CASE REPORT

Renal Tubular Acidosis Presenting as Nephrogenic Diabetes Insipidus

Debaditya Das, Rajiv Sinha and Subrata Dey
From Department of Pediatrics, Apollo Gleneagles Hospitals, 58, Canal Circular Road, Kolkata, India.

Correspondence to: Dr Debaditya Das, PGY-3 DNB Pediatrics, Apollo Gleneagles Hospital, Kolkata, India. dasdebaditya@yahoo.com
Received: February 16, 2018; Initial review: August 11, 2018; Accepted: January 23, 2019.

Background: Nephrogenic diabetes insipidus (DI) can be primary or secondary to various causes. ***Case Characteristics*:** One child with Fanconi syndrome with proximal renal tubular acidosis (RTA) due to nephropathic cystinosis, and other with Distal RTA with hearing loss. ***Observation***: Both cases showed features of nephrogenic DI, which resolved after treating the primary pathology. **Message**: Renal Tubular acidosis may cause nephrogenic DI.

Keywords: *ATP6V1B1 gene, Nephropathic cystinosis, Polyuria*.

Nephrogenic Diabetes Insipidus (DI) is characterized by passage of dilute urine despite inappropriately elevated serum osmolailty and lack of response to even extraneous vasopressin (*i.e.,* failed vasopressin challenge test). In children it is commonly linked to underlying genetic mutations in genes encoding Arginine-Vasopressin Receptor 2 (AVPR2) or Aquaporin 2 (AQP2) as well as acquired conditions like obstructive uropathy [1,2]. Renal tubular acidosis (RTA) presenting as nephrogenic DI has been rarely reported in the pediatric age group. We report two such cases one each of proximal (secondary to cystinosis) and distal RTA.

Case Reports

Case 1: A 2-year-old girl born out of consanguineous marriage presented with polyuria, polydipsia and failure to thrive. The *X*-rays of the child were consistent with rachitic changes. Investigations (***Table* I**) showed normal anion gap hyperchloremic metabolic acidosis, high sodium, low potassium, low phosphate and high alkaline phosphatase. Along with normal serum anion gap; urine anion gap was positive suggesting renal tubular acidosis. Elevated urinary phosphate (Tmp/GFR= 0.04 mg/dL) and glycosuria pointed it to be of proximal *i.e*. Type 2 variant, which was confirmed by furosemide challenge test wherein urinary pH dropped down to 5.1. Eye examination revealed cystine crystals in the cornea. Although the investigations were suggestive of nephropathic cystinosis; persisting hypernatremia led us to check paired serum and urine osmolality. The urine osmolality was low but serum osmolality was inappropriately elevated and there was no response to vasopressin challenge – confirming NDI. Genetic analysis showed homozygous 5' splice site mutation in *cystinosin* gene, further confirming cystinosis to be the underlying cause for the NDI. The child was started on indomethacin, phosphate supplementation, Shohl's solution along with cysteamine, which is the specific treatment for cystinosis. Repeat urinary osmolality tested three months after treatment was 523 mOsm/kg with a corresponding serum osmolality of 293 mOsm/kg.

Case 2: A 14-month-old girl born out of non-consanguineous marriage presented in a severely dehydrated state with history of increased thirst and passage of excessive urine. Initial investigation (***Table* I**) revealed hyperchloremic normal anion gap metabolic acidosis with hypokalemia along with hypernatremia. In presence of hypernatremia, paired urinary and serum osmolality testing was undertaken which suggested the diagnosis of DI (***Table* I**). This was confirmed to be of renal origin (NDI) after failed vasopressin challenge test. Serum phosphate levels were normal but alkaline phosphatase was high which along with *X*-ray findings was consistent with presence of underlying rickets. Ultrasound revealed bilateral nephrocalcinosis. Further work-up revealed elevated urinary calcium-creatinine ratio, normal urinary phosphate and positive urinary anion gap. A diagnosis of dRTA was made post furosemide challenge, as the lowest urinary pH post frusemide challenge was only 6. Genetic analysis showed a homozygous mutation of the *ATP6V1B1* gene, thus confirming the primary diagnosis of distal RTA with secondary NDI. The child also had moderate bilateral sensori-neural hearing deficiency. Repeat urinary osmolality tested two months after treatment was 769 mOsm/kg with a corresponding serum osmolality of 296 mOsm/kg.

