence rate of new cases of CDI was found to be 3 to 4 patients per 100 000 and the incidence of (presumable) congenital CDI was found to be 2 infants per 100 000 infants.

Diabetes insipidus can be defined as disease in which large volumes of dilute urine (polyuria) are excreted due to AVP deficiency (central diabetes insipidus), vasopressin resistance (NDI), or excessive water intake (primary polydipsia). The differential diagnosis between several overlapping conditions presenting with polyuria and polydipsia is puzzling, and the diagnosis and management of CDI remains a challenge before an identification of the underlying cause [4,6–9].

In many patients, CDI is due to the destruction or degeneration of neurons originating in the supraoptic and paraventricular nuclei. The known causes of these lesions include intracranial germ cell tumors, Langerhans cell histiocytosis (LCH), inflammatory/autoimmune conditions, vascular diseases, trauma resulting from surgery or an accident, metastases, and midline cerebral and cranial malformations [5–8]. Although the prevalence of idiopathic CDI has been commonly reported in up to 52% of patients (Table 1) [6,9–20], recent data indicate that it could be reduced to 4% after a systematic diagnostic work-up and an appropriately tailored long-term follow-up [9]. Hence, this regular approach allows to avoid diagnostic delay of intracranial germ cell tumors [21], to recognize the role of LCH-related CDI as a single organ localization at the level of pituitary/pituitary stalk, and to identify the inflammatory/autoimmune condition as the most frequent cause of idiopathic CDI [9,22].

This review focuses on clinical and biochemical diagnosis, the role of imaging in the differential diagnosis, management, long-term outcomes and future directions of CDI in the light of the recent knowledge.

Diagnosis of central dibetes insipius

Clinical manifestations

Clinical examination may provide important clues to possible underlying diagnoses [4]. The age at which symptoms develop, together with the pattern of fluid intake, may influence subsequent investigation of diabetes insipidus. The primary symptoms are persistent polyuria and polydipsia, and young children may have severe dehydration, vomiting, constipation, fever, irritability, sleep disturbance, failure to thrive and growth retardation. Nocturia in children often presents as enuresis. Early onset severe dehydration in males is highly suggestive of NDI; some mental retardation has been reported, probably caused by chronic and unrecognized dehydration before diagnosis has been established.

In a large cohort of patients with CDI of different etiologies [6], 40% of the patients displayed symptoms other than polyuria and polydipsia at presentation; while headache was not discriminatory, visual defect was associated with intracranial tumor. Growth retardation was not significantly more common in patients with CNS tumors, in contrast with previous reports indicating that such delays