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Case Report

Novel *AVPR2* Mutation Causing Congenital Nephrogenic Diabetes Insipidus

JMY ***Ma***, LCN ***Chan***, SC ***Chong***, HM ***Cheung***

Abstract A 7-month-old male infant presented with repeated vomiting and failure to thrive. Hypernatraemia, high serum osmolality, low urine osmolality, and lack of response to DDAVP, suggested diagnosis of nephrogenic diabetes insipidus. Genetic exome sequencing showed a novel *hemizygous c.802_834dup, p.(Lys268_Val278dup) variant in exon 3 of AVPR2 gene, with in-frame duplication of 11 residues starting from 268th codon (NM_000054.6)*. This variant is of uncertain significance; the clinical phenotype was compatible with nephrogenic diabetes insipidus. Treatment with indomethacin, hydrochlorothiazide led to good clinical outcome.

Key words *AVPR2 mutation; Congenital nephrogenic diabetes insipidus*

Introduction

Nephrogenic diabetes insipidus (NDI) is a rare condition characterised by excretion of large amount of dilute urine, due to the kidneys' insensitivity to vasopressin. We report a case of congenital NDI from a novel *hemizygous c.802_834dup, p.(Lys268_Val278dup) variant in exon 3 of AVPR2 gene (NM_000054.6)*, who presented with repeated vomiting, failure to thrive and life-threatening hypernatraemia.

Department of Paediatrics, Prince of Wales Hospital, 30-32 Ngan Shing Street, Shatin, N.T., Hong Kong SAR, China
JMY **Ma** (馬銘賢) *MBChB, MRCPCH*
LCN **Chan** (陳子昂) *MBChB, MRCPCH, FHKAM(Paediatrics)*
HM **Cheung** (張漢明) *MBBS, MRCPCH, FHKAM(Paediatrics)*

Department of Paediatrics, The Chinese University of Hong Kong; and Joint CUHK-Baylor Centre of Medical Genetics, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR, China
SC **Chong** (莊淑貞) *MBBS, MRCPCH, FHKAM(Paediatrics)*

Correspondence to: Dr JMY **Ma**
Email: just.ma03@gmail.com

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Case Report

A 7-month-old boy presented to our unit with repeated projectile vomiting. He was the first child of non-consanguineous parents, born at full term with normal antenatal and newborn metabolic screening results. The infant was fed on artificial formula milk since birth and developed recurrent projectile non-bilious vomiting since four months of age. His feeding regime was up to 160 ml/kg/day. He had normal bowel openings and urine output all along.

The infant was brought to a paediatrician for failure to thrive with all growth parameters dropping from 10th percentile at one month to less than 3rd percentile at six months of age. A presumptive diagnosis of global developmental delay and generalised hypotonia was made, and he was referred to our tertiary paediatric unit. Upon admission, the infant had fair hydration. Abdominal and neurological examination were unremarkable apart from mild central hypotonia. No dysmorphic features were identified.

An abdominal ultrasound scan ruled out pyloric stenosis. Blood tests revealed significant hypernatraemia and hyperchloraemia (Table 1). Other blood tests including complete blood count, liver function, creatinine, C-reactive-protein, amino acid, lactate, and glucose were normal.

Table 1 Blood results upon hospital admission

Plasma	Result (mmol/L)	Normal range (mmol/L)
Sodium	155	136-145
Chloride	117	98-107

Patient was kept nil-per-oral with intravenous rehydration for hypernatraemic dehydration. An NS:D5 solution (sodium concentration of 154 mmol/L) was given intravenously for daily fluid maintenance aiming to replenish his free water deficit over 36 hours, targeting a gradual reduction of plasma sodium by 0.5 mmol/L/hour.

Despite intravenous rehydration, the plasma sodium increased to 165 mmol/L after four hours. Patient was transferred to paediatric intensive care unit for close monitoring. Diabetes insipidus was suspected based on an elevated plasma osmolality of 323 mOsm/kg with a paired urine osmolality of 217 mOsm/kg. The spot urine sodium was less than 20 mmol/L, and the urine specific gravity was 1.0.

