Endocrine Therapies

Central Diabetes Insipidus

Assunta Albanese
Nirit Braha

Editor:
P. M. Holterhus

Kindly supported by FERRING Arzneimittel GmbH. On the content and design of this book FERRING Arzneimittel GmbH has no control and bears no responsibility.

Impressum

Herausgeber: Prof. Dr. P. M. Holterhus

Gesamtherstellung: biomedpark Medien GmbH
Schneidmühlstr. 21, 69115 Heidelberg
Tel. 06221/13 747 0
www.biomedpark.de

ISBN: 978-3-9816544-6-2

1. Auflage, Heidelberg 2016

Endocrine Therapies

Central Diabetes Insipidus

Assunta Albanese
Nirit Braha

Editor:
P. M. Holterhus

IMPORTANT NOTE:

Editors and authors have bestowed great care of this work, that the information provided in this publication reflect the current state of knowledge. However, the findings in medicine changes constantly through research and clinical experience. Authors, editors and publishers ask for understanding that they cannot assume any liability for the correctness and completeness of the information of any information in this book. Furthermore, the information does not supersede the individual judgment and decision of the doctor.

Foreword by the editor

This booklet/eBook in the series "Endocrine Therapies" („Endokrinologische Therapien") is the second one to be published in English. This decision was made in order to approach a broader international readership in the field of Paediatric Endocrinology. For this second English booklet/eBook, we decided to choose the topic "diabetes insipidus". It is an endocrine condition with which Pediatric Endocrinologists are frequently faced but which can be a considerable diagnostic challenge with many critical pitfalls. Therefore, a very well structured, step-wise diagnostic approach is indispensable for successful clinical management. I am very happy that I could convince Dr. Assunta Albanese, MPhil, FRCPCH, and her colleague Dr. Nirit Braha, MSc, MRCPCH from UK, to contribute this manuscript on "diabetes insipidus".

I personally know Dr. Assunta Albanese from many previous occasions where she gave excellent lectures on the diagnosis, treatment and follow up of diabetes insipidus to international fellows and consultants in Paediatric Endocrinology. I was particularly enthusiastic about her outstanding didactic abilities to teach this topic. Dr. Albanese trained in Medicine and Paediatrics at the University of Florence (Italy). She was a Research Fellow at the Institute of Child Health (London) for three years. Her postgraduate thesis was based upon "Constitutional Delay of Growth and Puberty". In 1999, she was appointed as Consultant in Paediatric Endocrinology at St George's and at the Royal Marsden NHS Foundation Trust where she runs the late effect endocrine service for oncological children. Her longstanding clinical prac-

tice includes general endocrinology, with a particular interest in disorders of growth and puberty, diabetes insipidus and hyponatraemia and endocrine late effects of cancer and its treatment. Dr. Albanese has published 69 manuscripts. She is a regular invited lecturer at National and International Conferences.

Dr. Albanese wrote this article together with her clinical fellow, Dr. Nirit Braha. She trained in Medicine at Guy's, King's & St. Thomas' School of Medicine, King's College London, UK. Dr. Braha is currently completing her training in Paediatrics. She has been involved in the clinical management of many complex cases of children with diabetes insipidus during her training in Paediatric Endocrinology and has gained an invaluable experience which has been incorporated in this review article.

Both authors together provide successfully a highly clinically useful up-to-date extract of diabetes insipidus in Paediatric Endocrinology. They cite the important key references in the field but they do not forget to deliver their rich clinical experience which has always been a typical feature of this series of booklets/eBooks.

Paul-Martin Holterhus

Foreword

Central diabetes insipidus is a potentially dangerous yet treatable condition, which often poses a diagnostic and therapeutic challenge.

Patients classically present with troubling polyuria and polydipsia. They are at risk of hypernatraemic dehydration in the event of trauma, intercurrent illness or general anaesthesia. They can benefit enormously from timely diagnosis and initiation of treatment with desmopressin.

Importantly, the diagnosis of central diabetes insipidus may be the first indication that significant pituitary pathology is present, from congenital abnormalities to malignancy and neurosarcoidosis.

This booklet/eBook offers a practical guide to the diagnosis, further investigation and treatment of central diabetes insipidus.

Assunta Albanese & Nirit Braha

Table of contents

Introduction

Central diabetes insipidus (CDI) is characterised by persistent polyuria and polydipsia. It is caused by an inability to secrete vasopressin in response to rising plasma osmolality.

In addition to its effects on daily life, CDI can result in rapid dehydration during intercurrent illnesses or if water is withheld or unavailable.

Here, we discuss the regulation of water balance, the aetiology of CDI, and an approach to clinical diagnosis and management.

Regulation of Water Balance

Water balance is determined by fluid intake, prompted by thirst, and by water retention or elimination by the kidneys through the actions of vasopressin and the renin-angiotensin system. Water balance is also affected by insensible losses through the skin, respiratory tract and gastrointestinal tract.

Plasma osmolality is an estimation of the osmolar concentration of plasma and is proportional to the number of particles per litre of solution. It is usually kept in a range of 282–295 mOsm/kg H_2O.[1] When water losses exceed intake, the water balance is negative and plasma osmolality rises.

Vasopressin

Vasopressin is a small peptide, nine amino acids in length. It is released by the posterior pituitary gland and regulates plasma osmolality by controlling the excretion of free water by the kidneys.[2]

Osmosensing neurons in the lamina terminalis and subfornical organs communicate with magnocellular neurons in the supraoptic and paraventricular nuclei of the hypothalamus.

