CURRENT TOPIC

Diabetes insipidus

Peter H Baylis, Tim Cheetham

Over the past two decades our understanding of the mechanisms that control water balance in health and disease has increased substantially. Following the establishment of reliable assay techniques to measure circulating vasopressin, the application of molecular biological methods to define hormonal and receptor abnormalities, and a greater knowledge of intracellular events within the renal tubular cells, it is now possible to characterise disorders of water balance more accurately.

The physiology of water homeostasis is briefly discussed before the pathophysiology, diagnosis, and treatment of diabetes insipidus are described in detail.

Physiology of water homeostasis

It is essential that body water, both intracellular and extracellular, remains stable to allow normal cellular functions to take place. In humans, the maintenance of normal water balance is achieved principally by three interrelated determinants: vasopressin, thirst, and the kidneys. The secretion of vasopressin from the posterior pituitary is under very precise control. Small changes in blood solute concentration (plasma osmolality) regulate vasopressin release.[1] An increase in plasma osmolality, usually indicating a loss of extracellular water, stimulates vasopressin secretion and, conversely, a decrease in plasma osmolality inhibits its release into the systemic circulation (fig 1). Vasopressin then acts on its major target organ, the kidneys. The hormone binds to its V_2 receptor (the antidiuretic receptor) on the basal aspect of the renal collecting tubular cell to activate an adenyl cyclase system that stimulates intracellular protein kinases. These, in turn, control the arrangement and insertion of "water channel" proteins (aquaporin 2) into the cell membrane to allow water to pass from the lumen of the nephron into the cells of the collecting duct along an osmotic gradient, thus concentrating the urine. Aquaporin 4, and possibly aquaporin 3, mediate the subsequent passage of water from within the cell into the renal interstitium and, finally, the circulation. A total of six aquaporins have been described (0–5) and they appear to function as regulators of water transport in a diverse range of tissues, including red blood cells, the lungs, the salivary glands, and the eye, as well as the renal tubule.[2]

Maximum antidiuresis is attained with plasma vasopressin concentrations of about 2–4 pmol/l (fig 2). Under normal conditions water balance is maintained by controlling renal water excretion so that plasma osmolality is confined to a narrow range of 282–295 mmol/kg. In circumstances where patients lose large amounts of body water through—for example, excessive heat, plasma osmolality may increase above 300 mmol/kg, but the increased vasopressin secretion giving plasma concentrations greater than 4 pmol/l will not be able to conserve any more renal water. Water balance, in this situation, is conserved by the ingestion of fluid driven by thirst. Indeed, studies suggest that the sensation of thirst is under very fine osmotic control similar to that of vasopressin secretion.[3]

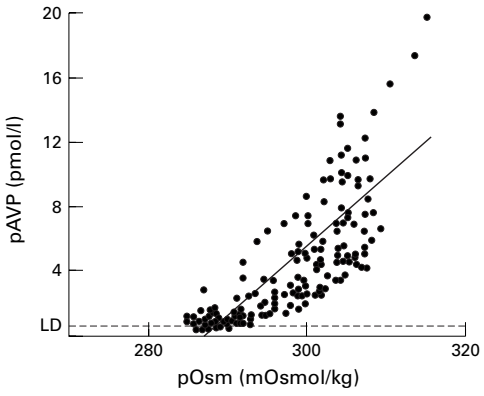

Figure 1 Relation between plasma arginine vasopressin (pAVP) and plasma osmolality (pOsm) in a group of healthy subjects. The solid line represents the mean regression between the two variables defined by pAVP = 0.41 (plasma osmolality − 285). LD represents the limit of detection of the assay (0.3 pmol/l).