DISCUSSION

Arginine-vasopressin (AVP) or anti-diuretic hormone (ADH) is synthesized in the magnocellular neurons of the supraoptic and paraventricular nuclei of the hypothalamus, and is primarily secreted as a response to an increase in serum osmolality [1]. In its effector organ *i.e.* the kidneys AVP acts on the V2 (AVPR2) receptors, and relocates the aquaporin 2 (AQP2) channels from intracellular vesicles to the apical plasma membrane. This relocation of the aquaporin 2 channels results in increased water permeability of the collecting ducts, enabling the kidneys to concentrate the urine [1].

Although NDI can occur as a primary phenomenon in young children due to genetic defects in the *AVPR2* and *AQP2* genes, it can also occur secondary to hereditary tubulo-pathies. In such cases, treating the primary disorder can lead to complete/partial resolution of the NDI and we can avoid serious irreversible damages. We hereby presented two cases of NDI secondary to proximal and distal RTA. The case series highlighted the importance of looking for red flag signs such as hypokalemia, acidosis and or features of rickets in children presenting with NDI. These signs would suggest a secondary cause rather than the classical aquaporin receptor resistance/aquaporin deficiency.

TABLE I BIOCHEMICAL PARAMETERS OF CHILDREN WITH NEPHROGENIC DIABETIS INSIPIDUS.

Parameters	*Case* 1	*Case* 2
Serum Na (meq/L)	156	153
Serum K (meq/L)	2.5	3
Serum Cl (meq/L)	125	125
Serum HCO^3 (meq/L)	11	6
Serum PO^4 (mg/dL)	1.6	3.5
Serum ALP (U/L)	1261	530
Serum Urea (mg/dL)	33	42
Serum Creatinine (mg/dL)	0.8	1.0
Venous Blood Gas		
pH	7.19	7.13
PCO_2	38	10
HCO_3	13	4.3
Anion gap	17	15.5
Urinary Indices		
pH	6.0	7.0
Na	39	19
K	19.5	25
Cl	52	17
Anion gap	+6.5	+27
TmP/GFR (mg/dL)	0.04	4.26
*Minimum Urinary pH	5.1	6.0
Serum Osmolality		
Pre-Vasopressin (mOsm/kg)	326	308
Post-Vasopressin (mOsm/kg)	322	303
Urine Osmolality		
Pre-Vasopressin (mOsm/kg)	210	249
Post-Vasopressin (mOsm/kg)	215	348

**Furosemide challenge test; Na: sodium; Cl: chloride; K: potassium; HCO_3: bicarbonate; PO_4: phosphate; ALP: Alkaline phosphatase.*

NDI secondary to cystinosis was described more than five decades ago [4,5]. The entrapment of intra-lysosomal cystine crystals can lead to dysfunction of the tubular cells, which although mainly damages the cells in the proximal tubule, can also compromise the function of any other tubular cell, including cells of the collecting duct [6]. Our second case of dRTA with NDI is quite unique, as the entity has not been described in pediatric age group. Kalyanasundaram, *et al*. [7] did describe a 28-day-old newborn with dRTA who also had features of NDI but unfortunately no mutation study was reported to substantiate the diagnosis [7]. Among adults there are reports of dRTA with NDI, but usually they have a secondary cause such as Sjogren syndrome [8].