In addition, baroreceptors in the left atrium, pulmonary vessels, aortic arch and carotid sinus detect changes in arterial blood pressure and blood volume and send signals via the vagus and glossopharyngeal

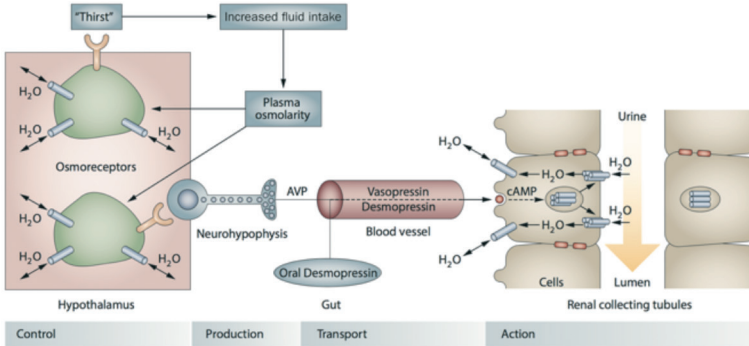


Figure 1: Vasopressin Synthesis, Release and Actions
Adapted from Robertson GL (2011)[3]

nerves to the brainstem. These are relayed to the magnocellular neurons of the hypothalamus.

In the hypothalamus, the magnocellular neurons synthesise preprovasopressin. Preprovasopressin is transported in neurosecretory granules from the neuronal cell body in the hypothalamus towards the axon terminal in the posterior pituitary. During this process, the prohormone is cleaved from neurophysin II and copeptin and amidated at its C-terminus, producing vasopressin. Vasopressin is stored at the nerve terminals until it is released into the bloodstream following neuronal activation (Figure 1).[3]

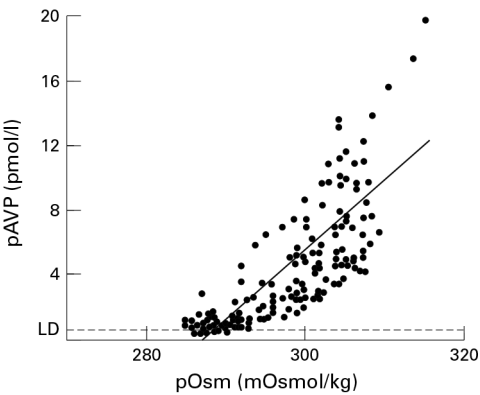
Vasopressin acts on the kidneys, binding to V2 receptors on the cell membranes of the collecting duct cells. It raises cell permeability to water by increasing the number of water channels known as aquaporins on the cell membrane. Aquaporins allow water to move down the osmotic gradient, out of the nephron into the bloodstream, increasing the amount of water reabsorbed into the bloodstream and concentrating the urine (Figure 1).[1, 3]

Vasopressin release is generally initiated at a plasma osmolality of approximately 280 mOsm/kg and suppressed when plasma osmolality falls below this threshold. Above 280 mOsm/kg, a 1% increase in plasma osmolality increases plasma vasopressin secretion by approxi-

mately 1 pg/mL. Maximally concentrated urine is produced at a plasma vasopressin concentration of 2–4 pg/mL[1] – though vasopressin may be secreted in concentrations as high as 20 pg/mL[4,5] (Figure 2).

Thirst

Thirst, the "conscious sensation of the need to drink", is stimulated by increases in plasma osmolality, detected by osmoreceptors in the thirst centre of the anterior hypothalamus, and by reductions in blood volume or blood pressure.[6, 7]



The solid line represents the mean regression between the two variables, defined by pAVP = 0.41 pmol/L (plasma osmolality – 285 mOsm/kg). LD represents the limit of detection of the assay (0.3 pmol/L).

Figure 2: Relationship between plasma arginine vasopressin (pAVP) concentration and plasma osmolality (pOsm) in a group of healthy subjects

Reproduced with permission from Baylis PH & Cheetham T (1998)[1]

Crucially, the set point for thirst is at a plasma osmolality 10 mOsm/kg higher than the threshold for vasopressin secretion. This is thought to provide a window for vasopressin-related regulation of plasma osmolality, above which thirst is initiated.[7] However, minor variations in the relationship between thirst sensation and plasma osmolality have been reported, and some researchers have not identified this window in human or animal studies.[6]

Although the sensation of thirst is satisfied by drinking before sufficient water has been absorbed from the gut to normalise plasma osmolali-

ty, this relief is short-lived unless the disturbance in plasma osmolality, blood pressure or blood volume has been corrected.[6]

In primary or psychogenic polydipsia, individuals may drink for other reasons, including social cues, pleasurable taste, hunger or dry mouth due to anxiety or medication. These patients may also have other behavioural difficulties. When water intake exceeds requirements, plasma vasopressin concentrations decrease to undetectable levels, allowing excretion of the excess water in the urine.

Central Diabetes Insipidus

In diabetes insipidus, large amounts of dilute urine are produced, leading to polydipsia. In CDI, polyuria is due to a deficiency in vasopressin secretion; nephrogenic diabetes insipidus results from a lack of renal response to vasopressin.

CDI may be congenital or acquired. Common causes are listed in Table 1, below.

Table 1: Causes of Central Diabetes Insipidus

* There is now evidence that some cases thought to be idiopathic may in fact have an autoimmune aetiology.[8]

Category	Conditions
Idiopathic*	
Cerebral Malformations	Septo-optic Dysplasia Holoprosencephaly Midline Craniofacial Defects Pituitary Agenesis
Familial	AVP-NPII Gene Mutations – mostly autosomal dominant inheritance, X-linked recessive inheritance also seen – leading to defective pro-hormone synthesis and AVP deficiency DIDMOAD Syndrome (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy, Deafness)
Neoplasia	Craniopharyngioma Germinoma Pinealoma Leukaemia/Lymphoma
Infections	Bacterial Meningitis Viral Encephalitis Congenital Cytomegalovirus and Toxoplasmosis Tuberculosis
Autoimmune, Inflammatory and Infiltrative Processes	Langerhans Cell Histiocytosis Systemic Lupus Erythematosus Neurosarcoidosis Lymphocytic Neurohypophysitis
Trauma	Head Trauma Hypoxic Injury Neurosurgery
Vascular	Intracranial aneurysms Reduced blood flow to the posterior pituitary gland, aetiology uncertain

Diagnostic Approach to Central Diabetes Insipidus

Signs and Symptoms

CDI classically presents with polyuria and polydipsia. Polyuria may be defined as the passage of large volumes of dilute urine, above 2 L/m^2/24 h, or approximately 40 ml/kg/24 h in older children and adults.[1] Patients report persistent thirst and increased fluid intake throughout the day and night and may experience secondary nocturnal enuresis. They typically crave cold water.

