Inherited secondary nephrogenic diabetes insipidus: concentrating on humans

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The promise of molecular medicine is to provide personalized medicine that is specific for the underlying molecular defect in the individual patient (9). To be able to fulfill this promise we must understand (patho)physiology. While increasingly sophisticated genetically modified mouse models provide ever more detail on mouse physiology, the applicability of these insights to humans often remains to be demonstrated. In contrast, the careful study of rare inherited human diseases provides a unique opportunity to gain direct insight into human physiology, yet is limited mostly to clinically indicated investigations.

Nephrogenic diabetes insipidus (NDI) is a good example of the fruitfulness of both approaches: inherited NDI was first described in 1892 (48), and almost exactly 100 years later the gene underlying X-linked NDI, AVPR2, was cloned by several groups, some working with patients with NDI, others with animals (42, 53, 58, 64). Only 1 year later, the apical water channel in the collecting duct (AQP2) was cloned from rat kidney (25), and subsequently mutations were identified in patients with autosomal recessive NDI (19). The study of primary inherited NDI has clearly helped to better understand the mechanisms of urinary concentration in the collecting duct: binding of arginine-vasopressin (AVP) to the basolateral AVP receptor AVPR2 initiates a signaling cascade which in the end results in the insertion of aquaporin-2 (AQP2) water channels in the apical membrane, so that water can move transcellularly along the concentration gradient from urine to the medullary interstitium (Fig. 1) (5, 24). A failure within this cascade will result in the clinical consequence of polyuria with hypotonic urine (hyposmuria). Of course, excretion of large volumes of hypotonic urine is not necessarily pathogenic: a visitor to the Oktoberfest enjoying one or more liters of beer will need to excrete large volumes of hypotonic urine to maintain volume homoeostasis (physiological polyuria). Moreover, even pathological polyuria does not necessarily indicate a failure to reabsorb water in the collecting duct but can be solute driven (e.g., glycosuria) or due to a failure to generate an interstitial concentration gradient (e.g., after loop diuretics). Clinically, these cases can be easily distinguished, as the urine is not hypotonic, but iso- or hypertonic. To maintain clear diagnostic definitions, we prefer to not subsume these conditions under the term “NDI” but rather restrict the latter to pathological AQP2-deficient states. The critical role of AQP2 also for secondary forms of NDI has been previously demonstrated (46). On a semantic level, the term NDI (“insipidus” means tasteless) would also not be appropriate for the non-AQP2-deficient polyuric conditions, as the urine would be either sweet (glycosuria) or salty (loop diuretics).

Clinically, AQP2 deficiency can be simply defined by the following two conditions: urine osmolality (Uosm) is inappropriate below plasma osmolality (Posm) during dehydration (Posm>normal); Uosm does not increase above Posm after administration of DDAVP.

In primary inherited NDI, this is easy to understand: in the absence or dysfunction of either AVPR2 or AQP2, AVP administration of DDAVP.
Inherited Diseases Associated with sNDI

