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DIABETES INSIPIDUS

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Introduction

Hello everyone, my name is Harleen Cheema, and I am a medical student at the University of Alberta. This podcast was developed in collaboration with Dr. Elizabeth Rosolowsky, a pediatric endocrinologist at the University of Alberta in Edmonton, Alberta. In this PedsCases Podcast, we will discuss Diabetes Insipidus.

By the end of this podcast, learners will be able to:

1. Explain the role of Antidiuretic Hormone (ADH) in the body.
2. Describe the clinical presentation of Diabetes Insipidus (DI) in infants, children, and adolescents.
3. List key initial investigations to refine the differential diagnosis in children presenting with frequent thirst and urination.
4. Describe the management and potential complications of DI.

Let's start by discussing a clinical case to understand the recognition and diagnosis of DI.

Ana is a 5-year-old girl, who presents to her family doctor's clinic complaining about constant thirst and the need to urinate very often, sometimes as often as every hour. She has been drinking 3-4 glasses of cold water every 2-3 hours. Ana's mother is also concerned that Ana has not been growing or gaining weight adequately. Since frequent thirst and urination are common symptoms of Diabetes Mellitus (DM), Ana's doctor checked a random glucose level. Normal lab measurements of glucose ruled out DM in Ana's case which led to an increased suspicion of Diabetes Insipidus (DI).

Before we talk about DI, let's talk about the role of Antidiuretic hormone (ADH) in the body.

ADH, also known as Arginine Vasopressin or Vasopressin, is a hormone produced in the hypothalamus and transported to the posterior pituitary via axons. It is released into nearby capillaries, and finally reaches kidneys via the bloodstream where it binds to receptors on the collecting ducts, allowing aquaporins (or the water channels) to be

inserted into collecting ducts. This allows water to be reabsorbed from the urine back into the bloodstream, making the excreted urine more concentrated.

Release of ADH is stimulated by increased serum osmolality, meaning increased amount of solute relative to water in the serum. Increased serum osmolality is sensed by osmoreceptors present in the hypothalamus, which results in ADH release and increased thirst. With minute increases in serum osmolality, ADH is released into the bloodstream. With slightly higher serum osmolality, thirst receptors in the hypothalamus get triggered. We start to feel thirsty and go looking for water. If it were the other way around, where thirst was activated before ADH release, the water we drink would get lost in the urine without the water-reabsorbing effects of ADH.

ADH is also released in response to a decrease in blood pressure and blood volume. But one would need to lose a lot of blood or sustain a big drop in the blood pressure to trigger ADH release.

So, to summarize, the most potent stimulant for ADH release is increase in serum osmolality, whereas loss of blood or significant drop in blood pressure are secondary triggers.

These 2 mechanisms – ADH and thirst (with access to water) – are essential to preserving serum osmolality.

Now that we have talked about the role of ADH in the body, let's talk about the role that ADH plays in Diabetes Insipidus, while also differentiating between Central DI and Nephrogenic DI.

DI is characterized by either relative or absolute lack of ADH activity leading to inability of the kidneys to concentrate urine. As a result, too much water is lost in the urine and the urine becomes dilute, reflecting a low urine osmolality. Consequently, the loss of water through urine causes serum osmolality to increase. This triggers thirst.

Central DI is caused by partial or complete deficiency of ADH secretion.

Nephrogenic DI, on the other hand, is caused by a lack of renal response to ADH, despite the presence of ADH.

Differentiating between the types of DI is important as each type demands a unique treatment plan.

It is important to differentiate central or nephrogenic DI from primary polydipsia, which is often termed compulsive water drinking and is characterized by a pathological intake of water. This results in physiological suppression of ADH secretion. Increased output of dilute urine in this case is an appropriate response to excessive water intake.

Now let's talk about Central DI and Nephrogenic DI in detail:

Central DI

The causes of Central DI may be congenital or acquired.

