Genetics and diagnosis of central diabetes insipidus

Génétique et diagnostic du diabète insipide central

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Abstract

Most of the central diabetes insipidus cases seen in general practice are acquired but the rare cases of hereditary autosomal dominant or recessive neurohypophyseal diabetes insipidus have provided further cellular understanding of the mechanisms responsible for pre-hormone folding, maturation and release. Autosomal dominant central diabetes insipidus is secondary to the toxic accumulation of vasopressin mutants as fibrillar aggregates in the endoplasmic reticulum of hypothalamic magnocellular neurons producing vasopressin. As well, Trpv1−/− and Trpv4−/− mice have shed new light on the perception of tonicity through the stretch receptors TRPVs expressed both in central and peripheral neurons. The genomic information provided by sequencing the AVP gene is key to the routine care of these patients and, as in other genetic diseases, reduces health costs and provides psychological benefits to patients and families. In addition, simple, inexpensive blood and urine measurements together with clinical characteristics and brain magnetic resonance imaging (MRI) could distinguish between central, nephrogenic and polydipsic cases.

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Diabetes insipidus is a disorder characterized by the excretion of abnormally large volumes (greater than 30 mL/kg body weight/day for an adult patient) of dilute urine (less than 250 mmol/kg) (Fig. 1). This definition excludes osmotic diuresis, which occurs when excess solute is being excreted, for example, glucose in the polyuria of diabetes mellitus. Other agents that produce osmotic diuresis are mannitol, urea, glycerol, contrast media, and loop diuretics. Osmotic diuresis should be considered when solute excretion exceeds 60 mmol/h. Four basic defects can be involved. The most common, a deficient secretion of the antidiuretic hormone (ADH) arginine vasopressin (AVP) is referred to as neurogenic (or central, neurohypophyseal, cranial, or hypothalamic) diabetes insipidus. Diabetes insipidus can also result from renal insensitivity to the antidiuretic effect of AVP, which is referred to as nephrogenic diabetes insipidus. Excessive water intake can result in polyuria, which is referred to as primary polydipsia: it can be due to an abnormality in the thirst mechanism, referred to as dipsogenic diabetes insipidus; or it can be associated with a severe emotional cognitive dysfunction, referred to as psychogenic polydipsia. Finally, increased metabolism of vasopressin during pregnancy is referred to as gestational diabetes insipidus.

1. Arginine vasopressin synthesis

The regulation of the release of AVP from the posterior pituitary is primarily dependent, under normal circumstances, on

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doi:10.1016/j.ando.2012.03.030
tonicity information relayed by central osmoreceptor neurons expressing TRPV1 [1] (Fig. 2) and peripheral osmoreceptor neurons expressing TRPV4 [2]. AVP and its corresponding carrier, neurophysin II, are synthesized as a composite precursor by the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus (for review see [3]). The precursor is packaged into neurosecretory granules and transported axonally in the stalk of the posterior pituitary. En route to the neurohypophysis, the precursor is processed into the active hormone. Pre-provasopressin has 164 amino acids and is encoded by the 2.5 kb AVP gene located in chromosome region 20p13 [4,5]. The AVP gene (coding for AVP and neurophysin II) and the OXT gene (coding for oxytocin and neurophysin I) are located in the same chromosome region, at a very short distance from each other (12 kb in humans) in head-to-head orientation. Data from transgenic mouse studies indicate that the intergenic region between the OXT and the AVP genes contains the critical enhancer sites for cell-specific expression in the magnocellular neurons [3]. It is phylogenetically interesting to note that cis and trans components of this specific cellular expression have been conserved between the Fugu isotocin (the homolog of mammalian oxytocin) and rat oxytocin genes [6]. Exon 1 of the AVP gene encodes the signal peptide, AVP, and the NH2-terminal region of neurophysin II. Exon 2 encodes the COOH-terminal region of neurophysin II and the glycopeptide. Provasopressin is generated by the removal of the signal peptide from pre-provasopressin and from the addition of a carbohydrate chain to the glycopeptide (Fig. 3). Additional posttranslation processing occurs within neurosecretory vesicles during transport of the precursor protein to axon terminals in the posterior pituitary, yielding AVP, neurophysin II, and the glycopeptide. The AVP-neurophysin II
Fig. 3. Structure of the human vasopressin (AVP) gene and prohormone. Cascade of vasopressin biosynthesis, signal peptide; AVP, arginine-vasopressin; neurophysin; glycoprotein.

complex forms tetramers that can self-associate to form higher oligomers [7]. Neurophysins should be seen as chaperone-like molecules facilitating intracellular transport in magnocellular cells. In the posterior pituitary, AVP is stored in vesicles. Exocytotic release is stimulated by minute increases in serum osmolality (hypernatremia, osmotic regulation) and by more pronounced decreases in extracellular fluid (hypovolemia, nonosmotic regulation). Oxytocin and neurophysin I are released from the posterior pituitary by the suckling response in lactating females.