Bartter syndrome. The occurrence of sNDI complicating Bartter syndrome is confusing and can result in diagnostic pitfalls. Bartter syndrome is due to loss-of-function mutations in proteins mediating salt reabsorption in the thick ascending limb of Henle’s loop (TAL) (38). The TAL is also called the urinary diluting segment as salt reabsorption from the water-impermeable TAL is critical for urinary dilution and generation of the medullary interstitial concentration gradient. Thus patients with Bartter syndrome typically are polyuric, but not due to an AQP2 deficiency but due to isosthenuria, i.e., an impairment to concentrate or dilute the urine. However, some of these patients clearly have hyposthenuria. We recently described in detail the case of a boy with antenatal Bartter syndrome and clinical AQP2 deficiency, based on persistent hypotonic urine, despite clinical dehydration with hypernatremia and no response to DDAVP (8). Interestingly, despite the genetic impairment of salt reabsorption in TAL in this boy, urine osmolality reached values as low as 63 mosmol/kgH2O, suggesting that other segments, presumably more distal, can compensate for the loss-of-function in TAL. Moreover, this compensation was markedly enhanced by treatment with indomethacin, which may be one reason for the clinical efficacy of this drug in Bartter syndrome (8). More such case reports exist, and the low urine osmolalities despite concomitant hypernatremia and lack of response to DDAVP in these patients can actually lead to an initial misdiagnosis of NDI (3). In fact, in the laboratory in Montreal, KCNJ1, the gene underlying Bartter syndrome type 2, is the first additional gene tested in samples from patients with a clinical diagnosis of NDI, but no identifiable mutation in SLC12A1, the gene underlying Bartter syndrome type 1, was markedly enhanced by treatment with indomethacin, which may be one reason for the clinical efficacy of this drug in Bartter syndrome (8). More such case reports exist, and the low urine osmolalities despite concomitant hypernatremia and lack of response to DDAVP in these patients can actually lead to an initial misdiagnosis of NDI (3). In fact, in the laboratory in Montreal, KCNJ1, the gene underlying Bartter syndrome type 2, is the first additional gene tested in samples from patients with a clinical diagnosis of NDI, but no identifiable mutation in AVPR2 or AQP2. If no mutation is found, SLC12A1, the gene underlying Bartter syndrome type 1, is studied next, simply because of the much greater size of this gene. Indeed, in cases with a clinical diagnosis of NDI analyzed in the years 2000–2011, the laboratory identified pathogenic mutations in AVPR2 in 148 cases, AQP2 in 22 cases, and KCNJ1 (6 cases) and NKCC2 (1 case) in an additional 7 cases.

Importantly, the sNDI appears to occur only in patients with Bartter syndrome type 1 and type 2 [i.e., those with mutations in either SLC12A1 (NKCC2) or KCNJ1 (ROMK)], but not in those with type 3 (due to mutations in CLCNKB), who may display polyuria due to an impaired medullary osmotic gradient, but in fact typically have some urinary concentrating ability (54). This may actually provide one clue toward a potential etiology: while Bartter type 3 patients typically have more severe plasma electrolyte abnormalities with respect to hypokalemia, hypochloremia, and alkalosis, they do not exhibit the hypercalciuria typical for type 1 and type 2 Bartter syndrome (14, 54). Another distinguishing feature between type 1, 2, and 3 Bartter syndrome is the highly elevated hyperprosta-
glandinuria is seen in the former, which is sometimes also referred to as “Hyperprostaglandin E-syndrome” (59). However, prostaglandins, especially E₂, are thought to activate AQP2 phosphorylation independently of AVPR2 (52), so the hyperprostaglandinuria is unlikely causative.

Understanding the mechanism of sNDI in Bartter syndrome is even more complicated by the fact that only a subset (~20% in our experience) of Bartter type 1 and 2 patients experience sNDI. The sister of the type 2 Bartter patient we reported previously (12) is homozygous for the same mutation in KCNJ1 and has comparable plasma biochemistries, yet her spot urine osmolalities in clinic are consistently above plasma osmolality. While maximally measured at only 367 mosmol/kgH₂O, this probably reflects the isostenuria typical for Bartter syndrome, but is not evidence for true AQP2 deficiency. Thus sNDI, based on this family, is unlikely a mutation-specific complication and variants in other genes may influence this phenotype. However, it is also possible that the sister may have a relative AQP2 deficiency, similar to that seen in partial NDI. To distinguish this from isostenuria due to an impaired medullary concentration gradient, quantification of AQP2 abundance would be required.