Intravenous DDAVP of 0.2 micrograms was given which showed no response in urine osmolality and urine output remained at 10 ml/kg/hour. Plasma sodium reached maximum level of 170 mmol/L. Computed tomography of the brain did not identify any lesions to cause central diabetes insipidus. With hypernatraemia, high serum osmolality, low urine osmolality, low urinary sodium excretion and lack of response to DDAVP, the diagnosis of nephrogenic diabetes insipidus was made. Oral hydrochlorothiazide (2 mg/kg/day) and oral indomethacin (1.5 mg/kg/day) were started. Concomitant oral nexium was given for gastric protection. Sodium concentration of intravenous fluid was titrated down to 30 mmol/L according to plasma sodium levels.

The infant was allowed to be tube fed with low solute high calorie milk tailored by dietician. A maximum solute load was set at 15 mOsm/H_2O/kg/day with total daily fluid at 140 ml/kg/day. Intravenous fluids were weaned off when the infant could tolerate enteral feeds. The plasma sodium gradually decreased not more than 0.5 mmol/L/hour reaching 145 mmol/L after 72 hours. Full oral feeding was achieved after training with no recurrence of vomiting.

The patient was discharged four weeks after admission with careful titration of medications and fluid intake. Home medications include hydrochlorothiazide and indomethacin. Management of sudden diuresis by replacing fluid deficit with free water was advised. Upon regular follow up three months later, patient enjoyed good weight gain with significant catch up of neurodevelopment.

Subsequent patient's genetic exome sequencing by DNA extraction showed a novel *hemizygous c.802_834dup, p.(Lys268_Val278dup) variant in exon 3 of AVPR2 gene, with in-frame duplication of 11 residues starting from 268th codon (NM_000054.6)*. The medical exome was enriched by capture system (Clinical Exome Solution v2, SOPHiA GENETICS). The targeted regions were sequenced simultaneously by parallel sequencing on Illumina platform (NextSeq 500) with paired end reads. Bi-directional sequence were assembled, alignment to reference gene sequences based on human genome build GRCh37/USCS hg19 by ELSA aligner and variant caller followed by bioinformatics analysis of the detected variants. The mutation hasn't been reported in literature or major genomic databases (human gene mutation, genome aggregation, ClinVar and ExAC). This variant is of unknown clinical significance (VUS) (PM2, PM4) according to American College of Medical Genetics and Genomics guideline.[1] Patient's phenotype was compatible with nephrogenic diabetes insipidus.

Discussion

Diagnosis of NDI can be challenging in infants. Paediatricians should have a high index of suspicion in patients presenting with good urine output despite repeated vomiting. Infants with persistent vomiting usually point towards gastrointestinal problems such as pyloric stenosis or gastro-oesophageal reflux. However, when feeding problem persists causing failure to thrive, other causes should be considered.[2] Serum renal function test may reveal hypernatraemia. Urinalysis could show low urine osmolality.

Approximately 90% of congenital NDI cases are caused by *AVPR2* gene mutation, where more than 250 mutations have been found. *AVPR2* gene mutation has X-linked inheritance, typically inherited in a recessive manner.[3] We report a novel *hemizygous c.802_834dup, p.(Lys268_Val278dup) variant in exon 3 of AVPR2 gene, with in-frame duplication of 11 residues starting from 268th codon (NM_000054.6)*. According to current literature, our patient is the first case of NDI phenotype with this mutation. Patient's mother and maternal aunt carries the same variant on their X chromosome, and both are asymptomatic. This mutation has X-linked recessive inheritance.

Though the variant was classified as VUS, there were case reports of NDI with similar in-frame duplications

involving codon 278, involving the transmembrane domains.[4,5] The transmembrane domains are essential for G-protein-coupled receptor function. The in-frame duplication may affect ligand binding through alternating transmembrane helix's structure, which affects intracellular signalling. Maternal grandfather's genotype and phenotype may potentially help reclassify the variant to be likely pathogenic. Unfortunately, the maternal grandfather's medical condition was not available. Overall, early genetic testing is crucial for diagnosis, identifying carriers, and counselling.

Persistent vomiting is a common presentation. Excessive diuresis induces a strong thirst behaviour, where thirsty infants are often irritable and will eagerly drink large amounts of fluid, leading to vomiting due to "overfeeding". Hypernatraemic dehydration is difficult to detect based on clinical examination alone. With the excessive urine output, clinicians may be falsely reassured of an adequate hydration state. With ongoing polyuria and poor feeding, young infants with NDI may be severely dehydrated on presentation.