Immunocytochemical and radioimmunologic studies have demonstrated that oxytocin and vasopressin are synthesized in separate populations of the supraoptic nuclei and the paraventricular nuclei neurons [8,9], the central and vascular projections of which have been described in great detail [10]. Some cells express the AVP gene and other cells express the OXT gene. Immunohistochemical studies have revealed a second vasopressin neurosecretory pathway that transports high concentrations of the hormone to the anterior pituitary gland from parvocellular neurons to the hypophyseal portal system. In the portal system, the high concentration of AVP acts synergistically with corticotropin-releasing hormone (CRH) to stimulate adrenocorticotrophic hormone (ACTH) release from the anterior pituitary. More than half of parvocellular neurons coexpress both CRH and AVP. In people, while passing through the median eminence and the hypophyseal stalk, magnocellular axons can also release AVP into the long portal system. Furthermore, a number of neuroanatomic studies have shown the existence of short portal vessels that allow communication between the posterior and anterior pituitary. Therefore, in addition to parvocellular vasopressin, magnocellular vasopressin is able to influence ACTH secretion [11,12].

2. Mammals are osmoregulators: the cellular perception of tonicity to stimulate thirst and vasopressin release

Mammals are osmoregulators: they have evolved mechanisms that maintain extracellular fluid (ECF) osmolality near a stable value. Yet, although mammals strive to maintain a constant ECF osmolality, values measured in an individual can fluctuate around the set-point owing to intermittent changes in the rates of water intake and water loss (through evaporation or diuresis) and to variations in the rates of Na intake and excretion (natriuresis). In humans, for example, 40 minutes of strenuous exercise in the heat [13,14], or 24 hours of water deprivation [15] causes plasma osmolality to rise by more than 10 mosmol/kg.

In a dehydrated individual, drinking the equivalent of two large glasses of water (∼850 mL) lowers osmolality by approximately 6 mosmol/kg within 30 minutes [16]. Similarly, ingestion of 13 g of salt increases plasma osmolality by approximately 5 mosmol/kg within 30 minutes [17]. Although osmotic perturbations larger than these can be deleterious to health, changes in the 1–3% range play an integral part in the control of body-fluid homeostasis. Differences between the ECF osmolality and the desired set-point induce proportional homeostatic responses according to the principle of negative feedback [1]. ECF hyperosmolality stimulates the sensation of thirst, to promote water intake, and the release of vasopressin to enhance water reabsorption in the kidney. By contrast, ECF hypoosmolality suppresses basal VP secretion in rats and humans [18].

As summarized elegantly by Bourque [1] early studies provided clear evidence that “cellular dehydration” (that is, cell shrinking) was required for thirst and vasopressin release to be stimulated during ECF hyperosmolality: these responses could be induced by infusions of concentrated solutions containing membrane-impermeable solutes, which extract water from...
vasopressin magnocellular neurons, ANP inhibits vasopressin (ANP). While circulating Ang-II and relaxin excite both OT and angiotensin II (Ang-II), relaxin, and atrial natriuretic peptide (ANP) in action potential firing rate [21]. The information encoded by vasculosum of the lamina terminalis (OVLT) lie outside the mechanical modulation of TRPV1 is well demonstrated [26].

The cellular basis for osmoreceptor potentials has been characterized using patch-clamp recordings and morphometric analysis in magnocellular cells isolated from the supraoptic nucleus of the adult rat. In these cells, stretch-inactivating cationic channels transduce osmotically evoked changes in cell volume into functionally relevant changes in membrane potential. In addition, magnocellular neurons also operate as intrinsic Na⁺ detectors. The N-terminal variant of the transient receptor potential vanilloid-1 (TRPV1, vide infra); OVLT serves as the brain’s primary osmoreceptor area [20] and neurons in this nucleus transduce hypertonicity into functionally relevant changes in action potential firing rate [21]. The information encoded by the electrical activity of these neurons is then relayed synaptically to diverse subsets of homeostatic effector neurons that induce appropriate osmoregulatory responses such as thirst, natriuresis, and antidiuretic hormone release [1,22–25]. The mechanical modulation of TRPV1 is well demonstrated [26].

