Nephrogenic Diabetes Insipidus

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Abstract

Purpose of the review

In nephrogenic diabetes insipidus (NDI), the kidney is unable to concentrate urine despite elevated concentrations of the antidiuretic hormone arginine-vasopressin. In congenital NDI, polyuria and polydipsia, are present from birth and should be immediately recognized to avoid severe episodes of dehydration. Unfortunately, NDI is still often recognized late after a “diagnostic odyssey” involving false leads and dangerous treatments.

Once diagnosed, appropriate treatment can be started. Moreover, laboratory studies have identified promising new compounds, which may help achieve urinary concentration independent of vasopressin.

Recent findings

a) MAGED2 mutations caused X-linked polyhydramnios with prematurity and a severe but transient form of antenatal Bartter's syndrome.

We distinguish two types of hereditary NDI: a "pure" type with loss of water only and a complex type with loss of water and ions. Mutations in the *AVPR2* or *AQP2* genes, encoding the vasopressin V2 receptor and the water channel Aquaporin2, respectively, lead to a "pure" NDI with loss of water but normal conservation of ions. Mutations in genes that encode membrane proteins involved in sodium chloride reabsorption in the thick ascending limb of Henle's loop lead to Bartter syndrome, a complex polyuric-polydipsic disorder often presenting with polyhydramnios. A new variant of this was recently identified: Laghmani et al. described 7 families with transient antenatal Bartter's syndrome, polyhydramnios and *MAGED2* mutations.

b) Multiple compounds have been identified experimentally that may stimulate urinary concentration independently of the vasopressin V2 receptor. These compounds may provide new treatments for patients with X-linked NDI.

Summary

A plea for early consideration of the diagnosis of NDI, confirmation by phenotypic and/or genetic testing and appropriate adjustment of treatment in affected patients!

Keywords

Nephrogenic diabetes insipidus, hypernatremic dehydration, thirst, AVPR2, AQP2,MAGED2, vasopressin V2 receptor bypassing compounds.

Introduction

NDI is a rare disease that needs special treatment. Unfortunately, as typical for rare diseases, the diagnosis can either be missed or misunderstood, leading to dangerous mistreatment. Although the pathophysiology and molecular diagnosis of congenital polyuric states has been well established [1] we still encounter cases where the diagnosis is late and where inappropriate diagnostic testing and treatments are done. The purpose of this review is to use one such example to demonstrate that simple diagnostic tests, including DNA sequencing, should be done as early as possible to potentially save the life and brain of these children with hereditary NDI.

In addition, we will review new findings in the differential diagnosis and potential new treatments [2]. We will also comment on experimental studies trying to bypass the vasopressin V2 receptor to increase urine concentration [3-8]

Case example

A 20-month-old boy with polyuria and a plasma sodium of 159 mmol/L.

A 20-month-old boy presents to his GP with polyuria/polydipsia (approximately 3 litres per day). There is a long history of feeding problems and vomiting. The child was initially assessed by a gastroenterologist, who performed an endoscopy but found no abnormalities. A diagnosis of gastro-oesophageal reflux was made. The GP requested a blood test which revealed hypernatremia with a plasma sodium (Na) of 159 mmol/l. He was admitted to his local hospital and the plasma Na corrected with increased fluid intake. He was then referred to another hospital for further investigations. A diagnosis of diabetes insipidus was suspected and confirmed with a water deprivation test, during which his plasma Na and osmolality rose to 159 mmol/l and 319 mosm/kg, respectively, with a urine osmolality (Uosm) of 100 mosm/kg. A DDAVP test the following day showed no response (Uosm pre: 63, post: 65 mosm/kg) and a diagnosis of NDI was made. However, with respect to his food aversion and potential motor development delay (walking independently achieved at age 20 months) an MRI was scheduled, which required general anesthesia. Despite the recent diagnosis of NDI, he was starved prior to the procedure without intravenous fluids. The scan was delayed and after ~8 h of no fluid intake, he became unwell and bloods at the time revealed a plasma Na of 174 mmol/l. The emergency response team was called

who administered 2 boluses of 20 ml/kg of 0.9% saline and he became unresponsive. He was therefore admitted to intensive care for intubation and placement of a central line and he received another 20 ml/kg bolus of 0.9% saline. A subsequent blood test now revealed a plasma Na concentration of 198 mmol/l. A subsequent MRI showed diffuse white matter abnormalities consistent with demyelination. He was extubated after 3 days, but showed severe muscle weakness with inability to walk or even lift his head off the pillow. Fortunately, he showed slow but steady improvement and was able to walk again after 4 weeks. Subsequent genetic testing showed a nonsense mutation c.599G>A; p.Trp200* in *AVPR2*, coding for the vasopressin V2 receptor.