Patients with CDI are usually able to maintain water balance and normonatraemia by increasing their fluid intake. They are at risk of hypernatraemic dehydration when they are denied access to water, for example, when fasted for surgery, or during episodes of gastroenteritis. Similarly, patients with impaired thirst responses, or who are unable to express their thirst may also develop hypernatraemic dehydration.

Glucocorticoids are required for renal excretion of water. Thus, symptoms of diabetes insipidus may be masked by ACTH (adrenocorticotrophic hormone) deficiency, and only become apparent when corticosteroid replacement therapy is started.[9]

Useful Questions to Ask in History-taking

- Fluid intake and Thirst
  - How much fluid do you drink in a day?
  - What kinds of fluids do you drink? – Note that intake of sugary or caffeinated drinks may cause diuresis.
  - Do you ever feel tempted to drink water from unusual places, such as the sink or the toilet?
- Urine output
  - What does your urine look like?
  - Are you passing large or small amounts of urine each time?
  - What color is the urine that you pass first thing in the morning?
- How does this affect your daily life?
  - Do you wake up at night to drink water and pass urine? How often?
  - Does your thirst or need to pass urine interfere with your daily activities or sleep?

- Onset
  - Did this start suddenly or gradually? – Note that loss of up to 90% of normal vasopressin secretion can occur without overt clinical manifestations: further loss results in onset of polyuria and polydipsia, so patients may perceive a sudden onset of symptoms.
- Family history
  - Does anyone else in the family have a similar problem?
- Red flags
  - Have you been experiencing any headaches, visual disturbances, seizures or funny turns?
  - Have you found that you bleed or bruise more easily than usual, or had any pain in your limbs or back?
  - Have you been experiencing any joint pain, rash or cough?
  - Have you had any recurrent fevers or swollen glands?
- Medication
  - Are you taking any regular medication?

During history-taking, it is also important to look for signs and symptoms of infection and malignancy, including intracranial pathology, leukaemia and lymphoma – some questions looking for red flag symptoms are outlined above – and to ask about any medication a child is taking which might result in vasopressin resistance. Examples include Lithium, Demeclocycline, Amphotericin B, Gentamicin, Colchicine, Foscarnet, Vincristine and Cyclophosphamide.[6, 10, 11]

Initial Investigations

If polyuria and polydipsia have been established during the history-taking, further investigation is required.

Meanwhile, parents should be advised not to restrict the patient's fluid intake until a diagnosis has been reached. They should be advised to offer only water, and avoid other fluids such as juice, soft drinks and milk. This may normalize fluid intake if the polyuria and polydipsia have been driven by primary polydipsia, soft drinks, caffeinated drinks or a high osmotic load.

The patient or their parents should be asked to measure and record how much fluid the patient drinks during each 24 hour period.

Some baseline investigations should be performed and the results reviewed before a water deprivation test is conducted.

Baseline Investigations in Polyuria and Polydipsia

1. An early morning urine sample should be tested for osmolality. A paired serum sample should be sent for urea and electrolytes and osmolality. In patients who do not drink at night, this is likely to be the most concentrated urine of the day.
2. Fasting glucose, serum calcium and potassium concentrations and thyroid function (free T4 and Thyroid Stimulating Hormone) should be tested to exclude other common causes of polyuria, including diabetes mellitus, hypercalcaemia, hypokalaemia and thyrotoxicosis.

Interpretation of Baseline Investigations

– A diagnosis of diabetes insipidus is made when the serum osmolality is > 300 mOsm/kg, or serum sodium > 145 mmol/L, and the urine is not appropriately concentrated (< 600 mOsm/kg).
– A urine osmolality of > 750 mOsm/kg excludes diabetes insipidus.
– If the plasma osmolality is normal and the urine osmolality is < 750 mOsm/kg, a water deprivation test is required to confirm or exclude a diagnosis of DI.
– In patients with a normal plasma osmolality who do not tend to drink at night and have an intermediate early morning urine osmolality (600–750 mOsm/kg), it is reasonable to send another early morning urine sample following a night during which the patient spontaneously did not drink, rather than immediately proceeding to a water deprivation test. This does not apply in cases where the patient does tend to drink during the night.
– Low plasma and urine osmolalities are more consistent with a diagnosis of primary polydipsia then DI.

Water Deprivation Test

A water deprivation test (WDT) is used to differentiate diabetes insipidus from primary polydipsia, by establishing whether a patient with polyuria and polydipsia can concentrate their urine appropriately in the face of water deprivation.

If the first stage of the test confirms diabetes insipidus, desmopressin is administered and monitoring continued to distinguish between central and nephrogenic diabetes insipidus.

Ensuring an Eucortisolaemic State

Since cortisol is required for the excretion of water, diabetes insipidus can be masked by cortisol insufficiency. The patient's cortisol status should ideally be assessed prior to the water deprivation test.

Water Deprivation Test Procedure

1. For safety reasons, a WDT should only be performed in a hospital setting where the patient can be closely monitored.
2. On the morning of the test, the patient should empty their bladder on waking, prior to a dry breakfast.
3. If they have had no fluids overnight, this urine should be sent for estimation of urine osmolality. Otherwise, it should be discarded.
4. The test should begin at 08:30 am, when fluid intake is stopped.
5. The patient's weight, heart rate and blood pressure should be checked at baseline and then hourly. Each time, their weight should be measured with the patient wearing the same clothes, using the same scales.
6. The threshold of 5% weight loss should be calculated and documented in advance, so it may be easily recognised during the test.
7. All urine produced should be collected. The timing, volume and specific gravity of the urine should be recorded at the bedside. An aliquot of each urine sample should be sent to the laboratory for urine osmolality, together with a serum sample sent to measure serum sodium and osmolality.
8. Especially in young children, capillary glucose should be monitored after 7 hours of fasting, or at any time should symptoms of hypoglycaemia develop.