Because the subfornical organ (SFO) and the organum vasculosum of the lamina terminalis (OVLT) lie outside the blood brain barrier, they can integrate this information with endocrine signals borne by circulating hormones, such as angiotensin II (Ang-II), relaxin, and atrial natriuretic peptide (ANP). While circulating Ang-II and relaxin excite both OT and vasopressin magnocellular neurons, ANP inhibits vasopressin cells, but not by infusions of solutes that readily equilibrate across the cell membrane (such as urea). Verney coined the term osmoreceptor to designate the specialized sensory elements. He further showed that these were present in the brain and postulated that they might comprise “tiny osmometers” and “stretch receptors” that would allow osmotic stimuli to be “transmuted into electrical” signals [19]. Osmoreceptors are therefore defined functionally as neurons that are endowed with an intrinsic ability to detect changes in ECF osmolality and it is now known that both cerebral and peripheral osmoreceptors contribute to the body fluid balance.

Although magnocellular neurons are themselves osmosensitive, they require input, by glutamatergic afferents, from the lamina terminalis to respond fully to osmotic challenges (Fig. 4).

Hyperosmoticity is sensed by organum vasculosum lamina terminalis (OVLT) neurons expressing transient receptor potential vanilloid-1 (TRPV1, vide infra); OVLT serves as the brain’s primary osmoreceptor area [20] and neurons in this nucleus transduce hypertonicity into proportional increases in action potential firing rate [21]. The information encoded by the electrical activity of these neurons is then relayed synaptically to diverse subsets of homeostatic effector neurons that induce appropriate osmoregulatory responses such as thirst, natriuresis, and antidiuretic hormone release [1,22–25]. The mechanical modulation of TRPV1 is well demonstrated [26].

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Tonicity information is relayed by central osmoreceptor neurons expressing TRPV1 and peripheral osmoreceptor neurons expressing TRPV4.

The osmotic regulation of the release of AVP from the posterior pituitary is primarily dependent, under normal circumstances, on tonicity information relayed by central osmoreceptor neurons expressing TRPV1 [1] and peripheral osmoreceptor neurons expressing TRPV4 [2].

The cellular basis for osmoreceptor potentials has been characterized using patch-clamp recordings and morphometric analysis in magnocellular cells isolated from the supraoptic nucleus of the adult rat. In these cells, stretch-inactivating cationic channels transduce osmotically evoked changes in cell volume into functionally relevant changes in membrane potential. In addition, magnocellular neurons also operate as intrinsic Na⁺ detectors. The N-terminal variant of the transient receptor potential channel (TRPV1) is an osmotically-activated channel expressed in the magnocellular cells producing vasopressin [29] and in the circumventricular organs, the OVLT and the SFO [21]. Since osmoregulation still operates in Trpv1⁻/⁻ mice, other osmosensitive neurons or pathways must be able to compensate for loss of central osmoreceptor function [21,29,30]. Afferent neurons expressing the osmotically activated ion channel, TRPV4 in the thoracic dorsal root ganglia that innervate hepatic blood vessels and detect physiological hypo-osmotic shifts in blood osmolality have recently been identified [2]. In mice lacking the osmotically activated ion channel, TRPV4, hepatic sensory neurons no longer exhibit osmosensitive inward currents and activation of peripheral osmoreceptors in vivo is abolished.
In a large cohort of human liver transplantees, who presumably have denervated livers, plasma osmolality is significantly elevated compared to healthy controls suggesting the presence of an inhibitory vasopressin effect of hyponatremia, perceived in the portal vein from hepatic afferents [2]. TRPV1 (expressed in central neurons) and TRPV4 (expressed in peripheral neurons) thus appear to play entirely complementary roles in osmoreception. Lechner et al. have thus identified the primary afferent neurons that constitute the afferent arc of a well-characterized reflex in man and more recently also in rodents [31]. This reflex engages the sympathetic nervous system to raise blood pressure and stimulate metabolism [32,33]. Of clinical interest, it has already been demonstrated that orthostatic hypotension and postprandial hypotension respond to water drinking [34–36]. Moreover, water drinking in man can prevent neutrally mediated syncope during blood donation or after prolonged standing [37]. Finally, water drinking is also associated with weight loss in overweight individuals [38]. Other peripheral sensory neurons expressing other mechanosensitive proteins may also be involved in osmosensitivity [39].