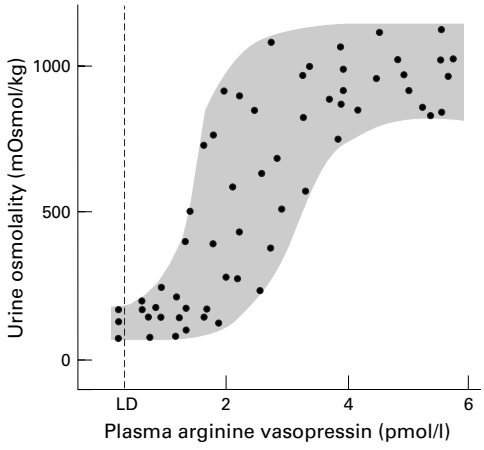

Figure 2 Relation between urine osmolality and plasma arginine vasopressin under various states of hydration. The stippled area is the normal reference range. LD represents the limit of detection of the assay (0.3 pmol/l).

Endocrine Unit, Royal Victoria Infirmary, Newcastle Upon Tyne NE1 4LP, UK
P H Baylis

Department of Child Health, Royal Victoria Infirmary
T Cheetham

Correspondence to:
Professor Baylis.

The polyuric disorders of water balance can be caused by abnormalities of any of these three factors that determine water balance.

Polyuric states

Polyuria is defined as the passage of large volumes of dilute urine, in excess of 2 l/m^2/24 h or approximately 40 ml/kg/24 h in older children and adults. Diabetes insipidus is synonymous with the term polyuria. Three primary pathogenetic mechanisms are responsible for polyuria. The first is a deficiency of osmoregulated vasopressin secretion known as cranial or hypothalamic diabetes insipidus. The second mechanism is a reduction in the renal response to adequate concentrations of circulating vasopressin, termed nephrogenic diabetes insipidus. Third, excessive persistent fluid intake is called dipsogenic diabetes insipidus, or more commonly primary polydipsia.

CRANIAL DIABETES INSIPIDUS

This disorder is defined as an abnormality of urine concentration resulting from the deficient secretion of osmoregulated vasopressin. Cranial diabetes insipidus has been reviewed by a number of workers.[4 5]

Older children with cranial diabetes insipidus will present with polyuria, polydipsia, nocturia, and nocturnal enuresis. There is a wide range in severity, from mild degrees that may escape early detection through to profound polyuria up to 400 ml/kg/24 h. Water balance and normonatraemia are maintained by adequate fluid intake. Patients with cranial diabetes insipidus who are denied access to water, or those with impaired thirst, will develop hypernatraemia. Glucocorticosteroids are necessary for the kidneys to excrete salt free water and so the symptoms of cranial diabetes insipidus may be masked by concomitant ACTH deficiency. Polyuria may then be apparent when corticosteroid replacement is instituted.

Table 1 gives the common causes of cranial diabetes insipidus.[5] Familial cranial diabetes insipidus is rare, accounting for about 5% of all cases. A number of kindreds have been shown to have nucleotide substitutions or deletions of the gene on chromosome 20, which encodes for the large vasopressin precursor molecule.[6] Interestingly, the clinical expression of the familial autosomal dominant disorder does not occur in infants, but more usually at 5–10 years.[7] There appears to be neuronal degeneration of the vasopressin synthesising neurones.

The DIDMOAD syndrome comprises cranial diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA), and deafness (D), as well as hydronephrosis and atonia of the bladder. It has an autosomal recessive inheritance owing to a defect of chromosomal or, possibly, mitochondrial DNA, but the precise genetic cause is unknown.[8] Patients with DIDMOAD syndrome rarely present in infancy, but commonly present in early childhood.

Most cases of cranial diabetes insipidus are acquired, although cerebral malformations can lead to presentation in infancy with the clinical picture described in greater detail in the following. Craniopharyngioma is a relatively common cause of cranial diabetes insipidus, and tumours of the pineal gland, germinoma or teratoma, and pituitary infiltrations with leukaemia and lymphoma can have a similar effect.[9] Infectious causes include congenital cytomegalovirus and toxoplasmosis, viral encephalitis, bacterial meningitis, and Guillain-Barré syndrome. Some patients have lymphocytic infiltration of the pituitary stalk, recognised by widening of the stalk, which can be seen by computed tomography or magnetic resonance imaging, which resolves within a few years.[10] Head trauma may cause transient cranial diabetes insipidus with polyuria lasting from 24 hours to a few weeks. A minority of these patients can have a period of antidiuresis after transient polyuria, only to develop persistent cranial diabetes insipidus subsequently (the triple phase response).[11]

A few studies have suggested the presence of circulating antibodies to the neurones that synthesise vasopressin in some patients with idiopathic cranial diabetes insipidus. These patients appear to have a higher than normal prevalence of other autoimmune disorders.[12] Patients with cranial diabetes insipidus do not have antibodies to vasopressin unless they have received injections of pitressin (pitressin tannate in oil).