Central DI is often caused by acquired anatomical lesions that cause damage to the posterior pituitary by pressure or infiltration. Some of the common acquired causes of central DI include brain tumors in the region, granulomatous diseases like sarcoidosis or infiltrative diseases like histiocytosis, and autoimmune causes such as lymphocytic hypophysitis. Surgical or traumatic injury to the hypothalamus, pituitary gland, or the pituitary stalk can also cause central DI.

Central DI can also be caused by genetic mutations or congenital malformations. The cells that make ADH might not have formed properly, or the mutations might have led to the anatomy not developing as expected. For example, infants with ectopic pituitary glands or with holoprosencephaly (failure of forebrain to develop normally) might develop central DI. Some mutations or malformations lead to multiple pituitary hormone deficiencies, including central DI.

Nephrogenic DI

Nephrogenic DI can be caused by congenital factors such as mutations of the ADH receptor.

More commonly in children, nephrogenic DI is due to acquired causes, including hypercalcemia and hypokalemia, chronic kidney diseases, and drugs like lithium, which can reduce the urine concentrating ability of the kidneys. Although there is an adequate amount of ADH present in patients with nephrogenic DI regardless of whether it is congenital or acquired, there is resistance to the action of ADH in the collecting tubules of the kidneys.

Now that we have talked about the types of DI, let's discuss the clinical presentation of DI along with an approach to diagnosis:

As seen in our patient, Ana, DI is suspected when the patient complains about excretion of large amounts of urine and increased thirst in the absence of the more common diagnosis of DM. Presentation may differ by age, but the common symptom is polyuria. Voluminous urine, also known as polyuria (urine output > 4 ml/kg/hr), occurs as a result of water not being reabsorbed due to abnormal ADH secretion or function. Increased thirst, or polydipsia, occurs as a result of increased serum osmolality. As a result, Infants and young children, in particular, those whose diet consists mostly of liquid calories, are especially prone to failure to thrive because of the preference to take in water. Polyuria, polydipsia, and failure to thrive are the cardinal features of DI in young children. Symptoms may differ, depending on whether the cause of DI is congenital or acquired. Infants with DI may present with weight loss and excessively wet diapers,

where parents say that the babies are soaking through their diapers and their sheets. They may also experience vomiting, irritability, and recurring fever without an apparent cause. Parents may also complain of difficulty with toilet training in younger children as well as secondary enuresis (i.e. a child who used to be potty trained now wets the bed). Children and adolescents with DI often experience disturbed sleep and excessive fatigue following the need to urinate frequently at night. Patients with DI can often exhibit signs of dehydration and hyperosmolality if the increased urine output is not compensated with adequate water intake. Dehydration could further result in hypotension, acute renal necrosis as a result of renal hypoperfusion, and hypovolemic shock. Hyperosmolality can also result in neurological symptoms resulting from osmotic water shifts from the intracellular compartment. Additionally, sudden correction of serum osmolality can also result in neurological symptoms, which can manifest as irritability, cognitive dysfunction, disorientation, and seizures.

Once polyuria and polydipsia are suspected from the patient's history, it is important to rule out other causes of polyuria and polydipsia.

Normal serum glucose and urinalysis rule out diabetes mellitus. Normal serum potassium and normal serum calcium rule out hypokalemia-induced and hypercalcemia-induced nephrogenic DI, respectively. Normal blood urea nitrogen makes intrinsic kidney disease less likely. Next, it is important to determine serum osmolality. Major solutes that comprise serum osmolality are sodium, glucose, and urea. Because glucose and urea are normal in most people, serum sodium can be used as a proxy for serum osmolality, so hypernatremia would be suggestive of DI.

The main diagnostic criteria to demonstrate in DI is an inappropriately dilute urine in the context of increased serum osmolality. Serum osmolality greater than 300 mOsm/kg at the same time as an inappropriately dilute urine is indicative of DI. In contrast, DI is ruled out if the urine is appropriately concentrated, with an osmolality greater than 600 mOsm/kg. If the levels are indeterminate, such as serum osmolality of less than 300 mOsm/kg and urine osmolality less than 600 mOsm/kg and clinical suspicion of DI remains, further work up is needed.