Lessons to be learned

Considering the diagnosis of NDI in a child with feeding difficulties and vomiting, yet strong thirst.

Gastro-esophageal reflux (GER) is a common problem in infants, but if the feeding difficulties persist and especially, if there is inadequate weight gain, other causes need to be considered. A simple blood test can help establish the problem in an acutely unwell child. Plasma Na levels can be normal in NDI, if the patient manages to keep up with the water losses by drinking sufficient quantities. Yet, especially, if the child is unwell, it will often reveal hypernatremia and thus point to a potential urinary concentrating defect.

At a plasma sodium level of 148 mmol/L vasopressin release by the posterior pituitary is maximal for osmotic stimulation [9]. In normal physiology, circulating vasopressin will encounter a functionally normal renal vasopressin V2 receptor; the consequent increase in cyclic AMP will lead to insertion of aquaporin 2 water channels into the luminal membrane of principal cells of the renal collecting duct and urinary osmolality will increase[10] (Figure 1). Typically, urine osmolality will be higher than 800 mosm/kg H_2O. However, maximal urine concentration ability still develops during the first year of life and infants thus may not be able to achieve more than 500 mosm/kg. Apart from vasopressin release, any hypernatremia will induce a strong thirst behaviour and, when asked, the parents of patients with NDI often provide the typical history of an extremely thirsty child, that so avidly drinks large amounts of water, that it often vomits afterwards. Older babies will typically want to preferentially drink water and avoid food. Thirst is extremely powerful and recent studies using optogenetics in mice helped decipher the projections of thirst neurons to conscious and behaviour brain areas [11,12]. This powerful drive is apparent in the typical drinking behaviour of the baby with NDI, obvious to anyone with experience in this condition. But, of course, NDI is a

rare disease and most likely, the person examining the child and taking the history will never have seen a patient with NDI before and thus may not consider the diagnosis. Rather, typical questions with respect to an infant with vomiting are asked, such as the frequency of wet diapers. Obviously, the high urine output in a baby with NDI will lead to frequent wet diapers. But rather than ringing alarm bells, that there seems to be excessive urine output in a baby with dehydration, this answer is often taken as reassurance that the baby cannot really be dehydrated, as it has such excellent urine output! This demonstrates the importance of considering the diagnosis of a urinary concentrating defect and then to obtain a blood test to assess for hypernatremia.

At a plasma sodium higher than 148, we know that endogenous vasopressin is maximally stimulated and should expect a urine osmolality higher than plasma osmolality. If this is not the case a diagnosis of diabetes insipidus is established. To distinguish central from nephrogenic diabetes insipidus, a dDAVP test should be performed with serial urine osmolalities following a subcutaneous or intravenous injection of dDAVP. Urine osmolalities will reach values above 500 mOsm/kg H_2O in central (neurohypophyseal) diabetes insipidus but will not change in NDI. A picture of a classical case has been published previously in 1967 by a Canadian physician working in a metabolic clinic in Vancouver [13] (Figure 2). This infant, described by Perry et al. looked dehydrated and malnourished, yet, after rehydration and improved nutrition, regained a healthy appearance, demonstrating that the disease can be treated. Unfortunately, this infant died a few years later as a result of repeated episodes of dehydration, which were not recognized and treated in time. This report was published years before the identification of the *AVPR2* gene and illustrates the severity of the disease, if not treated adequately. We were contacted by the mother and sister of this patient and we were able to reconstruct and link this family to the large Hopewell kindred [14]. The mother and sister both carried the W71X mutation in *AVPR2*, previously identified in this large kindred.

Emergency treatment of hypernatraemic dehydration in a patient with NDI: do not use 0.9% saline as this will result in excess sodium chloride administration and thus worsen the hypernatraemia.