Table 1 Causes of diabetes insipidus

Cranial diabetes insipidus
Familial
Autosomal dominant
DIDMOAD syndrome
Cerebral malformations
In association with septo-optic dysplasia
Laurence-Moon-Beidl syndrome
Acquired
Trauma (neurosurgery, head injury)
Tumours (such as craniopharyngioma, germinoma, optic glioma)
Idiopathic
Hypoxic/ischaemic brain damage
Lymphocytic neurohypophysitis
Granuloma (tuberculosis, sarcoid, histiocytosis)
Infections (congenital cytomegalovirus and toxoplasmosis, encephalitis, meningitis)
Vascular (aneurysm, malformations)
Nephrogenic diabetes insipidus
Familial
X linked recessive inheritance (V_2 receptor gene defect)
Autosomal recessive inheritance (aquaporin 2 gene defect)
Acquired
Osmotic diuresis (diabetes mellitus)
Metabolic (hypercalcaemia, hypokalaemia)
Chronic renal disease
Drugs (lithium, demeclocycline)
Postobstructive uropathy
Solute washout from renal medulla
Primary polydipsia
Compulsive or habitual
In association with psychological disturbance
Drugs (lithium, carbamazepine)
Hypothalamic lesion

DIDMOAD, crainia diabetes insipidus (DI), diabetes mellitus (DM), optic atrophy (OA, and deafness (D).

NEPHROGENIC DIABETES INSIPIDUS

Patients with nephrogenic diabetes insipidus, like those with cranial diabetes insipidus, develop hypertonic dehydration and also rely on their thirst mechanism and adequate fluid intake to maintain their water homeostasis. The renal tubules are totally or, more usually, partially resistant to vasopressin.

Table 1 give the causes of nephrogenic diabetes insipidus. The X linked form of the disorder is rare, but it will usually result in profound polyuria and consequent dehydration, vomiting, constipation, fever, irritability, and a failure to thrive in infancy.[13] Infants who are breast fed may present later than those who are bottle fed because of the reduced osmotic load, and their history may contain important clues such as a desire for water feeds as well as milk. There may also be a history of hydramnios. Episodes of dehydration and hypernatraemia may lead to developmental problems and mental retardation in later life.

Molecular studies of affected members of kindreds with nephrogenic diabetes insipidus have identified a number of genetic mutations or deletions of the gene that encodes for the antidiuretic (V_2) receptor located on Xq28.[13] The V_2 receptor is a classic seven domain transmembrane protein, and genetic abnormalities have been located in the transmembrane domain as well as the external and internal segments of the receptor. Some studies have defined another, rarer, form of autosomal recessive familial nephrogenic diabetes insipidus, which is caused by genetic abnormalities of the water channel protein aquaporin 2.[14 15]

Metabolic causes of nephrogenic diabetes insipidus are well recognised. The most common is diabetes mellitus, which induces an osmotic diuresis, thereby reducing the osmotic gradient across the renal tubule, which is necessary for the action of vasopressin. Hypercalcaemia and hypokalaemia impair the action of vasopressin on the distal nephron. Renal concentrating ability after prolonged metabolic disturbance may take a number of weeks to recover completely, despite correction of the disturbance.

PRIMARY POLYDIPSIA (DIPSOGENIC DIABETES INSIPIDUS)

Excessive fluid intake will suppress vasopressin secretion and induce polyuria. Patients usually remain normonatraemic despite large fluid intakes, although plasma osmolality may be low to normal or slightly reduced.

The causes of primary polydipsia include compulsive or habitual excessive fluid intake. Frank psychiatric illness or rare hypothalamic defects, which lead to increased thirst, are uncommon causes in children. A few patients who appear to be psychologically normal show a lowered osmotic threshold for the onset of thirst sensation, but normal osmoregulated vasopressin secretion.

