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Secondary nephrogenic diabetes insipidus as a complication of inherited renal diseases

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Abstract

Background/Aims—Nephrogenic diabetes insipidus (NDI) is a serious condition with large water losses in the urine and risk of hypernatremic dehydration. Unrecognised, repeated episodes of hypernatremic dehydration can lead to permanent brain damage. Primary NDI is due to mutations in either *AVPR2* or *AQP2*. NDI can also occur as a secondary complication, most commonly from obstructive uropathy or chronic lithium therapy. We observed NDI in patients with inherited tubulopathies and aimed to define the clinical and molecular phenotype.

Methods—We reviewed medical notes of four patients with clinical NDI and an underlying molecularly confirmed diagnosis of nephropathic cystinosis, Bartter syndrome, nephronophthisis and apparent mineralocorticoid excess, respectively.

Results—The patients all failed to concentrate their urine after DDAVP. None had an identifiable mutation in *AVPR2* or *AQP2*, consistent with secondary NDI. Patients experienced repeated episodes of hypernatraemic dehydration and in two cases NDI was initially thought to be the primary diagnosis, delaying recognition of the underlying problem.

Conclusion—The recognition of this potential complication is important as it has direct implications for the clinical management. The occurrence of NDI in these conditions provides clues for the etiology of aquaporin deficiency.

Introduction

The urinary concentrating mechanism involves active salt transport in the thick ascending limb of Henle's loop (TAL). Since the TAL is water impermeable, removal of salt dilutes the urine and concentrates the interstitium of the renal medulla, resulting in a large difference between the tonicity of urine and interstitium along the medullary collecting duct

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(CD) [1]. The associated osmotic force is enormous (19.2 mmHg/mosm/l) and therefore water will follow the osmotic gradient if the separating epithelial barrier becomes permeable. To adapt water excretion to the physiological demands of the body, water permeability in the collecting duct is regulated by the availability of aquaporin 2 water channels (AQP2) in the apical membrane of principal cells in response to signalling from the type 2 vasopressin receptor (AVPR2). Defects that affect salt transport in TAL therefore impair the generation of a concentration gradient and thus are typically associated with the excretion of urine isotonic to plasma (isosthenuria). In contrast, nephrogenic diabetes insipidus (NDI) is defined by the absence of functional AQP2 in CD even when vasopressin is present, resulting in the excretion of urine hypotonic to plasma (hyposthenuria). For this reason, NDI is sometimes also referred to as “aquaporin-deficient” DI [2,3].

Primary inherited NDI is due to mutations in the genes encoding AVPR2 or AQP2 [4]. NDI can also occur as a secondary complication, most often in obstructive uropathies or as a consequence of long-standing lithium therapy [5,6]. Here we present NDI as a complication in four inherited renal diseases: nephropathic cystinosis, Bartter syndrome, nephronophthisis and apparent mineralocorticoid excess. The underlying molecular defect in these diseases is not directly implicated in the availability of AQP2 in CD, yet our clinical data show hyposthenuria in the face of hypernatremic dehydration and after administration of 1-desamino[8-D-arginine] vasopressin (DDAVP), consistent with true aquaporin deficiency. The identification of this potential complication is important as patients are at risk of hypernatremic dehydration, with potentially serious implication for brain function. Moreover, it is important to recognize that NDI can occur as a secondary complication in order to avoid missing the underlying diagnosis.

Cases

We present 4 cases of inherited nephropathies, presenting with repeated episodes of hypernatraemia, associated with hyposthenuria and unresponsiveness to DDAVP. The clinical diagnosis in the 4 cases was cystinosis, nephronophthisis, Bartter syndrome and apparent mineralocorticoid excess (AME), respectively. Molecular confirmation of these diagnoses was established in each case. Patients exhibited the typical hemodynamic changes after intravenous DDAVP, i.e. a small decrease in blood pressure and increase in heart rate, consistent with intact AVPR2 signalling in the vasculature [7]. In addition, molecular analysis of the *AVPR2* and *AQP2* genes was unremarkable in all patients, suggesting that NDI was a secondary complication, rather than an incidentally present second inherited disease.