Most emergency protocols for any patient with hypernatraemic dehydration suggest initial treatment with 0.9% saline, due to concerns about lowering plasma sodium too rapidly [1]. Yet, the situation is different in NDI: because

of the ongoing losses of essentially pure water with the urine, infusion of 0.9% saline will result in excess sodium chloride administration and thus worsen the hypernatraemia as observed in our case example, where plasma Na increased to 198 mmol/L. In NDI, isotonic fluids should be reserved only for acute intravascular volume expansion in hypovolemic shock, which is an exceedingly rare complication, as extracellular fluid volume is usually preserved in hypernatremia. Thus, patients with NDI should be treated with hypotonic fluids, either enterally (water/milk) or, if need be, intravenously (5% Dextrose in water). In our example, simply allowing the desperately thirsty boy to drink would have likely resulted in normalization of plasma Na. Since the onset of hypernatremia was acute, due to the withholding of fluids for the MRI scan, the risk of brain edema from rapid lowering of plasma Na was low. Alternatively, water could have been administered intravenously. Of course, hypotonic fluids must never be administered as an intravenous bolus; instead, the infusion rate should only slightly exceed the urine output. The aim is to provide just enough water to safely normalize plasma sodium concentration at a rate of less than 0.5 mmol/l/h (10-12 mmol/l /d). The main risk of a rapid decrease in plasma sodium is cerebral edema and potentially death. Yet, in our example, the fear for this complication and misunderstanding of NDI led to administration of excess salt with a consequent rapid increase in plasma Na, leading to osmotic demyelination [15].

A tonicity balance (Figure 3) can easily demonstrate the excess NaCl administration with 0.9% saline and the emergency plan for NDI used at Great Ormond Street Hospital for Children is given in Box 1.

Confirm clinical diagnosis with sequencing of *AVPR2 (coding for the vasopressin V2 receptor)* and *AQP2 (coding for aquaporin 2)*

The identification of mutations in the genes that cause hereditary diabetes insipidus allows the early diagnosis and management of at-risk members of families with identified mutations. Next generation sequencing is increasingly available, but traditional sequencing is just as suitable, as these genes are small and relatively easy to sequence. We encourage physicians who follow families with diabetes insipidus, be it neurogenic (central), X-linked and autosomal NDI to recommend mutation analysis before the birth of an infant because early

diagnosis and treatment can avert the physical and mental complications associated with episodes of dehydration. In Montreal, diagnosis of X-linked NDI has been accomplished by mutation testing of cultured amniotic cells (n = 7), chorionic villus samples (n = 10), or cord blood obtained at birth (n =57). Three infants who had mutation testing done on amniotic cells or chorionic villous samples also had the diagnosis confirmed by cord blood testing. Of 74 offspring tested, 35 were found to be affected males, 22 were unaffected males, nine were non-carriers and the remainder were carrier females (M-F. Arthus, M. Lonergan, and D.G. Bichet, unpublished data). Affected patients were immediately given abundant water intake, a low-sodium diet and hydrochlorothiazide. They never experienced episodes of dehydration, and their physical and mental development is normal. Gene analysis is also important for the identification of non-obligatory female carriers in families with X-linked NDI. Most females heterozygous for a mutation in the V2 receptor do not have clinical symptoms; few are severely affected [16].

"Pure" vs "complex" NDI with loss of water and electrolytes, and polyhydramnios

Patients who have congenital NDI and bear mutations in the *AVPR2* or *AQP2* genes have a "pure" NDI phenotype with loss of water but normal conservation of sodium, potassium, chloride and calcium. Patients who bear inactivating mutations in the genes *SLC12A1*, *KCNJ1*, *CLCNKB*, *BSND or CLCNKA* and *CLCNKB* in combination, which encode membrane proteins (respectively the sodium–potassium–chloride cotransporter NKCC2, the potassium channel ROMK, the chloride channel Kb, the chloride channel Ka and Barttin) of the thick ascending limb of the loop of Henle have a complex polyuric-polydipsic syndrome with loss of water, sodium, chloride, calcium, magnesium and potassium. In the large experience of Seyberth and colleagues [17], who studied 85 patients with a hypokaliemic salt-losing tubulopathy, all 20 patients with KCNJ1 mutations (except one) and all 12 patients with SLC12A1 mutations were born as preterm infants after severe polyhydramnios. Postnatally, polyuria was the leading symptom in 19 of the 32 patients.