Apparent mineralocorticoid excess. Apparent mineralocorticoid excess (AME) is a rare disorder due to loss-of-function mutations in the gene HSD1B2 (62). The encoded enzyme catalyzes the conversion of cortisol, which can activate the mineralocorticoid receptor (MCR) to the inactive cortisone. As cortisol is present in human plasma in ~1,000-fold higher concentration than aldosterone, the enzyme is critical to protect the MCR from cortisol intoxication (17). Consequently, patients with AME suffer from increased MCR activity with enhanced salt reabsorption in the collecting duct and consequent hypertension. The biochemical electrolyte profile of these patients is virtually indistinguishable from Bartter syndrome type 1 and 2, characterized by a hypokalemic, hyperchloremic metabolic alkalosis with hypercalciuria (38). Associated with the hypercalciuria, nephrocalcinosis is typically present in both diseases. Yet, while patients with Bartter syndrome have hypovolemia and low blood pressure due to the impaired sodium reabsorption in TAL, patients with AME have hypervolemia and high blood pressure due to the enhanced sodium reabsorption in the collecting duct. Polyuria/polydipsia have long been recognized as typical features of AME (66), including a report on an inappropriately low urine osmolality in the context of an elevated plasma osmolality (49). Recently, we investigated this in detail in a girl with molecularly confirmed AME, who was initially misdiagnosed as NDI (12). We confirmed an inappropriately low urine osmolality (145 mosmol/kgH₂O) in the context of an elevated plasma osmolality (307 mosmol/kgH₂O) and an absent response to DDAVP, consistent with true AQP2 deficiency. Interestingly, treatment of the AME with the mineralocorticoid receptor blocker spironolactone and the epithelial sodium channel blocker amiloride completely reversed the electrolyte abnormalities and restored urinary concentrating capacity (12). The effect of the treatment was marked and almost instantaneous, so that the parents, used to seeing their little daughter (weight: 7.5 kg) drink about 2 liters of water/day, called in very concerned, as she suddenly was not interested in her water bottle anymore. Subsequent biochemical tests showed that she was in electrolyte homeostasis with good urinary concentrating ability demonstrated by a random urine osmolality of 705 mosmol/kgH₂O.

Renal Fanconi syndrome. Renal Fanconi syndrome is characterized by generalized proximal tubular dysfunction, including low-molecular-weight proteinuria, organic and aminoaciduria, glycosuria, bicarbonaturia with consequent metabolic acidosis, and hypercalciuria (6). Due to decreased reabsorption in the proximal tubule and/or increased secretion of potassium in the collecting duct, blood biochemistries in patients with renal Fanconi syndrome and intact glomerular filtration rate are also characterized by hypokalemia (11). Inherited forms of renal Fanconi syndrome are rare and can be isolated (63) or occur as part of systemic disorders, including cystinosis, tyrosinemia, Wilson’s disease, galactosemia, glycogen storage disease, ARC syndrome, and mitochondrial cytopathies (11, 13, 34). Incomplete forms are also seen in Lowe syndrome and Dent disease (6, 37). Detailed assessments of urinary concentrating capacity in these patients are not part of routine care of these patients, but a few reports on sNDI exist.

The presence of sNDI with cystinosis has been reported recurrently (12, 32, 36, 39, 41). However, in our own clinical experience, it is clearly not universal. While polyuria/polydipsia is a typical feature of the disease, this is likely due to the decreased proximal solute and fluid reabsorption. We have not assessed urinary concentrating ability in these patients systematically, but random urine osmolalities in 14 patients with cystinosis seen at Great Ormond Street Hospital have been consistently below that of plasma in 7, while in the other 7 they were as high as 613 mosmol/kgH₂O.

There are also two case reports of NDI associated with ARC syndrome (20, 43), but detailed data on urine and plasma osmolalities to support this diagnosis were not provided.

Distal renal tubular acidosis. Another inherited disorder associated with hypokalemia and hypercalciuria is distal renal tubular acidosis (dRTA). Several genes are known to cause dRTA, which all affect the ability of intercalated cells in the collecting duct to secrete protons (35, 65). Again, polyuria/polydipsia is a common symptom of this disease, and there are some case reports documenting associated NDI (10, 23), but no systematic data collection of urinary concentrating ability in these patients exists. In 15 patients seen at Great Ormond Street Hospital with a clinical diagnosis of dRTA, random urine osmolalities were mostly compatible with isostenuria, although in some patients they were as high as 691 mosmol/kgH₂O. Interestingly, however, data on urine osmolality at presentation were available in 2 of our patients and were 56 and 110 mosmol/kgH₂O, respectively. The typical electrolyte abnormalities of dRTA (hypokalemia, hyperchloremia, metabolic acidosis, hypercalciuria) are completely reversible with treatment (alkali supplementation), and in fact urine calcium excretion is used for monitoring of treatment adequacy. The low urine osmolalities at presentation were not in the context of elevated plasma osmolality, nor was a DDAVP test performed and thus a true diagnosis of NDI was not established. Nevertheless, these data and the subsequent increase in the random urine osmolality on treatment (to 340 and 371 mosmol/kgH₂O, respectively) are compatible with a hypothesis of NDI secondary to biochemical abnormalities.