A summary of the key biochemical values is given in table 1.

Case1: Cystinosis

A 2-year old girl with a history of failure-to-thrive developed diarrhoea and vomiting and presented acutely in status epilepticus and hypovolaemic shock with non-oliguric renal failure. Her weight was 5.9 kg. Plasma biochemistries on admission included sodium of 124 mmol/l, potassium of 6.9 mmol/l and creatinine of 390 mcmol/l. She was treated with Lorazepam and volume resuscitated. She remained polyuric around 8 ml/kg/h and with adequate volume substitution her creatinine stabilised around 90 mcmol/l with a measured ^{51}chromium-EDTA GFR of 17mls/min/1.73m^2. Based on features of a renal Fanconi syndrome and elevated leucocyte cystine levels, a diagnosis of nephropathic cystinosis was established. Molecular testing identified a homozygous 57 kb deletion in the *CTNS* gene.

Ultrasound of her kidneys showed them to be poorly differentiated and echogenic, but with no evidence of hydronephrosis.

She presented again at 2.5-years of age with vomiting and diarrhoea and hypernatraemia of 147 mmol/l. She was given a bolus of 0.9% saline, followed by 0.45% saline for urine output replacement and her plasma sodium rose to a maximum of 165 mmol/l, with an osmolality of 344 mosm/kg. A concomitant urine osmolality was 114 mosm/kg (see table 1). Plasma sodium gradually normalised with oral and intravenous water administration. She had further episodes of hypernatraemia (up to 184 mmol/l) associated with starving for surgical procedures (gastrostomy insertion and revision) and each time hypotonic urine was noted. Administration of DDAVP 0.3 mcg/kg intravenously failed to increase urine osmolality, consistent with a diagnosis of nephrogenic diabetes insipidus.

Case 2: nephronophthisis

A 6-y old boy was referred because of a long-standing history of polyuria/polydipsia and nocturnal enuresis. There was no family history of NDI or other renal diseases. A renal ultrasound was reported as normal with no evidence of hydronephrosis. He underwent a water deprivation test with subsequent pitressin administration (table 1) with a maximum urine osmolality of 396 mosm/kg. This was interpreted as a urinary concentrating defect, but a molecular analysis of AVPR2 and AQP2 revealed no mutation. He was re-investigated at the age of 9 years, at which time his maximal urine osmolality after DDAVP was 151 mosm/kg. He also showed signs of chronic renal insufficiency with an elevated creatinine of 98 umol/l, elevated PTH, borderline anaemia and proteinuria, quantified at 800mg/24h. A renal biopsy showed chronic tubulointerstitial fibrosis with some glomerular sclerosis. A diagnosis of nephronophthisis was suspected and confirmed by molecular analysis, which revealed a homozygous large deletion, including exon 5–20, within *NPHP1*.

Case 3: Bartter Syndome

A 4-y old girl presented with severe failure-to-thrive. Subsequent investigations revealed bilateral nephrocalcinosis, borderline hypokalemia, hypochloremia and metabolic alkalosis with hypercalciuria, leading to a diagnosis of Bartter syndrome. Molecular testing revealed a homozygous deletion in the *KCNJ1* gene (c.715 del G). A renal ultrasound revealed nephrocalcinosis, but no hydronephrosis. On routine investigations, urine osmolality was always below 160 mosm/kg. When she was starved in the context of gastrostomy insertion, her plasma sodium rose to 148 mmol/l with an elevated plasma osmolality of 304 mosm/kg. Concurrent urine osmolality was 191 mosm/kg with no substantial increase after DDAVP (max. 205 mosm/kg), consistent with a diagnosis of nephrogenic diabetes insipidus.