Diagnosis of the cause of diabetes insipidus

Before embarking on time consuming and expensive investigations it is essential that the 24 hour urine volume is documented and polyuria confirmed. Preliminary tests to measure blood glucose, serum calcium, and serum potassium should be performed to exclude common causes of nephrogenic diabetes insipidus. Although the osmolality of an early morning urine sample obtained at home will provide some information, it is difficult to interpret without a concomitant serum sample. Fluids should not be restricted at home until a diagnosis has been made.

Table 2 Protocol of water deprivation/desmopressin test

Preparation
Fluid given overnight before test
Avoid caffeine
Weigh patient
Liaise with laboratory before test begins
Dehydration phase
Draw blood and collect urine for osmolality measurements and urine volume measurement at 08:00
Restrict fluids—an eight hour fast will usually suffice
Weigh patient at two hourly intervals
Collect blood and urine for osmolality and volume measurements at regular intervals—ideally every two hours
Stop test if weight loss exceeds 5% of starting weight or if thirst becomes intolerable
Supervise test closely to avoid patient drinking
Desmopressin phase: if diabetes insipidus has not been excluded
Inject intramuscular, subcutaneous or intravenous desmopressin 0.3 µg (this can be administered by fine insulin syringe if given subcutaneously) or 5 µg intranasally after the dehydration phase (at about 16:00)
Allow patient to eat and drink up to 1.5 times the urine volume passed during dehydration phase and beyond
Collect urine for osmolality and volume at about 20:00
Draw blood and collect urine for osmolality and volume measurements at 09:00 next morning

The standard diagnostic approach to determine the pathogenetic mechanism causing polyuria is a fluid deprivation test coupled to a study to check urinary concentrating ability in response to exogenous vasopressin. Particular care is required in very young children, and this type of protocol is clearly unsuitable in infants. Numerous water deprivation tests have been described, but a commonly used protocol is based on Dashe's original test.[16] Table 2 gives an outline of the protocol. A seven hour fast is usually of sufficient duration[17]; it is important to allow free access to fluids before starting fluid restriction and to supervise the patient closely to avoid surreptitious drinking. After the administration of desmopressin, the patient may eat and drink, but fluid ingestion should be controlled (see table 2) to avoid copious fluid intake in a primary polydipsic child rendered antidiuretic who is then at risk of developing profound and symptomatic hyponatraemia.[18]

Table 3 gives a guide to the interpretation of the results from the water deprivation/desmopressin test. Plasma osmolality within the normal reference range (282–295 mmol/kg) combined with a maximum urine osmolality greater than 750 mmol/kg after dehydration excludes significant water imbalance. Although an unequivocal diagnosis can often be made from these results it is not unusual for urine osmolalities to fall within the range given in the final row (table 3) and a clear diagnosis cannot

Table 3 Interpretation of fluid deprivation and desmopressin tests in polyuric patients

Urine osmolality (mmol/kg)		
After fluid deprivation	*After desmopressin*	*Diagnosis*
< 300	> 750	Cranial diabetes insipidus
< 300	< 300	Nephrogenic diabetes insipidus
> 750	> 750	Primary polydipsia
300–750	< 750	? Partial cranial diabetes insipidus, ? partial nephrogenic diabetes, or ? primary polydipsia

be established. This is probably because after prolonged polyuria of any cause, the renal interstitial solute is "washed out", so that there is a reduction in the osmotic gradient across the distal renal tubular cell, which is essential for the action of vasopressin. Therefore, there will be a degree of renal resistance to vasopressin irrespective of the underlying cause of the polyuria. The greater the degree of polyuria the greater the resistance to vasopressin. Measurement of plasma vasopressin during the dehydration phase does not usually increase the discriminatory power of the test, although urinary vasopressin measurements may be helpful.[19]

In infants and younger children the clinical picture and results of investigations at presentation may leave little doubt about the diagnosis and the response to desmopressin will usually confirm the diagnosis.