3. Expression of the vasopressin gene in diabetes insipidus rats (Brattleboro rats)

The animal model of diabetes insipidus that has been most extensively studied is the Brattleboro rat. Discovered in 1961, the rat lacks vasopressin and its neurophysin, whereas the synthesis of the structurally related hormone oxytocin is not affected by the mutation [40]. Its inability to synthesize vasopressin is inherited as an autosomal recessive trait. Schmale and Richter [41] isolated and sequenced the vasopressin gene from homozygous Brattleboro rats, and found that the defect is due to a single nucleotide deletion of a G residue within the second exon encoding the carrier protein neurophysin (Fig. 6). The shift in the reading frame caused by this deletion predicts a precursor with an entirely different C terminus. The messenger RNA (mRNA) produced by the mutated gene encodes a normal AVG but an abnormal NPII moiety [41], which impairs transport and processing of the AVP-NPII precursor and its retention in the endoplasmic reticulum of the magnocellular neurons where it is produced [42,43]. Homozygous Brattleboro rats may still demonstrate some V2 (vide infra) anti-diuretic effects since the administration of a selective non-peptide V2 antagonist (SR 121463A, 10 mg/kg i.p.) induced a further increase in urine flow rate (200 to 354 ± 42 mL/24 h) and a decline in urinary osmolality (170 to 92 ± 8 mmol/kg) [44]. This decline in urine osmolality following the administration of a non-peptide V2 receptor antagonist could also be secondary to the “inverse agonist” properties of SR121463A: the intrinsic activity, or “tune”, of the V2R would be deactivated by the SR121463A compound (for the inverse agonist properties of SR121463A see [45]. There is also an alternative explanation to this relatively high urine osmolality of 170 since, in Brattleboro rats, low levels of hormonally-active AVP are produced from alternate forms of AVP preprohormone. Due to a process called molecular misreading, one transcript contains a 2 bp deletion downstream from the single nucleotide deletion that restores the reading frame and produces a variant AVP preprohormone that is smaller in length by one amino acid and differs from the normal product by only 13 amino acids in the neurophysin II moiety [46]. Oxytocin, which is present at enhanced plasma concentrations in Brattleboro rats, may be responsible for the antidiuretic activity observed [47,48]. Oxytocin is not stimulated by increased plasma osmolality in humans.

4. Central diabetes insipidus

4.1. Common forms

Failure to synthesize or secrete vasopressin normally limits maximal urinary concentration and, depending on the severity of the disease, causes varying degrees of polyuria and polydipsia. Experimental destruction of the vasopressin-synthesizing areas of the hypothalamus (supraoptic and paraventricular nuclei) causes a permanent form of the disease. Similar results are obtained by sectioning the hypophyseal-hypothalamic tract above the median eminence. Sections below the median eminence, however, produce only transient diabetes insipidus. Lesions to the hypothalamic-pituitary tract are often associated with a three-stage response both in experimental animals and in humans [49], which consists of:

- an initial diuretic phase lasting from a few hours to five to six days;
- a period of antidiuresis unresponsive to fluid administration. This antidiuresis is probably due to vasopressin release from injured axons and may last from a few hours to several days. Because urinary dilution is impaired during this phase, continued water administration can cause severe hyponatremia;
- a final period of diabetes insipidus. The extent of the injury determines the completeness of the diabetes insipidus, and as already discussed, the site of the lesion determines whether the disease will or will not be permanent.

A detailed assessment of water balance following transsphenoidal surgery has been reported [50]. One hundred and one patients who underwent transsphenoidal pituitary surgery at the National Institutes of Health Clinical Center were studied.
its antidiuretic effect [57, 58]. Maghnie et al. [51] studied 79 when they do, almost always result in secondary resistance to pressin occasionally develop during treatment with ADH and, and progression of histiocytosis of the Langerhans’ cells related to anterior pituitary and other nonendocrine hypothalamic dys-

function, and their response to treatment in 12 adult patients has also been reviewed [59]. None of the patients with central diabetes insipidus secondary to AVP mutations developed anterior pituitary hormone deficiencies.