Case 4: AME

A 2-y old girl was referred because of failure-to-thrive. Past medical history was remarkable for intrauterine growth retardation resulting in a C-section at 35 weeks gestation with a birth weight of 1.7 kg. She had been assessed for failure-to-thrive at 15-months of age and a diagnosis of NDI had been made based on an inappropriately dilute urine of 145 mosm/kg in the face of an elevated serum osmolality (307 mosm/kg) with elevated AVP levels in her plasma. Her biochemistries were notable for a hypokalaemic (2.6 mmol/l), hypochloraemic (96 mmol/l) metabolic alkalosis (bicarbonate 29 mmol/l) with intermittently elevated blood pressure (systolic 100–130 mmHg). Her urine osmolality was persistently below 150 mosm/kg and did not increase after DDAVP (see table 1), consistent with nephrogenic diabetes insipidus. The biochemical abnormalities with hypertension eventually suggested a diagnosis of apparent mineralocorticoid excess, which was confirmed with a urine steroid profile (high ratio of cortisol to cortisone metabolites). Mutation analysis revealed a homozygous mutation c.710C>T; p.A273V in the underlying gene *HSD11B2*.

Consequently, treatment with spironolactone and amiloride was commenced, resulting in normalisation of blood pressure and electrolytes. With the treatment, the parents noted a marked decrease in her water intake and a random urine osmolality was 705 mosm/kg, consistent with resolution of her NDI.

Discussion

Secondary NDI has previously been described as a complication of inherited renal diseases (see below). Yet our data here comprise the first description with molecular confirmation of the underlying diagnosis, clinical evidence for intact AVPR2 signalling in the vasculature and no identified mutation in primary NDI genes. We therefore provide solid evidence that secondary NDI occurs indeed as a secondary complication and not as the consequence of an incidentally present second disease. These cases highlight three key aspects:

- The importance of obtaining urinary indices in patients with hypernatremia. Recognition of this complication was delayed in two of the cases resulting in episodes of hypernatremic dehydration
- The need to consider a primary disorder if unusual aspects are present: NDI was mistakenly assigned as the primary diagnosis in two cases delaying recognition of the underlying disorder
- The occurrence of NDI as a secondary complication reveals clues about the underlying pathophysiology

Cystinosis

A case of nephropathic cystinosis presenting with “pitressin-resistant hyposthenuria” was described in 1967 and a few further case reports have followed [8–11]. With proximal tubular dysfunction, osmotic diuresis could contribute to urinary water losses, however, one would expect iso- to hypertonic urine, rather than the hypotonic urine seen in this case, which suggests true aquaporin deficiency. Whilst the initial presentation with hyponatremia appears to conflict with a diagnosis of NDI, this occurred during non-oliguric acute renal failure (creatinine 390 mcmol/l) and at a time of tubular dysfunction/necrosis, specific tubular defects like NDI cannot be detected. Of the four primary diseases presented here, it is perhaps easiest to rationalize the development of secondary NDI in cystinosis. The trapping of cystine in lysosomes results in cellular dysfunction, which in the kidney, primarily affects the proximal tubule, but can impair function of any cell [12]. We have not systematically investigated urinary concentrating ability in other patients with this disease. Random urine osmolalities in 5 patients with cystinosis followed at Great Ormond Street Hospital were consistently below plasma (data not shown), but in the absence of an elevated plasma osmolality and without administration of DDAVP this clearly does not constitute proof of NDI. Moreover, in two further patients, random urine osmolalities (320 and 352 mosm/kg, respectively) were above normal plasma osmolalities, suggesting that NDI is not a universal feature of this disease.