In older children (age > 5 years) a definitive diagnosis of cranial diabetes insipidus can be made by measuring the plasma vasopressin response to increasing plasma osmolality induced by a hypertonic 5% (850 mmol/l) saline infusion over a period of two hours at a rate of 0.05 ml/kg/h[20] or until a plasma osmolality of 300 mmol/kg is achieved. This is of value when a deprivation test has shown equivocal results, but is rarely used in children. The limited availability of a reliable arginine vasopressin assay and the practical difficulties that may accompany the administration of irritant hypertonic saline solution to children are possible reasons for this. Figure 3 indicates the normal response of healthy subjects and, in the hatched area, the subnormal vasopressin response diagnostic of cranial diabetes insipidus. Polyuric patients who have nephrogenic diabetes insipidus or primary polydipsia will have vasopressin values in the normal reference range.[4 21]

Direct measurement of plasma vasopressin after a period of water restriction confirms the diagnosis of nephrogenic diabetes insipidus when plotted against urine osmolality (fig 4). This test is particularly useful in identifying the partial forms of nephrogenic diabetes insipidus.[4 17]

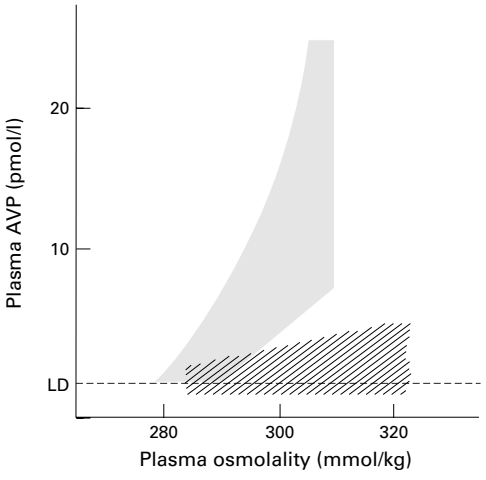

Figure 3 Relation between plasma arginine vasopressin (AVP) and plasma osmolality following hypertonic 5% saline infusion. The shaded area is the normal response. Patients with cranial diabetes insipidus show subnormal responses (hatched area).

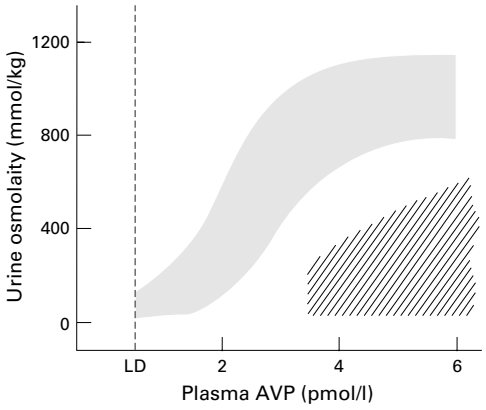

Figure 4 Relation between urine osmolality and plasma arginine vasopressin (AVP) after a period of fluid restriction. The shaded area represents the normal relation. Patients with nephrogenic diabetes insipidus have results displaced to the right of normal (hatched area).

The third diagnostic approach is to perform a therapeutic trial of low dose desmopressin. It is undoubtedly helpful in younger patients and if there is no facility to measure plasma vasopressin. After a period of three to four days during which daily weight, plasma sodium, urine volume, and osmolality are monitored, the patient is given a small dose of subcutaneous or intramuscular desmopressin daily for about seven to 10 days. A dose of 0.3–0.5 µg in younger children or 0.5–1.0 µg in teenagers is appropriate. Measurements are continued during the desmopressin trial and for a few days after stopping the drug. Patients with cranial diabetes insipidus will be identified by a reduction in thirst, a progressive reduction in urine output, and plasma sodium will remain in the normal range during desmopressin administration. Nephrogenic diabetes insipidus is characterised by a lack of response to desmopressin with a persistence of thirst and polyuria. Those with primary polydipsia will remain thirsty and develop progressive hyponatraemia.[4]