If urine osmolality value is not sufficient to make the diagnosis, a water deprivation test is performed in a closely monitored setting. The idea behind a water deprivation test is to restrict water intake and observe what happens to serum osmolality, urine osmolality, and urine output as well as assess the response to vasopressin. In someone with intact ADH secretion and function, the serum osmolality would increase; but water gets conserved by the kidney. Therefore, the urine output would decrease, and the urine osmolality would increase, so that patients would appropriately produce small volume of concentrated urine. This is normally the case in individuals with normal ADH secretion and function.

Now, what would happen in someone who could not produce ADH? As the serum osmolality increases and water continues to be lost through the kidneys, urine osmolality would decrease, and a more dilute urine would be produced. Water

deprivation test is used to measure ADH sufficiency where patients are water deprived for a very long time. The patient is kept from drinking water for several hours and monitored for dehydration and hypovolemia. During this time, serial measurements of weight, serum sodium and osmolality, urine osmolality and urine output are obtained. Diabetes insipidus is diagnosed when the serum osmolality increases past 300 mOsm/kg and the urine osmolality remains inappropriately dilute.

Back to our case

As we return our attention to Ana, her lab results showed that the serum calcium and potassium were normal. The initial serum sodium was 143 mmol/L and the urinalysis showed a specific gravity of 1.001, which is very dilute. This increased the family doctor's suspicion for DI. The family doctor referred the patient to the endocrinologist, who arranged for an urgent water deprivation test. Within several hours, her results showed a serum osmolality of 305 mOsm/kg and urine osmolality of 50 mOsm/kg, confirming a diagnosis of DI.

After a diagnosis of DI, what further investigations are needed?

Once the diagnosis of DI is made, it is important to differentiate between central and nephrogenic DI, since the treatments are different. A dose of vasopressin is administered.
If the urine osmolality increases with vasopressin and urine output falls, a diagnosis of central DI is confirmed, meaning ADH is not produced. Whereas if the urine osmolality remains low and does not increase with vasopressin, a diagnosis of nephrogenic DI is confirmed, meaning the kidneys are not responding to ADH.

If central DI has been diagnosed, it is essential to get magnetic resonance imaging (MRI) of the brain and pituitary gland to look for a lesion such as a germinoma or histiocytosis. It is also important to screen other pituitary hormone axes given the increased risk of concomitant anterior pituitary hormone deficits. If nephrogenic DI has been diagnosed, renal sonography should be done to look for a renal anomaly. Referral to endocrinology for central DI; referral to nephrology for nephrogenic DI should be made.

What do you think the water deprivation test might look like for someone with primary polydipsia? Since that individual can make ADH, with water restriction, urine output slows down and urine osmolality increases. Sometimes a person with primary polydipsia drinks so much water and produces so much urine that the usual kidney concentrating mechanisms are diluted, so the urine might not get as concentrated as someone without primary polydipsia who has normal ADH production. This makes the diagnosis of primary polydipsia versus partial DI tricky sometimes.

In summary, the main diagnostic criterion to demonstrate in DI is an inappropriately dilute urine in the context of increased serum osmolality. Additionally, it is important to

differentiate between central and nephrogenic DI, since each type requires a unique treatment plan.

Now let's talk about management of DI:

The goals of treatment in a patient with DI are to maintain normal osmolality through decreasing urine output and thirst, maintaining appropriate fluid balance, and promoting as best a quality of life as possibly acceptable for the patient. The two ways to manage diabetes insipidus are: (1) to give anti-diuretic hormone or vasopressin back if it's deficient as in central DI or (2) drink a lot of water in either type. You can imagine that it might get annoying and disruptive to be drinking water and urinating all the time. After all, we want the child to grow, to meet developmental milestones and to live a satisfying life.