Nephronophthisis

Nephronophthisis is classically associated with polydipsia and polyuria and hyposthenuria has been described in some cases [13,14]. Another case was described from suffering from NDI, but the data presented in the paper show a maximum urine osmolality of 434 mosm/kg, virtually excluding true aquaoprin deficiency [15]. Holliday et al presented a case of “pitressin-resistant hyposthenuria” in a 13-y old boy with medullary cystic disease, which today, presumably, would be classified as nephronophthisis [11]. We have not systematically assessed urinary concentrating ability in this diagnosis. Not uncommonly, patients with nephronophthisis present in end-stage renal failure, when such investigations

are meaningless. Assessing those presenting with early symptoms, like our patient, is likely to select for those with the most severe polyuria. The etiology of secondary NDI in patients with nephronophthisis is unclear. Key histological features of this disease are tubulointerstitial fibrosis, tubular atrophy and tubular basement membrane disruption [16]. With generalized disruption of tubular function one would expect isosthenuria, i.e. the inability to concentrate or dilute urine. Indeed, this was seen in our patient, when he was first assessed at the age of 6 years, when his maximum urine osmolality was 396 mosm/kg. And in another patient (9-y old boy with the common exon 5 deletion in NPHP1 identified by family screening due to an affected older sibling), we observed a maximal urine osmolality of 300 mosm/kg after DDAVP administration. This suggests that NDI may evolve in some patients during the course of the disease, as the tubulointerstitial fibrosis may affect CD more severely than earlier nephron segments.

Bartter syndrome

Bartter syndrome is perhaps the most surprising diagnosis to underlie secondary NDI. Bartter syndrome is due to an inability to reabsorb salt in TAL [17]. Salt reabsorption in TAL results in urinary dilution and generation of the interstitial concentration gradient, since this segment is water impermeable. For this reason, TAL is also referred to as the urinary diluting segment and TAL dysfunction is thus most commonly associated with isosthenuria [18]. The presence of hypotonic urine in such patients raises the question of how urine is diluted when the diluting segment is broken. Presumably, more distal segments, which are also water impermeable, are able to compensate for the loss of TAL function to some degree. In fact, hyposthenuria is seen in a substantial minority and we have previously described in detail a case of secondary NDI in Bartter syndrome, with a minimal measured urine osmolality of 63 mosm/kg [2]. Hyposthenuria has been described only in patients with mutations in either *SLC12A1* or *KCNJ1* (Bartter type 1 or 2) [18]. Nevertheless, there seems to be no clear genotype-phenotype correlation. Indeed, the sister of the patient presented here also suffers from Bartter syndrome with the same mutation identified. She underwent a DDAVP test with a maximum urine osmolality of 343 mosm/kg, consistent with isosthenuria. Therefore, it seems that other factors, genetic or environmental, lead to the complication of secondary NDI, and several have been suggested including:

- Hypokalemia is associated with decreased AQP2 expression [19]. However, plasma potassium levels in Bartter patients are very similar to those seen in Gitelman syndrome, where urine concentration is apparently unaffected. Moreover, the lowest plasma potassium levels are typically seen in patients with CLCKNB mutation, which do not have hyposthenuria [20].
- Hypercalciuria is thought to affect renal concentrating ability via activation of the calcium-sensing receptor CaSR, which is expressed on the luminal aspect of the collecting duct [21]. However, in a study of healthy subjects, the urinary calcium concentration was inversely related to urine volume, reflecting the concentration of the urine [22]. Thus the highest urine calcium concentration (17 mmol/l) was seen in the most concentrated urine (1258 mosm/kg), raising serious doubts about the ability of urinary calcium to impair renal concentrating ability.
- Nephrocalcinosis could potentially alter the physical relationship between tubular lumen, interstitium and vasa recta, impairing water reabsorption.
- High urinary flow and pressure may cause changes in the expression of AQP2 [6]. This is based on the observation that patients after relief of urinary obstruction experience a transient NDI [23]. Whilst ultrasound of the children presented here did not reveal any evidence for an obstructive uropathy, the high urinary flow seen in Bartter syndrome may cause similar changes [2].