Once the pathogenetic mechanism responsible for causing polyuria has been clarified, it is mandatory to search for the underlying cause of the type of diabetes insipidus. Magnetic resonance imaging of the pituitary, hypothalamus, and surrounding structures should be performed to look for pituitary and parapituitary masses, craniopharyngioma, pinealoma, or pituitary stalk abnormalities. In many patients (70%) with cranial diabetes insipidus there is a loss of the normal hyperintense signal in T1 weighted magnetic resonance imaging of the posterior pituitary,[22] although this may also be a feature of nephrogenic diabetes insipidus. In the former this is because of reduced vasopressin production and in the latter to enhanced release. The signal will be normal in primary polydipsia. It is important to perform serial magnetic resonance imaging in all cases of idiopathic cranial diabetes insipidus because of the possibility of evolving disease not detected initially.[23] Genetic studies to identify the abnormality in the precursor vasopressin molecule in familial cases might be appropriate.

Treatment

CRANIAL DIABETES INSIPIDUS

The drug of choice is desmopressin, which is a synthetic analogue of the native hormone, arginine vasopressin.[24] Two minor structural alterations to the vasopressin molecule have created a drug with prolonged antidiuretic action and minimal pressor activity. Desmopressin may be administered orally, intranasally, or parenterally. There are wide individual variations in the doses required to control diuresis.[25] Daily requirements for the preparations given by mouth vary from 100 to 1000 μg in two or three divided doses; for the intranasal preparations around 2–40 μg are given (in children older than 1 year); and for the parenteral preparations 0.1–1 μg are given. A low dose should be used initially and this can then be increased as necessary. As little as 0.5 μg of the nasal solution twice daily may suffice in neonates, and the hospital pharmacy can prepare a manageable volume by diluting standard desmopressin solution. This can then be administered by a 1 ml syringe, which will allow the small dose to be dropped accurately into the supine child's nostrils. The treatment of small children with diabetes insipidus can be very difficult, with rapid and sometimes unexplained changes in osmolality.[26] It is important for the family to be closely involved from the onset so that they are able to gauge what is an appropriate fluid intake and urine output. Desmopressin given by mouth has been shown to be particularly helpful in childhood[27] and many paediatricians now use this treatment beyond infancy. Dilutional hyponatraemia is the only potential hazard if desmopressin is administered in excess over a prolonged time period. This can be prevented in older children by adjusting the regimen to allow a periodic "breakthrough" when the urine output is allowed to increase.

Children with adipsia or hypodipsia are a difficult challenge and are best managed by fixing the desmopressin dose and fluid intake, initially in the hospital setting. Daily weights can be used as an index of fluid balance, but regular electrolytes will also be required, particularly in the initial phase.[28] The shorter acting preparation, lysine vasopressin, is not recommended because of its pressor activity. Rarely, direct treatment of the underlying cause of cranial diabetes insipidus cures the polyuria (for example, steroid treatment of hypothalamic sarcoidosis).

NEPHROGENIC DIABETES INSIPIDUS

Effective treatment of nephrogenic diabetes insipidus still poses major problems, except for forms that are drug induced or related to metabolic disorders (table 1). Withdrawal of the drug or correction of the metabolic disturbance often reverses the renal resistance to vasopressin, but correction may take a number of weeks.

The profound polyuria caused by the familial forms of nephrogenic diabetes insipidus are particularly difficult to manage. Salt restriction combined with the administration of a thiazide diuretic can reduce urine output by 40% in infants.[29 30] Thiazide diuretics act by enhancing sodium excretion at the expense of water and reducing the glomerular filtration rate. They may need to be administered with a potassium sparing drug such as amiloride. A similar reduction in urine flow may be achieved with the prostaglandin synthetase inhibitor indomethacin, given in doses of 1.5–3.0 mg/kg. A relatively new and promising approach is the combination of a thiazide, indomethacin, and desmopressin, which may reduce urine output by up to 80%. It is essential that all these patients drink adequate fluid volumes to quench their thirst.

PRIMARY POLYDIPSIA

It may be appropriate to reduce water intake once the diagnosis of compulsive or habitual water intake has been made. In older children there may be an underlying psychological or psychiatric disorder which must be treated to settle the water disturbance.

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