### 4.2. Rare forms

Inherited neurohypophyseal diabetes insipidus (OMIM 125700) [60] due to mutations in the AVP gene (OMIM 192340) [60] and Wolfgram syndrome 1 (OMIM 222300) [60] due to mutations in the WFS1 gene. Historically, Lacombe [61] and Weil [62] described a familial non–X-linked form of diabetes insipidus without any associated mental retardation. The descend-

ants of the family described by Weil were later found to have autosomal dominant neurogenic diabetes insipidus [63–65].

Patients with autosomal dominant neurohypophyseal dia-

betes insipidus retain some limited capacity to secrete AVP during severe dehydration, and the polyuria-polydipsic symp-

toms usually appear after the first year of life [66], when the infant’s demand for water is more likely to be understood by adults. In neurohypophyseal diabetes insipidus, termed familial neurohypophyseal diabetes insipidus (FNDI), levels of AVP are insufficient and patients show a positive response to treatment with dAVP. Growth retardation might be observed in untreated children with autosomal dominant FNDI [67]. Over 60 mutations in the prepro-arginine-vasopressin-neurophysin II AVP gene located on chromosome 20p13 have been reported in dominant FNDI (adFNDI). Knock-in mice heterozygous for a nonsense mutation in the AVP carrier protein neurophysin II showed progressive loss of AVP-producing neurons over several months correlated with increased water intake, increased urine output, and decreased urine osmolality. The data suggest that vasopressin mutants accumulate as fibrillar aggregates in the endoplasmic reticulum and cause cumulative toxicity to magnocellular neurons explaining the later age-of-onset [68, 69]. To date, recessive FNDI, with early polyuric manifestations has only been described in three studies [70–72]. Very early (first week of life) polyuric states are usually nephrogenic but we and others have observed autosomal recessive cen-

tral diabetes insipidus patients with early polyuria, dehydration episodes responding to dDAVP with specific mutations of the AVP gene [70–73]. A study by Christensen [74] examined the differences in cellular trafficking between dominant and recessive AVP mutants and found that dominant forms were concentrated in the cytoplasm whereas recessive forms were localized to the tips of neurites. The expression of regulated secretory proteins such as granins and prohormones, including pro-vasopressin, generates granule-like structures in a variety of neuroendocrine cell lines due to aggregation in the trans-Golgi [75]. Co-staining experiments unambiguously distinguished between these granule-like structures and the accumulations by pathogenic dominant mutants formed in the ER, since the latter, but not the trans-Golgi granules, co-localized with specific ER markers [68]. As studies concerning both dominant and recessive FNDI accumulate, it is becoming evident that FNDI exhibits a variable age-of-onset and this may be related to the cellular handling of the mutant AVP. This progressive toxicity, sometimes called a toxic gain-of-function, shares

<table>
<thead>
<tr>
<th>Etiology of hypothalamic diabetes insipidus in children and adults.</th>
<th>Children (%)</th>
<th>Children and young adults (%)</th>
<th>Adults (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary brain tumor&lt;sup&gt;a&lt;/sup&gt;</td>
<td>49.5</td>
<td>22</td>
<td>30</td>
</tr>
<tr>
<td>Before surgery</td>
<td>33.5</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>After surgery</td>
<td>16</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>Idiopathic (isolated or familial)</td>
<td>29</td>
<td>58</td>
<td>25</td>
</tr>
<tr>
<td>Histiocytosis</td>
<td>16</td>
<td>12</td>
<td>–</td>
</tr>
<tr>
<td>Metastatic cancer&lt;sup&gt;b&lt;/sup&gt;</td>
<td>–</td>
<td>–</td>
<td>8</td>
</tr>
<tr>
<td>Trauma&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2.2</td>
<td>2.0</td>
<td>17</td>
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<tr>
<td>Postinfectious disease</td>
<td>2.2</td>
<td>6.0</td>
<td>–</td>
</tr>
</tbody>
</table>

<sup>a</sup> Primary malignancy: craniopharyngioma, dysgerminoma, meningioma, adenoma, glioma, astrocytoma.

<sup>b</sup> Secondary: metastatic from lung or breast, lymphoma, leukemia, dysplastic pancytopenia.

<sup>c</sup> Trauma could be severe or mild.

Twenty-five percent of the patients developed spontaneous iso-
lated hyponatremia, 20% developed diabetes insipidus, and 46% remained normonatremic. Normonatremia, hyponatremia, and diabetes insipidus were associated with increasing degrees of surgical manipulation of the posterior lobe and pituitary stalk during surgery.