The pathogenesis behind the association of dRTA and NDI remains to be properly elucidated. Stehberger, *et al*. [9] demonstrated that mice lacking the AE1 (Band3) Cl-/HCO_3 Exchanger protein that caused dRTA in them, had urinary-concentrating defect associated with defective inner medullary AQP2 trafficking. However, our patient had a different mutation and whether a similar mechanism happens in this mutation needs to be explored. Other hypothesis includes implicating hypokalemia or hypercalciuria, which are often present in these children. Marples, *et al*. [10] showed that there is a down-regulation of AQP2 expression in rat kidneys due to hypokalemia. Hypercalciuria can be the other causative mechanism, as it is thought to activate calcium-sensing receptor CaSR expressed on the luminal side of the collecting duct and thereby modulate expression of AQP2 [11]. Unfortunately these are mere postulations as both hypokalemia and hypercalciuria are quite common in dRTA whereas NDI in dRTA is rare.

It is of utmost importance that whenever we are encountering a child with NDI, we should have a strong suspicion for any underlying secondary etiologies and associated features like rickets; persisting hypokalemia or acidosis should make us look for underlying RTA. Missing this diagnosis can be dangerous for the child as improper management of hypernatremia can have a catastrophic effect on the child's neurological outcome.

Contributors: DD: collected and analyzed the data and drafted the manuscript; RS: conceptualized the case series, edited the manuscript; SD: conceptualized the case series, edited the manuscript.
Funding: None; *Competing Interests*: None stated.

REFERENCES

1. Knoers NVAM, Levtchenko EN. Nephrogenic Diabetes Insipidus in Children. *In*: Avner ED, Harmon WE, Niaudet P, Yoshikawa N, Emma F, Goldstein SL, editors. Pediatric Nephrology, 7th ed. Berlin: Springer Reference; 2016. *p*. 1309-10.
2. Bichet DG, Oksche A, Rosenthal W. Congenital nephrogenic diabetes insipidus. J Am Soc Nephrol.1997;8:1951-8.
3. Bockenhauer D, van't Hoff W, Dattani M, Lehnhardt A, Subtirelu M, Hildebrandt F, *et al*. Secondary nephrogenic diabetes insipidus as a complication of inherited renal diseases. Nephron Physiol. 2010;116:23-9.
4. Holliday MA, Egan TJ, Morris CR, Jarrah AS, Harrah JL. Pitressin-resistant hyposthenuria in chronic renal disease. Am J Med. 1967;42:378-87.
5. Lemire J, Kaplan BS. The various renal manifestations of the nephropathic form of cystinosis. Am J Nephrol. 1984;4:81-5.
6. Bockenhauer D, van't Hoff W, Fanconi Syndrome. *In*: Geary DF, Schaefer F, editors. Comprehensive Pediatric Nephrology. Philadelphia: Mosby Elsevier; 2008. p. 433-50.
7. Kalyanasundaram S. Autosomal recessive distal renal tubular acidosis with secondary nephrogenic diabetes insipidus in newborn a case report. E journal TN MGR Medical University. Available at: *http://ejournal-tnmgrmu.ac.in/index.php/medicine/article/ view/1438*. Accessed September 6, 2018.
8. Nagayama Y, Shigeno M, Nakagawa Y, Suganuma A, Takeshita A, Fujiyama K, *et al*. Acquired nephrogenic diabetes insipidus secondary to distal renal tubular acidosis and nephrocalcinosis associated with Sjögren's syndrome. J Endocrinol Invest. 1994;17:659-63.
9. Stehberger PA, Shmukler BE, Stuart-Tilley AK, Peters LL, Alper SL, Wagner CA. Distal renal tubular acidosis in mice lacking the ae1 (band3) cl-/hco3- exchanger (slc4a1). J Am Soc Nephrol. 2007;18:1408-18.
10. Marples D, Frokiaer J, Dorup J, Knepper MA, Nielsen S. Hypokalemia-induced downregulation of aquaporin-2 water channel expression in rat kidney medulla and cortex. J Clin Invest. 1996;97:1960-8.