Of note, polyhydramnios was never seen during the pregnancies that led to infants bearing AVPR2 or AQP2 mutations. Thus, a history of polyhydramnios in a polyuric child should always alert to the possibility of antenatal Bartter syndrome.

While the most common causes of increased amniotic fluid include maternal diabetes mellitus, fetal malformations and chromosomal aberrations, twin-to-twin transfusion syndrome, rhesus incompatibility and congenital infections [18], in these conditions, polyuria usually does not persist after birth.
A novel renal cause of polyhydramnios was recently discovered: Laghmani et al. reported in 2016 patients with amniotic fluid index from 24 to 100 cms (normal <20 cm) bearing male fetus with a transient form of Bartter's syndrome and bearing *MAGED2* mutations [2]. MAGE-D2 was found to affect the expression and function of the sodium chloride cotransporters NKCC2 and NCC (the sodium-chloride co-transporter in the distal convoluted tubule), both key components of tubular salt reabsorption. This is again consistent with the concept that transient and permanent complex polyuric-polydipsic syndromes are associated with polyhydramnios, a tell-tale sign that can guide the genetic analysis.

Vasopressin V2 receptor by-passing compounds to increase urine concentration in patients with X-linked Nephrogenic Diabetes Insipidus.

The β3 adrenoreceptor stimulation of AQP2 could be useful to bypass a human, genetically non-functional, vasopressin V2 receptor as seen in X-linked (NDI) [3]. Migrabon [4], already used to treat overactive bladder, could potentially be proposed, in a research protocol, to improve urine concentration in well characterized patients with X-linked NDI .

There is also a luminal Frizzled d8 receptor, another member of the large family of seven transmembrane G-protein coupled receptors, expressed on the luminal membrane of principal cells and likely to increase direct transcription of AQP2 through a -catenin pathway (Fig 1) [5]. The soluble (pro)renin receptor (sPPR) is the agonist of this receptor and also induces an antidiuretic response in the same mouse model of NDI [6]. Of interest, sPPR acts downstream of the prostaglandin EP4 receptor, also previously shown to be of importance in the treatment of NDI mice and the Liver X Receptor agonist inactivates (pro)renin receptor transcription leading to downregulation of AQP2 and diabetes insipidus)[5].

Adenosine monophosphate kinase activation by Metformin has recently been found to increase urine osmolality in mice lacking a V2 receptor [7] and

erlotinib, an FDA approved epidermal growth factor inhibitor increased AQP2 membrane accumulation and ameliorated lithium induced NDI [8].

Re-purposing β3 adrenoreceptor agonists, metformin or ertolinib to test, after appropriate ethics approval, male adult patients bearing loss-of-function *AVPR2* mutations should be pursued by a consortium of investigators following a relatively large number of AVPR2-NDI patients with normal renal function and no dilation of the urinary tract. A fixed sodium and osmolar intake will be mandatory to assess the benefit of these new compounds.

Conclusion

New-born and young children with polyuro-polydypsic symptoms should be immediately referred to specialized centers with experience in treating hypernatremic dehydration and the ability to obtain rapidly a diagnosis.
The authors are accepting phone calls to guide the treatment of these children and the laboratories of the authors are accepting to sequence, free of charges, the DNA of these children.

Keypoints

- The diagnosis of congenital Nephrogenic Diabetes Insipidus can either be missed or misunderstood, leading to dangerous mistreatment.
- High plasma sodium, increased thirst and increased urine output with low osmolality are easy to recognize.
- Dehydration tests should not be done if plasma sodium is higher than 147 mmol/L with a urine osmolality less than 300 mosmol/kg H_2O.
- In contrast to other children who may have hypernatraemic dehydration, but whose kidney function is otherwise normal, children with nephrogenic diabetes insipidus should not receive intravenous saline as a rehydration fluid (except in the event of acute hypovolemic shock, when it is perfectly acceptable to give a resuscitation bolus of 10ml/kg of saline, pending results).