The etiologies of central diabetes insipidus in adults and in children are listed in Table 1 [51–53]. Rare causes of central dia-

betes insipidus include leukemia, thrombotic thrombocytopenic purpura, pituitary apoplexy, sarcoidosis and Wegener’s granu-

lomatosis [54]. A distinctive syndrome characterized by early diabetes insipidus with subsequent progressive spastic cerebel-

lar ataxia has also been described [55]. Five patients who all presented with central diabetes insipidus and hypogonadism as first manifestations of neurosarcoidosis have been reported [56]. Finally, circulating antibodies to vasopressin do not play a role in the development of diabetes insipidus [57]. Antibodies to vaso-

pressin occasionally develop during treatment with ADH and, when they do, almost always result in secondary resistance to its antidiuretic effect [57, 58]. Maghnie et al. [51] studied 79 patients with central diabetes insipidus who were seen at four pediatric endocrinology units between 1970 and 1996. There were 37 male and 42 female patients whose median age at diagnosis was 7 years (range, 0.1 to 24.8 years). In 10 patients, central diabetes insipidus developed during an infectious illness or less than 2 months afterward (varicella in 5 patients, mumps in 3 patients, and measles, toxoplasmosis, and hepatitis B in 1 patient each). Deficits in anterior pituitary hormones were doc-

umented in 48 patients (61%) a median of 0.6 year (range, 0.1 to 18.0 years) after the onset of diabetes insipidus. The most frequent abnormality was growth hormone deficiency (59%), followed by hypothyroidism (28%), hypogonadism (24%), and adrenal insufficiency (22%). Seventy-five percent of the patients with histiocytosis of the Langerhans’ cells had an anterior pitu-

itary hormone deficiency that was first detected at a median of 3.5 years after the onset of diabetes insipidus. The frequency and progression of histiocytosis of the Langerhans’ cells related to anterior pituitary and other nonendocrine hypothalamic dys-

function, and their response to treatment in 12 adult patients has

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mechanistic pathways with other neurodegenerative diseases such as Huntington’s and Parkinson’s.

4.2.1. Wolfram syndrome
Wolfram syndrome, also known as DIDMOAD, is an autosomal recessive neurodegenerative disorder accompanied by insulin-dependent diabetes mellitus and progressive optic atrophy. The acronym DIDMOAD describes the following clinical features of the syndrome: diabetes insipidus, diabetes mellitus, optic atrophy, and sensorineural deafness. An unusual incidence of psychiatric symptoms has also been described in patients with this syndrome. These included paranoid delusions, auditory or visual hallucinations, psychotic behavior, violent behavior, organic brain syndrome typically in the late or preterminal stages of their illness, progressive dementia, and severe learning disabilities or mental retardation or both. Wolfram syndrome patients develop diabetes mellitus and bilateral optical atrophy mainly in the first decade of life, the diabetes insipidus is usually partial and of gradual onset, and the polyuria can be wrongly attributed to poor glycemic control. Furthermore, a severe hyperosmolar state can occur if untreated diabetes mellitus is associated with an unrecognized posterior pituitary deficiency. The dilatation of the urinary tract observed in the DIDMOAD syndrome may be secondary to chronic high urine flow rates and, perhaps, to some degenerative aspects of the innervation of the urinary tract. The gene responsible for Wolfram syndrome located in chromosome region 4p16.1, encodes a putative 890 amino acid transmembrane protein referred as wolframin. Wolframin is an endoglycosidase H-sensitive glycoprotein, which localizes primarily in the endoplasmic reticulum of a variety of neurons including neurons in the supraoptic nucleus and neurons in the lateral magnocellular division of the paraventricular nucleus [76,77]. Disruption of the Wfs1 gene in mice cause progressive beta-cell loss and impaired stimulus-secretion coupling in insulin secretion but central diabetes insipidus is not observed in Wfs1−/− mice [78]. Miner1, another endoplasmic reticulum protein is causative in Wolfram syndrome 2 [79] and WFS1 negatively regulates a key transcription factor involved in ER stress signalling [80].