Central DI:

It is important to provide free access to water in children with DI. Rehydration therapy should be started upon assessment of level of dehydration.

dDAVP is currently the drug of choice in patients with central DI. dDAVP stands for d-amino, D-arginine vasopressin and is also known as desmopressin. It can be administered intranasally, parenterally, or orally and is typically given 2 to 3 times per day. The dose and frequency of desmopressin are based on individual response to medication. Patients and their caregivers are taught to wait for a big urine break-through before the next dose of desmopressin in order to excrete waste. Older children and adolescents will often describe feeling increasingly thirsty and needing to urinate more as their next dose of desmopressin is due. Management of DI can be especially challenging in infants who are dependent on fluids such as breast milk or formula and cannot verbally express thirst. Even in infants without DI, urine volume is high, and concentration is low due to large amounts of fluid ingested to meet nutritional needs. Giving desmopressin reduces the amount of fluid that the infant needs to consume. In addition, use of desmopressin in this population leads to an increased risk of water intoxication and hyponatremia if the infant continues to drink limitlessly. Therefore, in some cases, there may be consideration of use of specific diuretics to manage fluid and electrolytes, which is beyond the scope of this podcast.

Nephrogenic DI:

The management of nephrogenic DI can be more challenging. In this case, patients do not respond to anti-diuretic hormone because their kidneys are resistant. Because nephrogenic DI in children is often secondary to another cause, it is important to treat the underlying cause. Dieticians play an important role in helping patients manage nephrogenic DI in the first year of life when fluid intake and caloric consumption are combined. It is essential to minimize the osmotic load while ensuring that the child obtains adequate amounts of calories and protein. Some patients with nephrogenic DI

may require a gastrostomy tube to meet their fluid requirements. Specific diuretics are also considered useful therapy in nephrogenic DI.

In summary, the 2 ways to manage diabetes insipidus are: (1) to give anti-diuretic hormone or vasopressin back if it's deficient or (2) drink a lot of water, according to one's thirst.

Potential complications of managing DI

Once a patient has received desmopressin, it is very important to reduce the amount of fluid intake, whether this is taken in orally, or provided through an IV or feeding tube. Remember, once desmopressin has been given, the patient cannot get rid of extra water. The patient might become hyponatremic, and if severe, can develop headaches, confusion, irritability, and in some cases, seizures.

On the other hand, if desmopressin is withheld or not given at the right time, the patient must have access to more fluids. Again, this is generally not a problem for someone with an intact thirst mechanism and free access to water.

In summary, it is important to manage polyuria and polydipsia without causing hyponatremia because of overtreatment. Hyponatremia is a major complication associated with desmopressin treatment and occurs when the patient's water intake is not adjusted while taking desmopressin.

Case Conclusion

Let's return our attention to Ana. Given a diagnosis of DI, she was given vasopressin, and her urine osmolality concentrated appropriately. She was sent for an MRI scan of the pituitary region, which showed thickening of the pituitary stalk. She was diagnosed with central DI, started on desmopressin, and counseled about access to free water and listening to her thirst sensation to determine her need to drink water. Ana continues to do well and is closely followed up by her endocrinologist.

That brings us to the end of our podcast. Let's review a few key points:

Summary:

1. Anti-diuretic hormone (ADH) is produced in the hypothalamus, which then sends axons to the posterior pituitary from where it gets released into the bloodstream. ADH binds to receptors on the collecting ducts in the kidneys, allowing aquaporins to be inserted into collecting ducts, which allows water to be reabsorbed from the urine back into the bloodstream. The major stimulus for ADH release is an increase in serum osmolality.
2. DI is characterized by either relative or absolute lack of ADH activity leading to inability of the kidneys to concentrate urine. As a result, too much water is lost in the urine and the urine becomes dilute, reflecting a low urine osmolality. On the

other hand, the loss of water through urine causes serum osmolality to increase, which triggers thirst.

3. Central DI is caused by partial or complete deficiency of ADH. Nephrogenic DI, on the other hand, is caused by a lack of renal response to ADH, despite the presence of ADH.
4. DI can be managed by using desmopressin in the case of Central DI or treating the underlying cause and using specific diuretics in the case of nephrogenic DI. Patients on these drugs should be monitored carefully for potential complications. In both central and nephrogenic DI, patients should have access to free water and are advised to drink water according to their thirst.

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