HK J Paediatr (new series) 2020;**25**:243-245

Case Report

A Case Report of Congenital Nephrogenic Diabetes Insipidus with Compound Heterozygous Mutation of the Aquaporin-2 Gene in a Chinese Male Infant

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Abstract Congenital nephrogenic diabetes insipidus is a rare disorder that affects the kidneys' ability in urine concentration. Both diagnosis and management of the disease, especially during infancy are challenging. We report a five-month-old boy with failure to thrive and hypernatraemic dehydration. The diagnosis of nephrogenic diabetes insipidus was confirmed with water deprivation test and mutation analysis of the aquaprorin-2 (*AQP2*) gene. Parental genetic analysis showed that the proband is a compound heterozygote for two pathogenic *AQP2* variants.

Key words Aquaporin-2, *AQP2*; Congenital nephrogenic diabetes insipidus

Introduction

Nephrogenic diabetes insipidus (NDI) is an inherited or acquired disorder in which the kidneys fail to respond to arginine vasopressin (AVP), resulting in the inability to concentrate urine. Congenital nephrogenic diabetes insipidus (CNDI) usually presents in the first year of life with repeated vomiting, polyuria, polydipsia and failure to thrive.[1,2] Ninety percent of CNDI cases are caused by mutations of the arginine vasopressin V2 receptor (*AVPR2*) gene which are inherited in an X-linked recessive manner, while less than 10% of cases are accounted by mutations of the aquaporin-2 (*AQP2*) gene which have an autosomal recessive or an autosomal dominant mode of inheritance.[3,4]

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Received September 13, 2019

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Case Presentation

This is a five-month-old boy with a history of Haemoglobin H disease, presented to us with repeated regurgitation and failure to thrive. His birth history and perinatal history were unremarkable. He was noted to have generalised hypotonia and significant head lag upon examination. His growth charts revealed decreasing trend of body weight, body length and head circumference from 50th centile down to 3rd centile.

Investigations

The patient was found to have severe hypernatraemia with serum sodium level up to 167 mmol/L (Reference range: 136-145 mmol/L). He was initially treated as hypernatraemic dehydration with intravenous fluid. However, the serum sodium level rose to 177 mmol/L. His serum osmolality was 340 mOsm/kg H_2O (Reference range: 275-295 mOsm/kg H_2O) and his urine osmolality was inappropriately low (132 mOsm/kg H_2O). He was also noted to have high urine output of 12 mL/kg/hr.

Water deprivation test was performed, with the urine osmolality remaining low at 104 mOsm/kg H_2O and the urine output high despite the administration of DDAVP. Plasma anti-diuretic hormone was 30.7 pg/ml (ref: 1.0-13.3 pg/ml). The diagnosis of nephrogenic diabetes insipidus was biochemically confirmed.

Other investigations, including growth hormone,

cortisol and adrenocorticotropic hormone, and computed tomography of the brain were unremarkable. Ultrasound of the kidneys showed mildly prominent right renal pelvis and calyces, likely related to the polyuric state and distended urinary bladder.

Genetic Analysis

Genetic testing on *AVPR2* gene (OMIM*300538) detected no pathogenic variant. Subsequent genetic analysis on *AQP2* gene (OMIM*107777) was performed with DNA extracted from peripheral blood of the patient. All coding exons and their exon/intron boundaries of at least 40 nucleotides were sequenced bi-directionally. Two heterozygous pathogenic *AQP2* variants, M_000486.5: c.3G>T p.? and NM_000486.5:c.140C>T p.(Arg47Val), were detected, as shown in Figure 1. Compound heterozygosity was confirmed by genetic testing on the patient's non-consanguineous parents. His mother was confirmed to be an unaffected carrier of the former variant, NM_000486.5:c.3G>T p.?; while his father is an unaffected carrier of the latter variant, p.(Arg47Val).

Treatment and Follow Up

The patient was put on low renal solute load formula and required hydrochlorothiazide, amiloride and indomethacin. His serum sodium level gradually normalised. Despite these measures, his weight gain remained fair, gaining only 1.3 kg over six months. He subsequently underwent surgery for gastrostomy. Upon his latest visit at 20 months of age, his body weight caught up to 75th centile and his body height and head circumference caught up to 10th centile. His development has caught up to age-appropriate standards.

Discussion

Mutations in the *AQP2* gene account for 10% of the CNDI cases. To date, at least 68 different mutations in the *AQP2* gene causing CNDI have been described. Of these, most are missense mutations, which are responsible for recessive CNDI. Both *AQP2* variants detected in our patient were in exon 1 and have been reported in non-Chinese patients confirmed with CNDI.[5,6] To our understanding, our patient is the first reported case of *AQP2*-related CNDI in Hong Kong.