4.3. Syndrome of hypernatremia and hypodipsia
Some patients with the hypernatremia and hypodipsia syndrome may have partial central diabetes insipidus. These patients also have persistent hypernatremia that is not due to any apparent extracellular volume loss, absence or attenuation of thirst, and a normal renal response to AVP. In almost all the patients studied to date, the hypodipsia has been associated with cerebral lesions in the vicinity of the hypothalamus. It has been proposed that in these patients there is a “resetting” of the osmoreceptor because their urine tends to become concentrated or diluted at inappropriately high levels of plasma osmolality. However, using the regression analysis of plasma AVP concentration versus plasma osmolality, it has been shown that in some of these patients the tendency to concentrate and dilute urine at inappropriately high levels of plasma osmolality is due solely to a marked reduction in sensitivity or a gain in the osmoregulatory mechanism [81,82]. This finding is compatible with the diagnosis of partial central diabetes insipidus. In other patients, however, plasma AVP concentrations fluctuate in a random manner, bearing no apparent relationship to changes in plasma osmolality. Such patients frequently display large swings in serum sodium concentration and frequently exhibit hypodipsia. It appears that most patients with “essential hypernatremia” fit one of these two patterns. Both of these groups of patients consistently respond normally to nonosmolar AVP release signals, such as hypotension, emesis, or hypoglycemia or all three. These observations suggest that (a) the osmoreceptor may be anatomically as well as functionally separate from the nonosmotic efferent pathways and neurosecretory neurons for vasopressin and a hypothalamic lesion may impair the osmotic release of AVP while the nonosmotic release of AVP remains intact; and (b) the osmoreceptor neurons that regulate vasopressin secretion are not totally synonymous with those that regulate thirst.

5. Diabetes insipidus and pregnancy
5.1. Pregnancy in a patient known to have diabetes insipidus
An isolated deficiency of vasopressin without a concomitant loss of hormones in the anterior pituitary does not result in altered fertility, and with the exception of polyuria and polydipsia, gestation, delivery, and lactation are uncomplicated [83]. Patients may require increasing dosages of dDAVP. The increased thirst may be due to a resetting of the thirst osmostat [84]. Increased polyuria also occurs during pregnancy in patients with partial NDI [85]. These patients may be obligatory carriers of the NDI gene [86] or may be homozygotes, compound heterozygotes or may have dominant AQP2 mutations.

5.2. Syndromes of diabetes insipidus that begin during gestation and remit after delivery
Barron et al. [87] described three pregnant women in whom transient diabetes insipidus developed late in gestation and subsequently remitted postpartum. In one of these patients, dilute urine was present despite of high plasma concentrations of AVP. Hyposthenuria in all three patients was resistant to administered aqueous vasopressin. Because excessive vasopressinase activity was not excluded as a cause of this disorder, Barron et al. labeled the disease vasopressin resistant rather than NDI. A well-documented case of enhanced activity of vasopressinase has been described in a woman in the third trimester of a previously uncomplicated pregnancy [88]. She had massive polyuria and markedly elevated plasma vasopressinase activity. The polyuria did not respond to large intravenous doses of AVP but responded promptly to dDAVP, a vasopressinase-resistant analogue of AVP. The polyuria disappeared with the disappearance of the vasopressinase. It is suggested that pregnancy may be associated with several different forms of diabetes insipidus, including central, nephrogenic, and vasopressinase-mediated [85,89–91].
6. Polyuria and nocturia in central diabetes insipidus, nocturnal polyuria in enuretic children

Polyuria could be constant during the day but also present at night: the urine is normally most concentrated in the morning due to lack of fluid ingestion overnight and increased vasopressin secretion during the late sleep period [92]. Neurons in the suprachiasmatic nucleus, the brain biological clock, send axonal projections toward the supraoptic nucleus, one of the hypothalamic nuclei producing vasopressin [3], providing a possible anatomical substrate for the circadian modulation, an osmoregulatory gain during the late sleep period [92]. As a result, the first manifestation of a mild to moderate loss of concentrating ability is often nocturia. However, nocturia is not diagnostic of a defect in concentrating ability since it can also be caused by other factors such as drinking before going to bed or, in men, by prostatic hypertrophy, which is characterized by urinary frequency rather than polyuria. Psychogenic polydipsic patients tend to ingest large amounts of fluid during the day but not at night, therefore nocturia is rarely seen in primary polydipsic patients [93]. The pattern of nocturnal polyuria in enuretic children is similar to that observed in acute sleep deprivation and enuresis in children might be related to the failure of sleep to cause a reflex reduction in arterial pressure and urine production [94,95].

