Pediatric Diabetes Insipidus (DI) — Symptoms and Diagnosis

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Diabetes insipidus can be caused by central etiologies or by the renal tubular resistance to the effects of vasopressin. Absolute deficiency of vasopressin or vasopressin resistance is associated with renal tubular inability to uptake water and the production of large amounts of diluted urine. Patients become dehydrated and, depending on the severity of dehydration, their symptoms might differ. Treatment of central diabetes insipidus includes desmopressin with or without thiazide diuretics. Nephrogenic diabetes insipidus is treated with a low-solute diet combined with thiazide diuretics and indomethacin or aspirin.

Overview

Diabetes is a Greek word that is related to urination, whereas insipidus means without taste. This term was used to describe a condition that is characterized by **passing large amounts of urine that is diluted and has low-sodium content, hence tasteless**. Diabetes mellitus, on the other hand, is characterized by passing sweet urine due to hyperglycemia.

Two situations have been implicated in the etiology of Pediatric Diabetes Insipidus:

Central DI (also called: neurohypophyseal or neurogenic DI) occurs due to deficient secretion of antidiuretic hormone (ADH). The most common etiologies of central diabetes insipidus in children include head trauma, tumors and a variety of neurosurgical

procedures. Malignant neoplasms and destructive lesions of the pituitary gland or the hypothalamus are responsible for most cases.

Nephrogenic DI occurs when the renal tubule sare not responsive to vasopressin, which is caused by certain medications, chronic disorders or genetic conditions that affect the kidney.

Epidemiology of Diabetes Insipidus in Children

Incidence

The exact incidence of central diabetes insipidus due to tumors, malformations or neurosurgical procedures in children is **unknown**. The estimated incidence of central diabetes insipidus due to genetic causes is around 3 cases per 100,000. **X-linked nephrogenic diabetes insipidus is a very rare condition**. The estimated incidence of x-linked nephrogenic diabetes insipidus in boys is 4 cases per million.

Prevalence

Nephrogenic and central diabetes insipidus are more common in boys compared to girls. Genetic forms of central diabetes insipidus typically present within the first year of life. Additionally, inherited forms of nephrogenic diabetes insipidus are more commonly seen during early infancy and even in neonates.

Prognosis

The prognosis of central diabetes insipidus is **largely dependent on the etiology**. Primary central diabetes insipidus has an excellent prognosis if recognized early enough and properly treated. On the other hand, children with central diabetes insipidus secondary to invasive lesions, malformations or tumors usually have a less favorable prognosis.
Nephrogenic diabetes insipidus has been linked to an increased risk of learning difficulties and psychomotor delay, but the prognosis is usually **good if the child has adequate access to excessive amounts of water**.

Pathophysiology of Diabetes Insipidus

The reason for losing water loss in DI is different from that caused by diabetes mellitus. With DI, the renal tubular collecting ducts lack the ability to make urine concentrated owing to ADH deficiency or resistance to ADH.

The proves of urine concentration through water reabsorption by the collecting duct is regulated by the posterior pituitary gland which secretes ADH. Therefore, the lack of ability to conserve water through reabsorption in the collecting duct deprives the body of water, while not affecting sodium levels. This results in an extremely diluted, heightened urine output that leads to hypernatremia. This is followed by polydipsia, because the thirst mechanism stimulates replacement of body water.

Furthermore, production of ADH takes place in the posterior pituitary gland and is regulated by the paraventricular and supraoptic nuclei, which responds to alterations in osmolality. If the paraventricular or supraoptic nuclei or the posterior pituitary is destroyed by a tumor, pressure, or surgical operation, this results in reduced production

of ADH and central DI.

The most common etiologies

The most common etiologies of central diabetes insipidus in children include head trauma, tumors and a variety of neurosurgical procedures. Malignant neoplasms and destructive lesions of the pituitary gland or the hypothalamus are responsible for most cases.

An autosomal dominant variant of central diabetes insipidus is caused **by a mutation in the prepro-arginine vasopressin gene** on locus 20p13. An autosomal recessive form of the disease also exists and is characterized by central diabetes insipidus that is associated with diabetes mellitus, optic atrophy and mental retardation. The mutation responsible for this form of central diabetes mellitus has been localized to locus 4p16.

• Developmental abnormality of the brain • Injury to hypothalamus or pituitary • Tumors • Meningitis or encephalitis	• Inflammation (e.g., Wegener's or Histiocystosis • Genetic (familial DI) • Brain surgery

Nephrogenic diabetes insipidus

Nephrogenic diabetes insipidus is usually caused by an x-linked mutation that affects the antidiuretic arginine vasopressin V2 receptor gene found on locus Xq28. Autosomal recessive and autosomal dominant forms of nephrogenic diabetes insipidus also exist, but the ratio of the x-linked form of the disease to the other forms is 9:1.