Cystic kidney disorders. Nephronophthisis and related renal cystic disorders are typically described to present with polyuria/polydipsia (67). A key histological feature of the disease is...
tubulointerstitial fibrosis, and thus a defect in urinary concentrating ability is expected, but in the form of isosthenuria (30). Nevertheless, a few case reports of NDI in cystic kidney disorders exist: Holliday et al. (32) reported 1 case of “medullary cystic kidney disease” and another of “cystic disease of the kidney” with maximal urine osmolality of 150 and 200 mosmol/kgH2O, respectively, after administration of pitressin, and we reported a similar case in nephronophthisis with a maximum urine osmolality of 151 mosmol/kgH2O (12). Interestingly, this boy initially presented with isosthenuria and only later developed the sNDI, but eventually progressed to end-stage kidney disease. In our experience, the biochemical profile in children with these disorders typically shows signs of uremia, but not consistent electrolyte abnormality, that could be related to a urinary concentrating defect. Moreover, in our experience, most of these patients with cystic kidney disease, if they have a history of polyuria/polydipsia, have isosthenuria, as discussed above, rather than hyposthenuria. Yet again, this aspect has not been systematically investigated. In one patient with nephronophthisis due to a homozygous deletion in NPHP1 and marked polyuria and nocturnal enuresis, we performed a DDAVP test, which resulted in a maximal urine osmolality of 300 mosmol/kgH2O with a concomitant plasma osmolality of 294 mosmol/kgH2O, consistent with isosthenuria. Random urine osmolalities before transplant were available in five other children from our unit with genetically confirmed forms of nephronophthisis. These ranged between 191 and 351 mosmol/kgH2O, again more suggestive of isosthenuria.

Bardet-Biedl syndrome is an autosomal recessive disorder that is characterized by obesity and a number of other abnormalities, including hypogonadism in men, mental retardation, retinal dystrophy, and polydactyly. Renal abnormalities, most commonly in the form of nephronophthisis-like cystic degeneration of the kidneys, but calycal abnormalities can also be part of this syndrome (1, 33). In those with renal involvement, polyuria and polydipsia are among the most common earliest symptoms (1). A urinary concentration defect can be detected when kidney function is near normal and in the absence of major cyst formation (44). Bardet-Biedl-derived renal epithelial cells are nonciliated, and the vasopressin V2 receptor, which is activated by ADH in normal individuals, is localized in the primary cilium (44). In vitro, these cells did not respond to luminal vasopressin and did not activate luminal AQP2, suggesting that ciliary dysfunction may underlie some forms of sNDI.

An impaired urinary concentrating capacity has long been shown in autosomal dominant polycystic kidney disease (ADPKD) (18, 26, 68), including in children (22). Yet, this only manifested in a submaximal urine osmolality (typically around 700 mosmol/kgH2O), still well above plasma levels and was correlated with severity of structural abnormalities on ultrasound. Thus these studies have shown no clinical evidence for AQP2 deficiency, and the impaired concentrating ability may thus reflect interstitial changes with an impaired medullary concentration gradient.

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis. This is another autosomal recessive syndrome with mutations in either claudin16 or 19, which affects paracellular ion transport in the TAL (28). As the name indicates, the disease is characterized by marked hypercalciuria. Since sodium is also transported paracellularly in this segment, these patients also have a degree of salt wasting, and hypokalemic alkalosis is commonly seen before advanced CKD develops. Polyuria/polydipsia is a recognized feature of the disease, but, again, precise data on urinary concentrating ability are lacking (56).

Implications for Mechanisms

Hypercalciuria. The most common, but not universal, biochemical features of the disorders listed above are hypokalemia and hypercalciuria, which are typical features in Bartter and renal Fanconi syndrome, as well as in AME and dRTA, yet usually not in cystic kidney disorders. Hypokalemia and hypercalciuria have been individually linked to altered AQP2 expression: potassium depletion in rats leads to polyuria, with decreased abundance of AQP2 in the apical membrane (45). However, the underlying mechanism is unclear. Hypercalciuria is thought to affect AQP2 expression via the calcium-sensing receptor (CaSR), which is present in the apical membrane of medullary collecting duct cells and inhibits cAMP formation (16, 29). Indeed, it is hypothesized that this might be an evolutionarily important mechanism to prevent stone formation in the urinary tract (15), and there are some data on short-term changes in urinary concentration with hypercalciuria (57). Moreover, a report on an animal model of hypercalciuria, TRPV5 knockout mice, reveals significant polyuria compared with wild-type or heterozygote littermates (31). However, no data on clinical or actually measured Aqp2 deficiency are given. In fact, several lines of evidence argue against a clinically relevant role of the CaSR alone in sNDI: the risk of dehydration seems evolutionarily more important than the risk of urolithiasis.