7. Plasma sodium and osmolality in central diabetes insipidus

Plasma sodium and osmolality are maintained within normal limits (136 to 143 mEq/L for plasma sodium; 275 to 290 mOsmol/kg for plasma osmolality) by a thirst-AVP-renal axis [1,2]. Thirst and AVP release, both stimulated by increased osmolality, is a “double negative” feedback system [96]. Even when the AVP component of this “double negative” regulatory feedback system is lost, the thirst mechanism still preserves the plasma sodium and osmolality within the normal range, but at the expense of pronounced polydipsia and polyuria. Thus, the plasma sodium concentration or osmolality of an untreated patient with diabetes insipidus with unlimited access to water may be slightly greater than the mean normal value, and a decrease in plasma sodium and osmolality might be observed in primary polydipsic patients, but these small increases have no diagnostic significance [97]. Polyuric patients should be asked about their thirst and their way to quench it: cold water will quench thirst more effectively in severely polyuric and dehydrated patients, irrespective of their etiology (central vs. nephrogenic). Primary polydipsic patients may tend to absorb large quantities of water ice-cold or not. Glucose-induced osmotic diuresis is more frequent than any cause of non-osmotic polyuria. High plasma glucose levels with polyuria could also be observed in brain-dead patients with diabetes insipidus receiving glucose infusions at a rate exceeding 500 ml/hour which corresponds to the maximum (25 g/hour) possibility for glucose metabolism.

The polyuria observed in post-obstructive diuresis is appropriate representing an attempt to excrete the fluid retained during the period of obstruction [98].

8. Diagnostic work-up for central diabetes insipidus

Excepting the context of brain trauma, brain surgery or long term lithium administration where the diagnosis of polyuria is obvious, a logical approach to the patient with polyuria is to search for arguments supporting known causes of polyuric states. Such arguments may be:

- morphological (brain magnetic resonance imaging), including the presence of a hypothalamic tumour or mass related to a granulomatous or inflammatory process;
- hormonal, suggesting that the posterior pituitary involvement is not isolated but rather associated with other signs of anterior pituitary deficits;
- systemic with the presence of a generalized inflammatory process or pituitary metastasis;
- hereditary with other members of the family affected with central or nephrogenic diabetes insipidus.

An abrupt onset of polyuria in an adult would suggest acquired central diabetes insipidus. Magnetic resonance imaging of the hypothalamic structures and of the posterior pituitary should be obtained to assess the posterior pituitary normal “bright spot”, a possible surrogate of the posterior pituitary vasopressin content, and any accompanying lesions. Clinical and biochemical indices of associated anterior pituitary/hormone deficiency should also be obtained [51] since additional deficits in anterior pituitary hormones were documented in 61% of patients, a median of 0.6 years after the onset of diabetes insipidus. The most frequent abnormality was growth hormone deficiency (59%) followed by hypothyroidism (28%), hypogonadism (24%), and adrenal insufficiency (22%). Seventy-five percent of the patients with Langerhans cell histiocytosis had an anterior pituitary hormone deficiency that was first detected a median of 3.5 years after the onset of diabetes insipidus.

In this context, the dehydration test is rarely necessary and only recommended for patients with isolated polyuria, a normal pituitary stalk and hypothalamic region on magnetic resonance imaging and with no familial history of polyuria. If plasma osmolality and/or sodium concentration under conditions of ad libitum fluid intake are above 295 mmol/kg and 143 mmol/L, the diagnosis of primary polydipsia is excluded [99].

Water restriction tests have been described in detail elsewhere [100]. If severe polyuric symptoms and signs are documented, water should be restricted only to two to four hours during day-time in infants, plasma sodium should be available every two hours during testing and should not exceed 145–148 in children and adults since a maximal endogenous vasopressin stimulation (more than 3.5 pg/mL) should occur at this level with a maximal urine osmolality response (higher than 800 mOsm/kg H2O). If delays of more than 60 minutes are encountered to obtain plasma sodium or urine osmolalities during dehydration tests, these tests...
should be done in other institutions where almost immediate laboratory reports are obtained after blood samplings. Much progress has been accomplished since the identification of a single base deletion in the vasopressin gene as a cause of autosomal recessive diabetes insipidus in the Brattleboro rat [41]. Early molecular detection of hereditary central diabetes insipidus cases is highly recommended [67].

Disclosure of interest

The author declare that he has no conflicts of interest concerning this article.

References


