Diabetes insipidus

Rupinder Singh Kochhar

Stephen Ball

Abstract

Diabetes insipidus (DI) describes the excess production of dilute urine. It is caused by the lack of production or action of the hormone vasopressin (AVP). Diagnosis requires a targeted history and examination. Confirmation requires referral to specialist services with expertise in diagnosis and management. Lack of AVP can be treated with synthetic AVP analogues. Additional approaches can be needed for specific forms of DI. Combined defects in AVP production and thirst perception require a structured programme of fluid intake and antidiuresis. Clinicians should be aware of both systemic and locally progressive pathologies that can present with DI.

Keywords Adipsia; diabetes insipidus; hypernatraemia; hyponatraemia; MRCP; polydipsia; polyuria; vasopressin

Key points

- Diabetes insipidus (DI) can be caused by lack of vasopressin (AVP) production (cranial DI) or a diminished response of the kidneys to AVP (nephrogenic DI)
- Confirming polyuria and excluding metabolic causes are the first steps of management
- Confirming the diagnosis involves a thorough history, physical examination and specialized investigation such as a water deprivation test or hypertonic saline test
- Treatment of these disorders requires careful attention to fluid and electrolyte balance, and should be done in consultation with an endocrinologist

Introduction

Diabetes insipidus (DI) is characterized by excess production of dilute urine – more than 40 ml/kg/24 hours in adults and more than 100 ml/kg/24 hours in children.

Urine concentration is regulated by vasopressin (AVP), a nine-amino-acid peptide produced by magnocellular neurones within the supraoptic nucleus and paraventricular nucleus of the hypothalamus. AVP is released into the circulation from nerve terminals in the posterior pituitary gland. Production is directly related to plasma osmolality and inversely related to plasma volume. The principal site of action of AVP is the kidney, where it increases the synthesis and assembly of water channels (aquaporin 2 (AQP2)), leading to increased free water reabsorption. These effects are mediated through interaction with a G-protein-coupled cell surface receptor (AVP-R2), found on target cells lining the luminal surface of the distal nephron.[1]

Classification and aetiology

There are three subtypes of DI, each reflecting a specific element of the physiology and/or pathophysiology of the AVP axis:

- cranial or hypothalamic DI (HDI): a relative or absolute lack of AVP
- nephrogenic DI (NDI): partial or total resistance to the renal antidiuretic effects of AVP
- dipsogenic DI (DDI, primary polydipsia): inappropriate high fluid intake in excess of the ability to excrete free water.

Hypothalamic diabetes insipidus

Presentation with HDI occurs when 80% of hypothalamic magnocellular neurone AVP production has been lost. Several pathological processes can be involved. All lead to either the destruction of AVP neurones, or the interruption of the transport or processing of AVP as it moves along the axons of these neurones for release at nerve terminals in the posterior pituitary (Table 1). The condition can appear for the first time or become worse in pregnancy as residual AVP is degraded by increased placental enzyme (vasopressinase) activity. Up to 50% of

Aetiology of HDI

Primary	Genetic	Wolfram's syndrome, autosomal dominant, autosomal recessive
	Developmental syndromes	Septo-optic dysplasia
	Idiopathic	
Secondary	Trauma	Head injury, post-surgery (transcranial, trans-sphenoidal)
	Tumour	Craniopharyngioma, germinoma, metastases, pituitary macroadenoma
	Inflammatory	Sarcoidosis, histiocytosis, meningitis, encephalitis, infundibuloneurohypophysitis, Guillain–Barré syndrome, autoimmune
	Vascular	Aneurysm, infarction

Classification describes primary and secondary (acquired) causes. All result in decreased production of AVP through direct or indirect damage to hypothalamic AVP magnocellular neurones.

Table 1

Rupinder Singh Kochhar *MB BS MD MRCP is a Specialist Registrar with North Western Deanery currently working at Manchester Royal Infirmary, UK. Competing interests: none declared.*

Stephen Ball *BSc PhD FRCP is Consultant and Honorary Professor of Medicine. He studied Basic Science at Birmingham University before pursuing undergraduate and postgraduate medical studies in London. Middle-grade training in diabetes and endocrinology included a period in the USA as a Medical Research Council (UK) and Howard Hughes Fellow. He combines clinical medicine, research and teaching. He is a member of the Council of the Society for Endocrinology and a Senior Editor of Clinical Endocrinology. He is also a European Endocrine Society representative within European Guideline groups. Competing interests: none declared.*

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children and young adults with HDI have an underlying tumour or central nervous system malformation. Familial HDI comprises 5% of cases.[2]

Nephrogenic diabetes insipidus

Renal resistance to AVP can be the result of the adverse effects of specific drugs (e.g. lithium toxicity). These effects can be temporary but sometimes persist. NDI can also occur after obstructive nephropathy, acute kidney injury and electrolyte disturbances (e.g. hypokalaemia, hypercalcaemia). Prolonged polyuria of any cause can result in partial NDI through disruption of the intrarenal solute gradient that is an obligatory requirement for the production of concentrated urine.