Clinical observations and laboratory results should be tabulated. An example is shown in Table 2.

Table 2: Water Deprivation Test

Time (hrs)	Serum Sodium (mmol/L)	Serum Osmolality (mOsm/kg)	Urine Specific Gravity	Urine Osmolality (mOsm/kg)	Urine Volume	Heart Rate	BP (mmHg)	Weight (kg)
0								
1								
2								
3								
4								
5								
6								
7								

Top Tips for the Smooth Running of Water Deprivation Tests

- If the history clearly suggests that the patient can comfortably go for a certain period of time without drinking, they may be fluid restricted for that length of time before the test begins. Otherwise, fluid restriction should not begin until 8:30 am when the test should start.
- Patients with diabetes insipidus who are deprived of water may experience an intense desire to drink from unusual sources, including the toilet, so they should never be left alone. Parents or nursing staff should closely supervise the patient for the duration of the WDT. A sudden dilution in urine osmolality can be suggestive of unauthorised intake of fluids.
- Liaison with the biochemistry laboratory should take place beforehand so that samples will be processed urgently and results communicated to the medical team as soon as they become available.
- Desmopressin should be ordered from pharmacy in advance so that it will be available for the patient if necessary.
- The WDT is usually expected to last 7 hours, but to avoid making a diagnosis based on a single borderline set of values or ending the test without diagnostic results, the test may be prolonged, unless the patient's vital signs suggest hypovolaemia.

– If the patient's weight falls by 5% from the starting weight, but they are haemodynamically and biochemically stable, the test can be continued.
– An inability to pass urine or very low urine output during the test, while the patient is clinically stable, is suggestive of normal urinary concentrating ability and therefore a good indication to continue the test.
– With young children, it is often impossible to obtain precisely timed urine samples. Therefore, all urine samples given should be collected and sent for osmolality testing.
– Where the patient wears nappies, adhesive urinary collection bags or urinary bags with drainage tubes can be used. The child's dry nappies should be weighed before starting the test, and the child should wear a nappy over the urinary collection bag, so that if there is a leak from the bag, the urine volume can be calculated using the weight of the nappy and bag. In unusual situations where sampling is very difficult, urinary catheterisation may be considered.

Water Deprivation Test Interpretation

Normal Response:

- Urine osmolality > 750 mOsm/kg

  or

- Urine osmolality > 600 mOsm/kg and stable for 2 consecutive hours

The test can be stopped as the patient does not have diabetes insipidus.

Abnormal Response:

- Serum osmolality > 300 mOsm/kg and urine osmolality < 600 mOsm/kg

The test can be stopped as this is diabetes insipidus. The DDAVP test is needed to differentiate central from nephrogenic diabetes insipidus.

Uncertain Response:

- If the maximal urine osmolality is between 450-600 mOsm/kg and plasma osmolality < 300 mOsm/kg

  and

- The WDT cannot be extended further

The diagnosis is probably primary polydipsia or partial diabetes insipidus.

Dealing with Uncertain Results from the Water Deprivation Test

After prolonged polyuria of any cause, including primary polydipsia, the renal interstitium is diluted, and the osmotic gradient across the distal renal tubular cell, essential for the action of vasopressin, is reduced.[1] The kidneys do not respond well to vasopressin during the WDT or to desmopressin in the DDAVP test, irrespective of the underlying cause of the polyuria. The measurement of plasma AVP (arginine vasopressin) and/or copeptin levels can be helpful but only if taken at a time when the plasma osmolality is > 295 mOsm/kg.

Otherwise, if the brain MRI (magnetic resonance imaging) scan demonstrates normal hypothalamic and pituitary morphology, and the pituitary "bright spot" is present, which is suggestive of the presence of pre-formed vasopressin, gradual fluid restriction over 7–10 days under close supervision may be indicated. Careful monitoring including daily early morning paired plasma and urine osmolality, blood pressure, heart rate and weight is needed.

This will either unmask a partial diabetes insipidus or demonstrate normal urinary concentrating ability when a normal daily fluid intake is achieved and the patient remains eunatraemic.

An alternative approach is to perform the hypertonic saline infusion test. This test can help distinguish partial central diabetes insipidus from primary polydipsia, particularly where the water deprivation test is inconclusive, or serious behavioural problems prohibit its use.[12] A hyperosmolar state is induced using a hypertonic saline infusion and the AVP response is measured. Further detail may be found in the paper entitled *Hypertonic saline test for the investigation of posterior pituitary function* by Mohn, Acerini, Cheetham et al.[12]

Desmopressin or DDAVP Test

The Desmopressin or DDAVP test is used to distinguish between CDI and nephrogenic diabetes insipidus (NDI) in patients who have been unable to concentrate their urine in response to water deprivation.

DDAVP Test Procedure

1. The DDAVP (Desmopressin Acetate) test should be performed the morning after the WDT. It can also be performed at the end of the WDT if the WDT is completed by the early afternoon.
2. The patient may take a light meal before commencing the DDAVP test and is not allowed to drink during the first hour. Afterwards, they may drink fluids in volumes strictly equal to the previous hour's urine output.

   However, if the test is being performed at the end of the WDT, the patient may also drink fluids in volumes strictly equal to the previous hour's urine output in the first hour following the administration of DDAVP.
3. The bladder should be emptied before administering DDAVP.
4. DDAVP should be administered intramuscularly. Doses are shown in Table 3.
5. Over the following four hours, monitor at hourly intervals:
   - Patient's weight, blood pressure, heart rate and thirst sensation
   - Urine volume, specific gravity and osmolality
6. The test ends four hours after DDAVP administration.
7. At the end of the test, samples for plasma sodium and osmolality and urine osmolality are collected and sent.
8. The patient should then be observed in hospital for 12 hours, with careful monitoring of fluid balance to ensure that they do not develop either water intoxication or dehydration.
9. Serum urea and electrolytes and osmolality, together with urine osmolality should be checked at 12 hours after the end of the DDAVP test and also on the following morning.