Figure 1
Schematic representation of the effect of arginine vasopressin to increase water permeability in the principal cells of the collecting duct. AVP is bound to the V2 receptor, AVPR2 (a G-protein-linked receptor) on the basolateral membrane. The basic process of G-protein-coupled receptor signaling consists of three steps: a hepta-helical receptor that detects a ligand (in this case, AVP) in the extracellular milieu, a G-protein that dissociates into alpha subunit bound to GTP and beta and gamma subunits after interaction with the ligand-bound receptor, and an effector (in this case, adenylyl cyclase) that interacts with dissociated G-protein subunits to generate small-molecule second messengers. AVP activates adenylyl cyclase 6 increasing the intracellular concentration of cyclic adenosine monophosphate (cAMP). The topology of adenylyl cyclase is characterized by two tandem repeats of six hydrophobic transmembrane domains separated by a large cytoplasmic loop and terminates in a large intracellular tail. Generation of cAMP follows receptor-linked activation of the heteromeric G-protein (Gs) and inter-action of the free Gas-chain with the adenylyl cyclase catalyst. Protein kinase A (PKA) and possibly the Exchange factor directly activated by cAMP (EPAC) are the target of the generated cAMP. On the long term, vasopressin also increases AQP2 expression via phosphorylation of the cAMP responsive element binding protein (CREB), which stimulates transcription from the AQP2 promoter. Cytoplasmic vesicles carrying the water channel proteins (represented as homotetrameric complexes) are fused to the luminal membrane in response to AVP, thereby increasing the water permeability of this membrane. Microtubules and actin filaments are necessary for vesicle movement toward the membrane. The stimulation of adenyl cyclase by the □-3 adrenergic receptor and the stimulation of AQP2 expression through the frizzled d8-□-catenin pathway are also represented.
(from [10] with permission.)

Figure 2 A typical historical picture of a dehydrated and malnourished infant (A) with NDI, and (B) looking healthy after rehydration and improved nutrition. This infant died a few years later as a result of repeated episodes of dehydration. This report was published years before the identification of the *AVPR2* gene. We were contacted by the mother and sister of this patient and we were able to reconstruct and link this family to the large Hopewell kindred (Bichet and Arthus, unpublished data). The mother and sister both had the W71X mutation. Reproduced with permission from [13].

Figure 3. Simplified tonicity balance for a patient with NDI, excreting hypotonic

urine and receiving 0.9% saline.
When considering separately the balances for water and Na, the excess Na administration form 0.9% saline becomes immediately obvious. The square box in the middle represents the total body water compartment of a patient with NDI. A patient with NDI excretes hypotonic urine, typically with a Na concentration <10 mmol/l. If 1 liter of urine output is replaced with 1 liter of 0.9% saline, this will not change the fluid balance, but lead to a net gain of 144 mmol of Na. In a patient of 10 kg with estimated 7 liters of total body water, this would lead to an increase in the plasma Na concentration of approximately 144mmol / 7 l = ~ 20 mmol/l.

Box 1. Emergency plan for patients with NDI.

Congenital nephrogenic diabetes insipidus

The patient has a genetic kidney disorder called **nephrogenic diabetes insipidus**. In this disorder, his kidneys are unable to reabsorb water normally. The effect is that he loses large amounts of water and will therefore pass large amounts of urine, and as a consequence, will have to drink large amounts of fluid. We provide medication, such as Indometacin and Chlorothiazide, to reduce the amount of water losses in the kidneys.

In the event of episodes of vomiting or extra water losses (fever, diarrhoea, etc.), he is at risk of **hypernatraemic dehydration** (dehydration with a high sodium level in the blood). He is also at risk of hypernatraemic dehydration if he is unable to drink adequate quantities of water. Unlike in children with normal kidney function, the presence of good urine output in the case of vomiting and/or diarrhoea is **not** a reassuring sign, but an extra risk for severe dehydration. Hypernatraemic dehydration can be missed on clinical examination and if in any doubt, a blood test should be performed to assess his plasma electrolytes.

In contrast to other children who may have hypernatraemic dehydration, but whose kidney function is otherwise normal, children with nephrogenic diabetes insipidus should **not** receive intravenous saline as a rehydration fluid (except in the event of acute shock, when it is perfectly acceptable to give a resuscitation bolus of 10ml/kg of saline, pending results).

The appropriate fluid to use is **5% glucose**, which provides the free water, which is being lost. This should initially be prescribed at maintenance fluid rates appropriate for his age and size, pending adjustment, according to the plasma blood tests.

Management of children with nephrogenic diabetes insipidus can be complex, and we are happy to be called for advice.

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