Regardless of the etiology, the presence of this complication presents a therapeutic dilemma. Bartter syndrome is primarily a salt-wasting disorder and supplementation with large quantities of salt (10 mmol/kg/d is not unusual) is considered a mainstay of treatment [17]. Yet, in NDI, salt restriction is crucial to minimize renal solute load and thus urine output [1]. Indeed, in our experience salt supplementation in babies with Bartter syndrome and secondary NDI is associated with persistent hypernatremia and the older patients do not seem to exhibit the profound salt craving seen in uncomplicated Bartter syndrome patients, but are rather preoccupied with drinking of water.

AME

A urinary concentrating defect has long been recognized in patients with this disorder [24]. Considering he overlap of biochemical and radiological features (hypokalaemic metabolic alkalosis with hypercalciuria and nephrocalcinosis) it is tempting to speculate that the aetiology is similar to that in Bartter syndrome. This would make a flow/pressure-dependent origin of the secondary NDI unlikely, as AME is not primarily a polyuric disorder: the defect is enhanced sodium reabsorption in the collecting duct, which has no direct implications for urine flow. The most fascinating aspect of the case presented here is the complete reversibility of NDI, once AME was treated and biochemistries had normalised: whilst at presentation and before appropriate treatment, urine osmolality was consistently below 200 mosm/kg with a maximum of 129 mosm/kg after DDAVP, a first morning urine osmolality under appropriate treatment was 705 mosm/kg (see table 1), excluding the presence of NDI at this point. This reversibility excludes nephrocalcinosis as a potential etiology, as this remained unchanged. Thus, of the four potential causes of secondary NDI in Bartter syndrome discussed above, only hypokalemia and hypercalciuria or the combination of both could provide a common explanation for the occurrence of NDI in both Bartter syndrome and AME. In this context, it would be interesting to assess the urinary concentrating ability in patients with distal renal tubular acidosis (dRTA), another disorder associated with hypokalemia and hypercalciuria. Indeed, polyuria and dehydration are well-recognised symptoms at presentation [25,26]. Impaired urinary concentration and altered AQP2 trafficking were shown in AE1-deficient mice, a mouse model of dRTA [27]. Indeed, coexistence of dRTA and NDI have been described previously, although the etiology in that case was thought to be tubular damage from light-chain excretion due to a myeloma [28]. Measurements of urine osmolalities at presentation or during inadequate treatment (hyopokalemic acidosis and hypercalciuria present) were available in 5 children with dRTA followed at Great Ormond Street Hospital and ranged from 110 to 366 mosm/kg, suggesting a variable concentration defect. However, we have not performed DDAVP tests to confirm this. Since appropriate treatment normalises the biochemical abnormalities in this disorder, one would expect resolution of a potential concentrating defect, as well. Indeed, random urine osmolalities obtained in clinic, when plasma biochemistries were normal and no hypercalciuria was present were typically well above plasma (max. 650 mosm/kg).

Clinical Relevance

Regardless of the mechanism, the diagnosis of NDI as a secondary complication is important, as these patients are at risk of hypernatremic dehydration. We know from patients with untreated NDI that recurrent hypernatremic episodes can be associated with developmental delay [29]. Early recognition and appropriate management are thus critical. Whilst water intake driven by thirst keeps patients safe, they are at risk, if this is impaired because of vomiting or, as in 2 of the cases presented here, if they are starved before procedures. These patients need hypotonic fluids rather than the isotonic replacement preferred in most hospitals and close biochemical monitoring. It is also important to recognize NDI in these cases as a complication, in order to avoid missing the underlying diagnosis: the boy presented here with nephronophthisis was misdiagnosed as primary NDI