Table 3: DDAVP Doses for the DDAVP Test

Age	Intramuscular DDAVP dose
< 2 years	400 nanograms
2–12 years	0.5–1 micrograms
12–18 years	1–2 micrograms

In our centre, we use the intramuscular route for the WDT, other protocols have been published.

Top Tips for the Smooth Running of the DDAVP Test

- DDAVP can be administered nasally or intramuscularly but many clinicians prefer the latter route as it provides more certainty that the drug has been administered and absorbed.
- To avoid water intoxication at the end of the DDAVP test, the patient should only be allowed to drink maintenance fluids plus replacement of any fluid deficit over the following 12 hours.

Interpretation of the DDAVP Test

Central Diabetes Insipidus:

- If the urine/plasma osmolality ratio >1.5

or

- >50% increase in urinary osmolality and reduction in urine volume are seen in the 4 hours after DDAVP[13]

Nephrogenic Diabetes Insipidus:

- <10% increase in urinary osmolality is seen during the four hours after DDAVP administration[14]

Uncertain Response:

- A 10–50% increase in urine osmolality is seen

Partial nephrogenic diabetes insipidus

or

Longstanding central diabetes insipidus: Prolonged vasopressin deficiency can cause down-regulation of Aquaporin-2 channels in the renal collecting tubules, leading to a diminished renal response to DDAVP.[13]

Dealing with Equivocal Results from the DDAVP Test

A therapeutic trial of DDAVP may be performed, whereby a patient is given a small dose of subcutaneous or intramuscular desmopressin daily for 7–10 days with close monitoring of fluid balance and serum sodium concentrations and paired plasma and urine osmolality.[1]

In CDI, the medullary tonicity will gradually re-establish and the response to DDAVP will improve.

In partial NDI, there may be no significant response to this dose of DDAVP but a larger dose may be sufficient to elicit a response.[13]

Management of Central Diabetes Insipidus

Once the diagnosis of CDI has been made, thorough investigation is required, as there is a high probability of identifying a pathological cause.[14]

1. Magnetic Resonance Imaging

MR imaging of the brain and pituitary gland is vital to:

- Identify an underlying tumour or malformation
- Confirm the presence or absence of the posterior pituitary "bright spot"
- Measure the thickness of the pituitary stalk
- Examine the size and morphology of the anterior pituitary

MRI should be performed before and after enhancement with Gadolinium diethylenetriamine pentaacetic acid.[15]

If initial imaging does not reveal the aetiology of the diabetes insipidus, repeat MRI at intervals of 4–6 months is recommended for the following 2 years, followed by annual MRI scans for 3 years.[14]

Posterior pituitary "bright spot"

The posterior pituitary "bright spot" is a characteristic hyperintense signal on T1-weighted imaging of the posterior pituitary. This is thought to represent vasopressin contained in neurosecretory granules, and is consistent with functional integrity of the posterior pituitary gland.[16]

In CDI, due to reduced vasopressin secretion, the posterior "bright spot" is often absent, or if present, is small and tends to disappear with time on subsequent imaging.[14, 16]

In NDI, the pituitary bright spot is often present, but may also be reduced or absent due to enhanced vasopressin release. Conversely, in CDI due to inactive vasopressin and in primary polydipsia, the signal is normal or increased in size and intensity.[14, 17]

Pituitary Stalk Thickening

In approximately one third of children with CDI, thickening of the pituitary stalk, defined as exceeding 3 mm, is seen on MRI.[14, 16] Pituitary stalk thickening is not a specific finding and may, for example, be seen in lymphocytic hypophysitis as well as in pituitary germinoma. It may also increase or resolve over time.[14, 16, 17]

A progressive increase in stalk thickness or increase in the size of the anterior pituitary should alert physicians to the possibility that a germinoma may be present. Conversely, a subsequent decrease in the stalk thickness may suggest an inflammatory or autoimmune aetiology.[16, 17]

Biopsy should be reserved for patients with progressive thickening of the pituitary stalk, for patients with severe thickening of the pituitary stalk (above 6.5 mm), or who have other radiological abnormalities, such as enlargement of the anterior pituitary or third ventricle involvement.[14, 16]

Given the high risk of identifying a pathological cause of central diabetes insipidus, MRI follow-up every 4–6 months, is recommended in patients with pituitary stalk thickening.[14]

If, after 2 years, there has been no progression, imaging frequency may be reduced to annual MRI for a further 3 years.[14]

Please see Table 4 for a summary of MRI findings and management recommendations.

Table 4: Clinical Management Following Diagnosis of Central Diabetes Insipidus
Adapted from di Lorgi N et al. (2012)[14]

Pituitary Stalk Size and Other MRI Findings	Baseline Investigations	MRI Follow-up	Biopsy?
Normal pituitary stalk (1.0 – 3.0 mm) **Or** Minimal pituitary stalk thickening (3.1 – 3.9 mm)	Anterior pituitary function testing in all patients. If there are additional symptoms and signs or progression is seen on follow-up MRI, perform investigations as for patients with moderate or severe pituitary stalk thickening, below.	MRI every 4–6 months. If no progression has been seen after 2 years, MRI frequency may be reduced to annual scans for a further 3 years.	Not required.
Moderate pituitary stalk thickening (4.0 – 6.5 mm) **Or** Severe pituitary stalk thickening (> 6.5 mm) **With or without:** • Enlargement of the anterior pituitary gland • Third ventricle involvement	In all patients: • Anterior pituitary function testing • Serum tumour markers • Inflammatory markers • Angiotensin Converting Enzyme levels • Cerebrospinal fluid cytology and tumour markers • Skeletal survey • Chest X-ray • Ophthalmic review Consider: • Computed Tomography (CT) Chest scan • Bone scan • Extracranial biopsy • Ear, nose and throat assessment • Dermatology assessment • Any other test clinically indicated	MRI every 4–6 months	Consider biopsy if progression on MRI, concerning clinical features or abnormal baseline investigations. Lower threshold for biopsy in patients with: • Thicker stalk measurements • Anterior pituitary enlargement • Third ventricle involvement