- Genetic receptor or aquaporin mutations
- Chronic renal disease
- Renal malformations

Causes of increased urine volume

The cause of increased urine volume and urine dilution in diabetes insipidus is either the **deficiency of the arginine vasopressin or resistance to the hormone**. Central diabetes insipidus is characterized by a partial or absolute deficiency of the arginine vasopressin hormone, whereas nephrogenic diabetes insipidus is characterized by renal tubular resistance to this hormone. Water uptake in the renal tubules is impaired in either case and polyuria develops.

Clinical Presentation of Diabetes Insipidus in Children

Children with diabetes insipidus can present with **non-specific symptoms** such as poor feeding, failure to thrive and irritability. Children might become feverish due to dehydration. Constipation and excessively wet diapers can also be the presentation in infants. Older children usually show irritability, symptoms suggestive of dehydration, polyuria, nocturia, and polydipsia. Central diabetes insipidus usually has an acute and sudden onset.

Physical examination

Physical examination reveals:

- Dry mucous membranes
- Increased capillary refill time
- Tachycardia
- Decreased tearing

Hypotension is a late presentation of severe dehydration and possibly hypovolemic shock. Infants and children with severe dehydration have decreased skin turgor and a weak pulse.
If dehydration and hypernatremia are not corrected, children might develop **seizures**. Long-term sequalae of uncorrected hypernatremia include the development of mental retardation and learning disorders. Seizures put the infant at an **increased risk of sudden death**. Death can be caused by either the seizure itself or by hypovolemic shock.

Diagnostic Workup for Diabetes Insipidus in Children

Urine analysis

The first diagnostic test for the workup of diabetes insipidus is to perform a urine analysis to check the **urine specific gravity of a first morning urine sample**. The urine is usually diluted. Serum sodium and serum osmolarity should also be checked in the child. In most cases, serum sodium levels are elevated and serum osmolarity can be greater than 300 mOsm/kg.
When the above investigations show clues suggestive of diabetes insipidus, a **24-hour urine collection** is indicated. The total urine output is usually elevated, while the number of osmoles excreted per day is low.

Water deprivation test

To confirm the diagnosis of diabetes insipidus and **differentiate between central and nephrogenic forms** of the disease, a water deprivation test is indicated. Urine and blood osmolality are first checked at baseline. Afterwards, we deprive the patient from water after breakfast. Water deprivation should be limited to 7 hours for children and 4 hours for infants. During the deprivation period, one should **attempt to measure serum and urine osmolality every two hours**. If polyuria persists, intranasal desmopressin is administered.
The interpretation of the water deprivation test is as follows:
The normal response for the water deprivation test and desmopressin is to see a urine-to-serum osmolality ratio of 1.5 or higher or an increase in that ratio of 1.0 or more from baseline. This normal response is expected in central diabetes insipidus, but not in nephrogenic diabetes insipidus.
Once the diagnosis of central diabetes insipidus is made, one should start looking for **possible structural causes**. A cranial magnetic resonance imaging study is indicated to exclude pituitary gland tumors, cysts, or hypoplasia.

Treatment of Diabetes Insipidus in Children

Hospitalization

Once the diagnosis of diabetes insipidus is made, the child should be admitted to hospital for inpatient care. The goals of inpatient care are to **correct dehydration and establish and etiology of diabetes insipidus**. Children with pituitary gland lesions that are known to cause central diabetes insipidus should be offered a neurosurgical consultation and surgical intervention if necessary.
After adequate **intravenous rehydration** of the patient, **desmopressin should be started for patients with central diabetes insipidus**. Desmopressin is available in intranasal, oral and parenteral forms. Thiazide diuretics might be also needed to lower the urine output and can be combined with desmopressin.

Oral Hydration is preferred. Children who cannot regulate their own drinking by thirst are in grave danger.

NASAL DDAVP	Oral DDAVP
Rapid onset	Slower onset
Damage to nasal mucosa	Variable GI absorption
Not good for infants	Easy to administer to infants

Desmopressin is ineffective in the treatment of nephrogenic diabetes insipidus. Thiazide diuretics, amiloride, and indomethacin, coupled with a low-solute diet, are the mainstay treatment option for nephrogenic diabetes insipidus in children.

References

Roth, Karl S. 2015. “Pediatric Diabetes Insipidus.” Available at: http://emedicine.medscape.com/article/919886-overview

Notes