NDI presenting in childhood is most commonly caused by inherited defects in AVP action. X-linked familial NDI results from loss-of-function mutations in the renal AVP-R2 receptor. Autosomal recessive or dominant NDI can be caused by loss-of-function mutations in the AVP-dependent water channel AQP2.[3]

Dipsogenic diabetes insipidus (primary polydipsia)

Persistent inappropriate fluid intake leads to appropriate polyuria. If it exceeds the limit of renal free water excretion, it can result in hyponatraemia. DDI can be associated with the following abnormalities of thirst perception:

- low threshold for thirst
- exaggerated thirst response to osmotic challenge
- inability to suppress thirst at low plasma osmolalities

Structural lesions can be present, but neuroimaging is normal in most cases. DDI is associated with affective disorders.

Epidemiology

DI is rare. The prevalence of HDI is estimated at 1/25,000 with equal gender distribution. The prevalence of the other forms is unclear. Although most cases present in adulthood, familial HDI and NDI characteristically present in childhood.

Diagnosis and investigations

DI presents with polyuria and polydipsia.

- Polyuria must be distinguished from simple frequency without excess urine volume, commonly seen in urinary infection or prostatic enlargement.
- Nocturnal symptoms are usually the first clue, as nocturia is often the first manifestation of the loss of urinary concentration capability.
- Characterizing the onset of polyuria can be helpful in differentiating the underlying cause. Relatively abrupt onset is commonly a feature in HDI, as opposed to a more gradual onset in NDI and DDI.

History and examination can reveal important features suggestive of:

- systemic disease
- associated endocrinopathy
- an associated neurological problem suggestive of structural disease
- drug toxicity.

The initial approach should be to confirm excess urine volume and exclude simple metabolic causes such as hyperglycaemia and hypercalcaemia.

Measuring plasma sodium concentration and urinary osmolality (preferably early morning) is helpful in the early work-up of disorders of urinary concentrating ability:

- A low plasma sodium concentration with a low urine osmolality is suggestive of DDI.
- A normal plasma sodium concentration associated with urine osmolality >600 mosmol/kg excludes a diagnosis of DI.

Definitive diagnosis requires referral to an endocrine service for testing AVP production and action in response to osmolar stress. The water deprivation test measures renal concentrating capacity in response to dehydration, and is an indirect assessment of the AVP axis. It is usually followed by assessment of renal response to the synthetic AVP analogue desmopressin (DDAVP). Characteristic findings are:

- in DDI, urine concentration is normal in response to dehydration.
- in HDI, urine concentration fails in response to dehydration but not to DDAVP.
- in NDI, urine concentration fails in response to both manoeuvres.

In practice, many results are indeterminate.[4]

Direct measurement of AVP production during graded hyperosmolar stimulation is the gold standard method for diagnosing and classifying DI (Figure 1). Recent data suggest that measurement of co-peptin, an inactive fragment of the AVP precursor that is released in proportion to AVP, may prove to be an alternative.[5]

Confirmation of HDI should lead to further pituitary function testing and cranial magnetic resonance imaging. NDI requires renal tract imaging and additional renal function studies.

Diabetes insipidus and hypernatraemia

There is a close neuroanatomical relationship between the hypothalamic structures responsible for osmoregulation of thirst

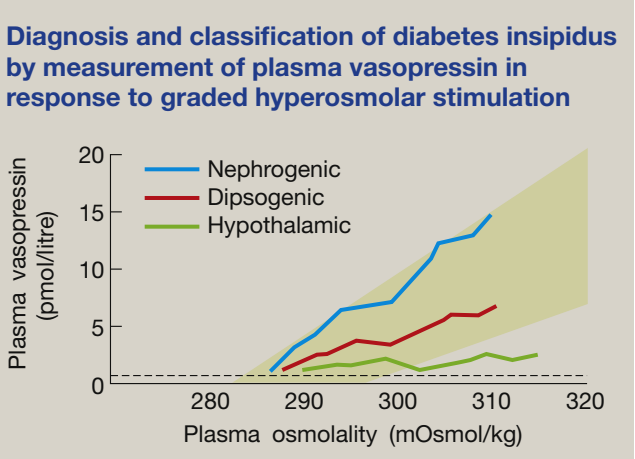

Figure 1 Hypertonic saline infusion test.

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