2. Anterior Pituitary Function Testing

The majority of patients with CDI will have associated anterior pituitary deficits, of which Growth Hormone (GH) deficiency is the commonest form.[18, 19]

A study by Werny et al.[18] of 147 children with CDI evaluated at Seattle Children's Hospital found that 60% had GH deficiency, 59% had TSH deficiency and 57% had ACTH deficiency. However, patients with genetic or familial CDI did not have associated anterior pituitary dysfunction.

Following a diagnosis of CDI, patients' anterior pituitary function should therefor be evaluated. This may involve baseline or dynamic pituitary test, to assess their GH/IGF-1 (Insulin-like Growth Factor) axis, hypothalamic pituitary-adrenal axis, pituitary-gonal axis, thyroid function and prolactin concentration.

Since anterior pituitary deficits may evolve over time, surveillance should continue, even if the initial results are normal. At each appointment, children's weight and height should be plotted on a growth chart and pubertal staging assessed.

3. Tumour Markers

Suprasellar tumours causing endocrine dysfunction include craniopharyngiomas and germ cell tumours. Germ cell tumours include germinomas, which are relatively rare, but respond well to chemotherapy and irradiation, and non-germinomatous germ cell tumours, (NGGCT) which carry a worse prognosis.[20]

α-fetoprotein (AFP) and β-human chorionic gonadotrophin (HCG) are helpful in the diagnosis, prognosis and monitoring of patients with germ cell tumours. They can also help differentiate germinomas from NGGCT.[20]

In general, elevated serum or cerebrospinal fluid (CSF) AFP concentrations, and high HCG concentrations are strongly predictive of NGGCT. However, HCG can also be moderately raised in germinoma.[20]

Therefore, if a thickened pituitary stalk is visualized on MRI, serum and CSF samples should be sent for HCG and AFP as well as for CSF cytology.

However, a negative result for tumour markers does not exclude NGGCT[20] so ongoing clinical and MRI follow-up is still required. Liaison with Paediatric Oncology is recommended.

4. Autoantibodies

Vasopressin cell autoantibodies (AVPc-Abs) have been identified in up to 75% of children and young adults with idiopathic CDI and can be associated with pituitary stalk thickening.[21–23] This is suggestive of an autoimmune aetiology.

However, AVPc-Abs have also been identified in patients with Langerhans Cell Histiocytosis and germinoma, so even where autoantibodies are present, close clinical and MRI follow-up are still required.[21, 23]

5. Genetic Testing

The AVP-NPII gene is located on chromosome 20p13. The AVP-NPII gene product is synthesised as a pre-prohormone, including AVP peptide, the carrier protein neurophysin-II (NPII) and co-peptin.[22]

Numerous mutations have been identified which lead to a defective pre-hormone and vasopressin deficiency in familial CDI, most of which show autosomal dominant inheritance,[22] though autosomal recessive and X-linked recessive inheritance patterns have also been documented.[24]

Genetic testing following a diagnosis of CDI may be helpful where there is a strong familial history and where no other cause of CDI has been identified.

6. The Search for Extracranial Lesions

Where a cause for CDI has not been found, or LCH is suspected on clinical grounds, dermatology review, chest X-ray, skeletal survey and ear, nose and throat examination are recommended. This may reduce the need for intracranial biopsies.[22]

Other causes of CDI, such as vascular abnormalities, leukaemia with central nervous system (CNS) involvement, CNS tuberosclerosis, neurosarcoidosis and Wegener's granulomatosis should also be considered and investigations performed as appropriate.[22]

7. Treatment with DDAVP

Patients with intact thirst responses and unlimited access to water will be able to drink sufficiently to avoid dehydration and maintain normal serum osmolality and high-normal serum sodium concentrations. This

comes at the expense of marked polyuria and polydipsia, which can interfere with activities of daily living and night-time rest.

DDAVP, or desmopressin, is the treatment of choice for CDI. It is a synthetic analogue of arginine vasopressin and has a prolonged antidiuretic action with minimal pressor effects. Treatment is aimed at alleviating symptoms of polyuria and polydipsia. However, once a day, pre-dose breakthrough polyuria should be encouraged to avoid water intoxication.

If hyponatraemia occurs during DDAVP therapy, particularly during intercurrent acute illness in patients with coexisting hypocortisolism, the DDAVP dose should be withheld until the patient becomes polyuric and their serum sodium normalises. If DDAVP is continued or there is ongoing replacement of excreted free water, cerebral oedema can ensue.

Patients and parents should be advised that water intake should be guided solely by thirst, and to avoid incidental or social drinking. They should be warned of the risk of water intoxication and educated about its signs and symptoms.

Desmopressin treatment should be initiated with the lowest dose that gives the desired antidiuretic effect. The maximum effect may not be seen until 1–2 days after the first dose, as the renal concentrating capacity may be reduced by chronic water diuresis.

Desmopressin may be given orally, sublingually, intranasally or parenterally – see Table 5. Desmopressin should be commenced once daily in the evening at first, and then at an increased dosage and frequency according to daily fluid intake/output. There is broad inter-individual variation in the dosage and administration frequency required to control thirst and diuresis.

If, for any reason, the route of administration needs to be changed, the dosages of the different forms of DDAVP are *not* directly interchangeable.

Unfortunately, treatment is usually life-long: even when the underlying cause has been eliminated, recovery of vasopressin secretion is uncommon.