The *AQP2* gene is located on chromosome 12q13 and codes for the 271-amino acid *AQP2* protein, a transmembrane protein characterised by six transmembrane domains connected by five loops and intracellular N- and C-termini, which is a vasopressin-regulated water channel at the apical membrane, the principal cells of the collecting duct. Mutations of *AQP2* result in CNDI which is characterised by the lack of responsiveness of the collecting duct to the antidiuretic action of vasopressin.[4] It has been postulated that the start codon mutation, *AQP2* c.3G>T p.?, may lead to abolition of the translation start site or use of an alternative in-frame initiation codon at position 46, the second ATG located in exon 1, which would result in elimination of the entire first and a small part of the second transmembrane domains of the *AQP2* protein. Mutations located in the first transmembrane domain leading to improper function of the *AQP2* protein have been reported.[5] Functional study suggested that the *AQP2* p.(Arg47Val) missense variant, causes protein misfolding and endoplasmic reticulum retention, hence retaining 40% of the water permeability of the wildtype *AQP2* protein.[6]

Many different treatment regimens have been employed

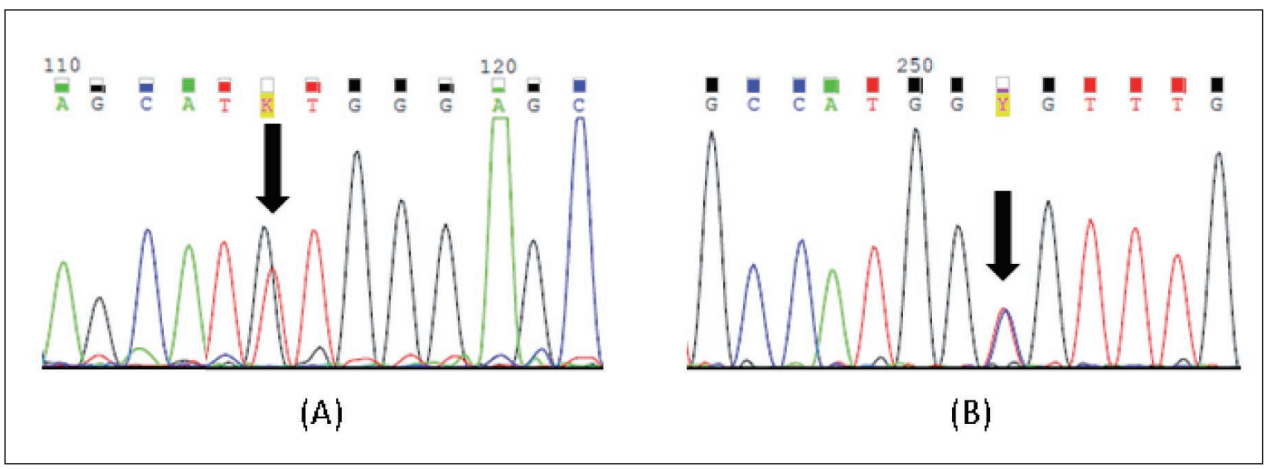

Figure 1 Electropherogram of two heterozygous pathogenic *AQP2* variants detected in the proband, (A) NM_000486.5:c.3G>T p.? and (B) NM_000486.5:c.140C>T p.(Arg47Val). The affected nucleotide is marked by an arrow.

by paediatricians worldwide in the treatment of CNDI, with the aim of preventing hypernatraemic dehydration, which may lead to developmental disability consequently. Current treatment strategies focus on relieving symptoms by diet modification and use of various combinations of medications.

By minimising the osmotic load without compromising caloric and fluid intake in affected infants can reduce urinary water loss whilst enabling normal growth and development.[3]

Infants who are formula fed usually present earlier than those who are breastfed as commercial formula is known to contain higher salt and protein content, which puts affected infants more susceptible to severe hypernatraemia and dehydration. Our patient has been formula fed all along and his symptoms developed since three months of age, but only presented to us at five months. A low renal solute load formula was given as recommended by dietitian.

Currently, there is no consensus on a specific regimen in treating children with CNDI. Different drug combinations have been reported over the years, most of which include the use of diuretics. In the Midwest Pediatric Nephrology Consortium's (MWPNC) study, up to 93% paediatricians chose thiazides as the main class of drug in treating patients with NDI.[7] Thiazides reduce urine output by increasing sodium and water reabsorption in the proximal tubules and delivering less water to the collecting ducts. However, hypokalaemia often results as a side effect. Therefore, potassium sparing agents such as amiloride are commonly used in combination with thiazides to ameliorate the potassium loss. Other combinations of medications include non-steroidal anti-inflammatory drugs (NSAIDs), for example indomethacin. The mechanism by which NSAIDs reduce water excretion in humans remains unclear, but it has been reported that the combination regimen of thiazides with NSAIDs is superior to single-drug therapy.[8] Our patient was treated with a combination of hydrochlorothiazide, amiloride and indomethacin, which partially reduced his urine output. However, his weight gain remained unsatisfactory and required insertion of a gastrostomy which is also the most common intervention for failure to thrive in the MWPNC study.

Conventional treatment only focuses on symptomatic treatment but not curative therapies. A possible therapeutic approach to rescue the plasma membrane expression of functional misfolded mutant proteins is the use of chemical chaperones to promote escape from the endoplasmic reticulum. Since several *AQP2* mutations do not lead to a complete loss of function, different molecules able to re-establish proper protein folding have been analysed. In contrast, for those *AQP2* mutations caused by deletions, insertions, splicing, or rearrangements, it is impossible to consider this therapeutic option.[4] With the increase in understanding of *AQP2* at molecular level, new treatment strategies may be emerging in the near future. Therefore, genetic analysis for CNDI patients to confirm the underlying genotyping is not only important for the confirmation of the mode of disease inheritance, genetic counselling and family planning but also have an implication to the disease management and the potential use of novel therapeutic agents. It is recommended that all patients with CNDI should undergo genetic analysis for *AVPR2* or *AQP2* for the definitive diagnosis.

In summary, we reported a case of a Chinese male infant with *AQP2*-related CNDI who was treated with a combination of hydrochlorothiazide, amiloride and indomethacin, and required gastrostomy insertion for optimal growth and development.

Declaration of Interest

There is no conflict of interest to declare.

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