for years until the recognition of the advancing renal insufficiency prompted further investigations which correctly identified the underlying problem. Similarly, the girl with AME first received a diagnosis of NDI with the biochemical abnormalities attributed to the subsequent thiazide treatment. AME is a potentially fatal disorder, but easily treatable, so establishing the correct diagnosis is of crucial importance. There are also reports in the literature of cases of Bartter syndrome being misdiagnosed as primary NDI and it is likely that the diagnosis of Bartter syndrome in our case here was delayed until 4 years of age because of the co-existent secondary NDI, as the resulting low concentration of urine electrolytes can be seen as incompatible with Bartter syndrome [30]. The presence of features atypical for primary NDI, such as polyhydramnios, hypercalciuria/nephrocalcinosis, hypokalemia (before instigation of thiazide treatment), chronic renal impairment or renal Fanconi syndrome and, of course, the absence of an identifiable mutation in known NDI genes should prompt investigations into a potential primary disorder. The treatment of primary NDI usually entails thiazide diuretics. The mistaken use of such drugs in a salt-wasting disorder like Bartter syndrome could have potentially devastating consequences, as compensatory avid salt-reabsoprtion in DCT is thought to compensate for the salt losses from TAL [2].

Conclusion

NDI can occur as secondary complication in various disorders. In the face of hypernatremia, urine indices must be assessed, as the presence of a concentrating defect clearly alters management. Moreover, a diagnosis of primary NDI must be challenged if unusual features are present to identify a potential underlying disorder.

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Table 1

pertinent biochemistries of the four cases

Shown are biochemistries from plasma and urine during episodes of dehydration and after administration of vasopressin analogues (shown is the result from the aliquot with the highest osmolality obtained within 3 hours after an intravenous injection of 0.3 mcg/kg DDAVP). Note that urine osmolality remains well below plasma osmolality during dehydration, as well as after DDAVP, consistent with NDI. In case 2 the NDI appears to have developed with time, as urine osmolality at the age of 6 years was above that of plasma. Case 4 recovered urinary concentrating ability after treatment of her AME. ND: not determined

Case 1: cystinosis		**Dehydration episodes**		**DDAVP**	
				pre	**post**
Age (years)		2.5	3.5	3.5	
Plasma	Na (mmol/l)	165	182	148	
	K (mmol/l)	4.4	3.8	3.7	
	Osmolality (mosmol/kg)	344	365	296	
	Creatinine (μmol/l)	1068	113	89	
Urine	Na (mmol/l)	33	45	8	
	Ca (mmol/l)	ND	ND	ND	
	Osmolality (mosmol/kg)	114	125	52	57
Case 2: nephronophthisis			Pitressin 0.9 units	DDAVP	
				pre	post
Age (years)		6	6	9	
Plasma	Na (mmol/l)	146	146	144	
	K (mmol/l)	4.2	ND	ND	
	Osmolality (mosmol/kg)	303	306	ND	
	Creatinine (μmol/l)	53	ND	98	
Urine	Na (mmol/l)	ND	ND	39	
	Ca (mmol/l)	ND	ND	ND	
	Osmolality (mosmol/kg)	360	396	130	151
Case 3: Bartter syndrome			DDAVP		
			pre	post	
Age (years)		7	8		
Plasma	Na (mmol/l)	148	137		

Case 1: cystinosis		Dehydration episodes		DDAVP	
				pre	post
	K (mmol/l)				
Osmolality (mosmol/kg)		304	291		
Creatinine (μmol/l)		33	25		
Urine	Na (mmol/l)	33	15		
	Ca (mmol/l)	2.8	ND		
Osmolality (mosmol/kg)		191	205	167	
Case 4: apparent mineralocorticoid excesss			DDAVP		Post AME treatment
			pre	post	
Age (years)		1.2	2.2		2.3
Plasma	Na (mmol/l)	146	136		136
	K (mmol/l)	3.7	2.3		5.0
Osmolality (mosmol/kg)		307	293		ND
Creatinine (μmol/l)		42	43		45
Urine	Na (mmol/l)	21	8		156
	Ca (mmol/l)	ND	1.52		0.6
Osmolality (mosmol/kg)		145	107	129	705