Table 5: Starting Doses of Desmopressin by Age and Route of Administration
Source: British National Formulary – Children[25]

Route of Desmopressin Administration	Age range	Initial dose – adjusted according to response
Oral (Desmopressin Acetate)	Neonate	1–4 micrograms 1–3 times daily
	Child 1 month–2 years	10 micrograms 1–3 times daily
	Child 2–12 years	50 micrograms 1–3 times daily
	Child 12–18 years	100 micrograms 1–3 times daily
Sublingual (Desmopressin Base)	Child 2–18 years	30–60 micrograms 1–3 times daily
Intranasal (Desmopressin Acetate)	Neonate	100–500 **nanograms**
	Child 1 month–2 years	2.5–5 micrograms 1–2 times daily
	Child 2–12 years	5–20 micrograms 1–2 times daily
	Child 12–18 years	10–20 micrograms 1–2 times daily
Subcutaneous or intramuscular injection (Desmopressin Acetate)	Neonate	100 **nanograms** once daily Intramuscular route only
	Child 1 month–12 years	400 **nanograms** once daily
	Child 12–18 years	1–4 micrograms once daily

Challenging Situations

Hypodipsic and Adipsic Patients with CDI

CDI with hypodipsia or adipsia may result from congenital midline CNS malformations, hypothalamic surgery, head trauma, suprasellar malignancy or ruptured intracranial aneurysms.

Management is more difficult because patients cannot spontaneously adjust their fluid intake to compensate for changes in urine output and often have concomitant cognitive dysfunction.

The most practical approach is to set a fixed dose of DDAVP and obligatory urine output, varying fluid intake to achieve water balance.[26] Fluid intake is adjusted according to changes in diet, ambient temperature, illness or physical activity.

This approach requires daily weights with regular re-calibrations to allow for growth; monitoring of urine output and weekly measurements of plasma sodium.[26] The latter can be performed using point-of-care test kits at home, to reduce the number of hospital attendances for blood tests. The family will need to be educated about the treatment regimen and have flexible access to appropriate advice.

Infants with CDI

Neonates and young infants need large fluid intakes to meet their calorie requirements and are at risk of water intoxication and hyponatraemia when DDAVP is added and they cannot eliminate their water load.[27] Death has been reported related to a hyponatraemic seizure in an infant treated for CDI with DDAVP.[28]

As before, small doses of DDAVP should be used initially, starting with once daily administration, perhaps starting in the evening if the frequency of feeding is less at night than during the daytime.[28] DDAVP dose and frequency may be increased as needed to maintain serum sodium in the normal range.

Alternatively, infants with CDI can be managed without the use of DDAVP, by adding large volumes of free water to their fluid intake. For example, a standard infant formula can be diluted to one-half or two-thirds of normal strength with water, reducing the renal solute load. However, oral intake would need to be increased to meet caloric needs, which itself may cause polyuria.

For infants able to concentrate their urine to 70–100 mOsm/kg, a low-solute formula such as Similac PM 60/40 or breast milk can be used to reduce the solute load and obligate urine output, allowing fluid balance to be achieved with a more modest volume of free water supplementation of 30 ml per 120–160 ml of formula.[27]

Finally, in severe CDI (urine osmolality <60 mOsm/L), thiazide diuretics such as chlorthiazide may be used as an alternative to DDAVP. Thiazide diuretics affect tubular sodium handling and interfere with renal diluting mechanisms, increasing urine osmolality.[27]

Oral chlorthiazide may be given at 5 mg/kg twice daily to achieve a urine osmolality of 100–150 mOsm/L, with a concomitant reduction in free water losses.[27] Infants are given a low-solute formula or breast milk, supplemented with free water 20–30 ml for every 120–160 ml formula.[27]

As infants are weaned to solid foods, and from breast or formula milk to cow's milk, the renal solute load of their feeds substantially increases and they tend to need to change to DDAVP.[27]

In all cases, close monitoring of weight and serum sodium concentrations is essential.

Summary

CDI results from inadequate vasopressin secretion by the posterior pituitary gland. It leads to polyuria and polydipsia, and can cause hypernatraemic dehydration in patients who are denied access to water or are unable to experience or express thirst.

Water deprivation testing followed by a DDAVP test can confirm the diagnosis, though results can sometimes be difficult to interpret.

Following diagnosis, it is important to establish the aetiology of CDI, with anterior pituitary function testing, measurement of tumour markers, skeletal survey and cranial MRI.

Treatment with DDAVP is effective and usually lifelong. Patients and their families need to be aware of the risk of water intoxication with prolonged DDAVP treatment. However, with careful use, DDAVP can relieve symptoms of polyuria and polydipsia, dramatically improving the wellbeing and quality of life of patients with central diabetes insipidus.

Glossary

ACTH	Adrenocorticotrophic hormone
AFP	α-fetoprotein
AVPc-Abs	Vasopressin cell autoantibodies
CDI	Central diabetes insipidus
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computed tomography
DDAVP	Desmopressin acetate
DI	Diabetes insipidus
DIDMOAD Syndrome	Diabetes insipidus, diabetes mellitus, optic atrophy, deafness
GH	Growth hormone
HCG	β-human chorionic gonadotrophin
LCH	Langerhans cell histiocytosis
MRI	Magnetic resonance imaging
NDI	Nephrogenic diabetes insipidus
NGGCT	Non-germinomatous germ cell tumor
NPII	Neurophysin-II
pAVP	Plasma arginine vasopressin
pOsm	Plasma osmolality
TSH	Thyroid stimulating hormone
WDT	Water deprivation test