Avoidance of 0.9% saline in acute management of hypernatraemic dehydration in NDI patients is crucial. NDI patients excrete hypotonic urine excessively leading to pure water loss. Infusion of 0.9% saline will cause net gain of sodium which worsens the hypernatraemia and causes further diuresis as the body attempts to excrete the excessive solute load by passing large amounts of dilute urine. Hence, patients should be treated via enteral route with water or milk, or intravenously with 5% dextrose and minimal sodium concentration.[2] Treating diuresis is easier when child is old enough to indicate thirst, as they can drink water freely. Intravenous fluids should be discontinued when patient is able to drink to allow the thirst mechanism to self-regulate.[6]

Minimising osmotic load to <15 mOsm/H_2O/kg/day, while maintaining high calorie-to-solute ratio allows adequate nutrition for growth.

Major stay of medical treatment includes hydrochlorothiazide, amiloride and indomethacin.[6] Fine tuning of these medications are required, depending on urine output and potential electrolyte disturbances. Thiazides paradoxically reduces urine output by blocking the urinary diluting mechanism in the distal tubule and increases urinary sodium excretion, leading to intravascular volume depletion. This enhances sodium and water reabsorption in the proximal tubule, hence less water is delivered to the defective distal tubule.[7] Hypokalaemia is a common side effect, where potassium supplements can be added. Alternatively, amiloride can be used with hydrochlorothiazide for potassium-sparing effect.

Indomethacin, a prostaglandin synthesis inhibitor, reduces urine output and has an additive effect to thiazides.[8] Indomethacin's exact mechanism remains unclear. It is hypothesised that prostaglandins impair proximal tubule sodium reabsorption.[9] Prostaglandin inhibitor reduces urine output by allowing proximal sodium reabsorption and subsequent water reabsorption, as the proximal tubule is water permeable.[10]

Long term care of NDI patients requires good carer support including meticulous measurement of fluid input and urine output. In case of sudden diuresis, fluid deficit should be replaced with free water. Patient's condition and initial management of diuresis should be added into hospital alert system to prevent complications.

Declaration of Interest

The authors have no conflict of interest to declare.

References

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: A joint consensus recommendation of the American College of Medical Genetics and genomics and the Association for Molecular Pathology. Genet Med 2015;17:405-24.
2. Bockenhauer D, Bichet DG. Nephrogenic diabetes insipidus. Curr Opin Pediatr 2017;29:199-205.
3. Spanakis E, Milord E, Gragnoli C. AVPR2 variants and mutations in nephrogenic diabetes insipidus: Review and missense mutation significance. J Cell Physiol 2008;217:605-17.
4. Tsukaguchi H, Matsubara H, Aritaki S, Kimura T, Abe S, Inada M. Two novel mutations in the vasopressin V2 receptor gene in unrelated Japanese kindreds with nephrogenic diabetes insipidus. Biochem Biophys Res Commun 1993;197:1000-10.
5. Tajima T, Nakae J, Takekoshi Y, et al. Three novel AVPR2 mutations in three Japanese families with X-linked nephrogenic diabetes insipidus. Pediatr Res 1996;39:522-6.
6. Rees L, Bockenhauer D. Webb NJA, Punaro MG. Paediatric nephrology. Oxford, UK: Oxford University Press; 2019.
7. Magaldi AJ. New insights into the paradoxical effect of thiazides in diabetes insipidus therapy. Nephrol Dial Transplant 2000;15:1903-5.
8. Usberti M, Dechaux M, Guillot M, et al. Renal prostaglandin E2 in nephrogenic diabetes insipidus: Effects of inhibition of prostaglandin synthesis by indomethacin. J Pediatr 1980; 97:476-8.
9. Kokko JP. Effect of prostaglandins on renal epithelial electrolyte transport. Kidney Int 1981;19:791-6.
10. Bockenhauer D, Bichet DG. Pathophysiology, diagnosis and management of nephrogenic diabetes insipidus. Nat Rev Nephrol 2015;11:576-88.