Urinary calcium concentrations in our patients with sNDI were typically <3 mmol/l and thus well below the EC50 of the CaSR (~6 mmol/l). Indeed, when assessed in humans, a direct (rather than an inverse) relationship between urine osmolality and urinary calcium concentration is seen, with urinary calcium concentrations as high as 14 mM in the most concentrated urines (40).

When urine volume in patients with idiopathic hypercalciuria is compared with controls, no difference is seen, despite a twofold higher urinary calcium concentration in the patients (2). Patients with inactivating mutations in the CaSR have neither a urinary concentrating defect nor an increased risk of nephrolithiasis (47, 55).

Hypokalemia. Hypokalemia is often cited as a cause for impaired urinary concentration, as indeed animal models show decreased Aqp2 expression with low plasma potassium (51). Yet again, clinical observations argue against isolated hypokalemia as causative for sNDI, as patients with Gitelman syndrome or Bartter type 3 have plasma potassium values equal or even lower than those with Bartter syndrome type 1 and 2, yet they typically do not experience sNDI (14, 54).

Combined biochemical abnormalities. Thus, if the biochemical abnormalities were causative, it would need to be a combination of both hypokalemia and hypercalciuria. A compelling argument for a causative role of the biochemical abnormalities is the observed complete reversibility of the sNDI with normalization of biochemistries after appropriate treatment. In this context, it is interesting to note the recent report of a urinary concentrating defect also in the mouse model of...
AME (Hsd11b2 −/− mice), which was indeed associated with a deficiency in Aqp2 mRNA (21). Curiously, the obvious experiment of confirming the reversibility of the urinary concentrating defect was not performed, despite the published clinical experience in humans. However, even the combination of hypokalemia and hypercalciuria cannot be the sole explanation, as only a minority of patients with Bartter syndrome type 1 and 2 exhibit signs of sNDI. This observation also argues against solute-driven polyuria as a cause in these patients. We previously speculated that the large urine volumes secondary to the TAL dysfunction in the Bartter patients may affect urinary concentrating ability in a manner akin to urinary obstruction (8). Moreover, patients with AME have no primary TAL dysfunction, making solute-driven polyuria as a cause of AQP2 deficiency unlikely.

Ciliary dysfunction. The recent data on the importance of cilia in urinary concentration suggest yet another potential mechanism (44). Yet, this may only explain the occasionally observed sNDI in ciliopathies, but not in the other diseases discussed here.

Conclusions

Monogenic diseases provide a unique opportunity to study the pathophysiological consequences of a defined and specific molecular defect. Clinical observations made in these patients complement investigations in genetically modified mice. While animal experiments can be more invasive, the relevance of the results to human physiology can only be inferred, whereas observations in patients provide direct insight. With respect to the occurrence of sNDI, the observations discussed here point to a reversible phenomenon, probably related to biochemical abnormalities. Yet, clearly, clinicians need to take a more careful look at urinary concentrating ability in their patients to get more comprehensive data for the various disorders discussed here. Further investigations in humans into the mechanism could be performed, for instance, by urinary exosome analysis to assess expression of involved proteins, such as AQP2 (27). These data should be complemented by animal experiments. The hypothesis of sNDI in the context of hypokalemia and hypercalciuria being reversible could be easily assessed in the appropriate mouse models of, for instance, AME or dRTA. Moreover, it could be tested in experiments in isolated, perfused kidneys. This complementary approach highlights the importance and possibilities of collaboration between clinicians and physiologists.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

AUTHOR CONTRIBUTIONS

Author contributions: D.B. analyzed data, drafted manuscript, and approved final version of manuscript; D.G.B. prepared figures; D.B. and D.G.B. edited and revised manuscript.

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