References

1. Baylis PH, Cheetham T. Diabetes insipidus. Arch Dis Child. 1998;79:84-89.
2. Robertson GL, Shelton RL, Athar S. The osmoregulation of vasopressin. Kidney International. 1976;10:25-37.
3. Robertson GL. Vaptans for the treatment of hyponatraemia. Nat Rev Endocrinol. 2011;7:151-61.
4. Zerbe RL, Miller JZ, Robertson GL. The reproducibility and heritability of individual differences in osmoregulatory function in normal human subjects. J Clin Lab Med. 1991;117(1):51-9.
5. Robertson GL, Shelton RL, Athar S. The osmoregulation of vasopressin. Kidney International. 1976;10:25-37.
6. Baylis PH, Thompson CJ. Osmoregulation of vasopressin secretion and thirst in health and disease. Clin Endocrinol. 1988;29:549-76.
7. Robertson GL, Aycinena P. Neurogenic Disorders of Osmoregulation. Am J Medicine. 1982;72:339-53.
8. de Bellis A, Colao A, Bizzarro A, di Salle F, Coronella C, Solimeno S, Vetrano A, Pivonello R, Pisano G, Lombardi G, Bellastella A. Longitudinal study of vasopressin cell antibodies and of hypothalamic-pituitary region on magnetic resonance imaging in patients with autoimmune and idiopathic complete central diabetes insipidus. J Clin Endocrinol Metab. 2002;87(8):3825-29.
9. Kleeman CR, Czaczkes JW, Cutler R, Boston R. Mechanisms of impaired water excretion in adrenal and pituitary insufficiency. IV. Antidiuretic hormone in primary and secondary adrenal insufficiency. J Clin Invest. 1964;43(8):1641-48.
10. Makaryus AN, McFarlane SI. Diabetes insipidus: Diagnosis and treatment of a complex disease. Cleveland Clin J Med. 2006;73(1):65-71.
11. Choudhury D, Ahmed Z. Drug-associated renal dysfunction and injury. Nature Clinical Practice – Nephrology; 2006; 2(2):80-91. 12. Mohn A, Acerini CL, Cheetham TD, Lightman SL, Dunger DB. Hypertonic saline test for the investigation of posterior pituitary function. Arch Dis Child. 1998;79:431-4.
13. Verbalis JG. Diabetes Insipidus. Rev Endocr Metab Disorders. 2003;4:177-85.

14. di Lorgi N, Napoli F, Allegri AEM, Olivieri I, Bertelli E, Gallizia A, Rossi A, Maghnie M. Diabetes insipidus – Diagnosis and management. Horm Res Paediatr. 2012;77:69-84.

15. Maghnie M. Diabetes insipidus. Horm Res. 2003;59(1):42-54.

16. Magnhie M, Villa A, Arico M, Larizza D, Pezzotta S, Beluffi G, Genovese E, Severi F. Correlation between Magnetic Resonance Imaging of the posterior pituitary and neurohypophyseal function in children with diabetes insipidus. J Clin Endocrin Metab. 1992;74(4):795-800

17. Maghnie M, Genovese E, Bernasconi S, Binda S, Aricò M. Persistent High MR Signal of the Posterior Pituitary Gland in Central Diabetes Insipidus. Am J Neuroradiol. 1997;18:1749-52.

18. Werny D, Elfers C, Perez FA, Pihoker C, Roth CL. Pediatric central diabetes insipidus: Brain malformations are common and few patients have idiopathic disease. J Clin Endocrinol Metab. 2015;100(8):3074-80.

19. Maghnie M, Cosi G, Genovese E, Manca-Bitti ML, Cohen A, Zecca S, Tinelli C, Gallucci M, Bernasconi S, Boscherini B, Severi F, Aricò M. Central diabetes insipidus in children and young adults. New Eng J Med. 2000;343:998-1007.

20. Qaddoumi I, Sane M, Li S, Kocak M, Pai-Panandiker A, Harreld J, Klimo P, Wright K, Broniscer A, Gajjar A. Diagnostic utility and correlation of tumor markers in the serum and cerebrospinal fluid of children with intracranial germ cell tumors. Childs Nerv Syst. 2012;28:1017-24.

21. Maghnie M, Ghirardello S, Bellis AD, di Lorgi N, Ambrosini L, Secco A, De Amici M, Tinelli C, Bellastella A, Lorini R. Idiopathic central diabetes insipidus in children and young people is commonly associated with vasopressin-cell antibodies and markers of autoimmunity. Clin Endocrin. 2006;65:470-8.

22. Ghirardello S, Garrè ML, Rossi A, Maghnie M. The Diagnosis of Children with Central Diabetes Insipidus. J Pediatr Endocr & Metab. 2007;20:359-75.

23. Scherbaum WA, Czernichow P, Bottazzo GF, Doniach D. Diabetes insipidus in children. IV. A possible autoimmune type with vasopressin cell antibodies. J Pediatr. 1985;107(6):922-5.

24. Hansen LK, Rittig S, Robertson GL. Genetic basis of familial neurohypophyseal diabetes insipidus. Trends Endocrinol Metab. 1997;8:363-72.

25. BMJ Group, Tavistock Square, London, Pharmaceutical Press, Royal Pharmaceutical Society, London. British National Formulary for Children. August 2015.
26. Ball SG, Vaidja B, Baylis PH. Hypothalamic adipsic syndrome: diagnosis and management. Clin Endocrinol. 1997;47:405-9.
27. Rivkees SA, Bunbar N, Wilson TA. The management of central diabetes insipidus in infancy: Desmopressin, Low renal solute load formula, Thiazide diuretics. J Pediatr Endocrin & Metab. 2007;20:459-69.
28. Pogacar PR, Mahnke S, Rivkees SA. Management of central diabetes insipidus in infancy with low renal solute load formula and chlorothiazide. Curr Opinion Pediatrics. 2000;12:405-11.

Correspondence:

Dr. Assunta Albanese
Department of Paediatric Endocrinology
St George's Hospital
Blackshaw Road
London SW 17 0 QT
a.albanese@nhs.net

Dr. Nirit Braha
Department of Paediatric Endocrinology
St George's Hospital
Blackshaw Road
London SW 17 0 QT
nirit.braha@nhs.net

biomedpark Medien GmbH, Heidelberg • ISBN 978-3-9816544-6-2