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CASE REPORT

Nephrogenic diabetes insipidus : Old deletion, new effect. A case report of a family from Greece

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Abstract

Congenital, X-linked, Nephrogenic Diabetes Insipidus (NDI) is a rare disorder in which the kidney is insensitive to the antidiuretic hormone, vasopressin. The gene responsible for this type of NDI, the V2 vasopressin receptor, has been cloned and mapped to Xq28.

We report the case of a boy, 2.5 month old, who presented with nephrogenic diabetes insipidus (NDI). The mother and the 7 year old sister of the boy also had the NDI phenotype but did not seek medical attention until the presentation of the boy to our department. The mutational analysis of the patient showed the R337stop mutation, also founded to the mother's genotype analysis. The allele separation in mother revealed the second X chromosomal allele with a 12-bp in-frame deletion. The same in-frame deletion was also found in his sister's genotype. This deletion of four amino acids (Arg-247 to Gly-250) has been previously described but was suggested not to be linked with the NDI phenotype. However, in our case, the only possible cause of NDI phenotype in the boy's sister was the 12-bp in-frame deletion. Hippokratia 2011; 15 (4): 356-357

Key words: nephrogenic diabetes insipidus, 12bp-ICL3 deletion mutant

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Nephrogenic diabetes insipidus (NDI) is a disease characterized by the inability of the kidneys to concentrate urine in response to vasopressin. It can be divided in two forms, acquired or congenital NDI. Acquired NDI is the most common form and can be seen in several pathological conditions such as renal hypoplasia, interstitial nephritis, chronic renal failure, obstructive uropathy, sickle cell disease, hypokalaemia, hypercalcemia. Congenital NDI is a rare disorder secondary to either mutations in the AVPR2 gene that codes for the vasopressin V2 receptor or to mutations in the AQP2 gene that codes for the vasopressin-depended water channel aquaporin 2. Mutations in the gene located on Xq28 coding for the V2 receptor of vasopressin (AVPR2 gene) are responsible for the X-linked mode of inheritance, while mutations of AQP2 gene are found in the autosomal recessive and dominant traits of the disease[1,2]. About 90% of symptomatic patients are males. Although most of the female carriers with heterozygote V2R gene mutations are usually asymptomatic, some female carriers have been reported with mild or even severe NDI phenotype due to skewed X-inactivation, as it is known till now[3]. The first manifestations can be recognized during the first weeks of life. Infants suffer from nonspecific symptoms such as polyuria, polydipsia, unexplained fever, vomiting, anorexia, failure to thrive. If this condition is not recognized early, congenital NDI children may experience several episodes of hypertonic dehydration that can be complicated by cerebral edema and convulsions.

Case report:

A 2.5 month old boy presented in the emergency department of our hospital with fever (38.5°C) twice a day and no other symptoms for the last two days.

On examination his weight and height were at 90th percentile for age, his blood pressure was 96/61 mmHg (on the 50th percentile for age, gender and height). From the clinical examination there were normal findings. Laboratory investigations revealed: sodium 165mmol/L, chloride 130mmol/L, serum osmolality 334mmol/L, urine osmolality 117mosm/kg, urine S.G. 1001. Sepsis control was negative. During his stay in hospital his urine volume was till 9ml/kg/h. ADH was 24ng/ml, aldosteron and renine between normal ranges.

Based on the hypernatriaemia, serum hyperosmolality, urine hyposmolality, and low SG of urine, a d DAVP (1-deamino-8-D-arginine vasopressin) test was performed and the urinary osmolality remained unchanged. MRIs of brain and pituitary gland were normal, renal ultrasonography presented normal kidneys with anterioposterior diameter of left renal pelvic 6mm. Voiding cystourethrography revealed bilateral vesicoureteral reflux (3rd grade on the right and 4th grade on the left side).

Nephrogenic diabetes incipidus was diagnosed and genotype tests for the patient, his mother and sister were performed at the Institute for Biochemistry, Faculty for Medicine, University of Leipzig, Germany

The boy's sister (9 year old) and mother (37 year old) presented with polyuria, polydipsia (mother has been

drinking over 9 litters of water per day), decreased urine osmolality, but without severe symptoms during their infancy. No medical treatment had been given to them.

The patient was treated with hydrochlorothiazide 1mg/Kg per day and indomethacine 1mg/Kg per day, was fed with milk formula with low sodium concentration and unrestricted water intake[4]. Over the following months the patient presented with no fever, normal growth, normal plasma sodium. Because the urine volume was still high, the dose of hydrochlorothiazide increased in 2mg/kg/day. One year later, the boy was still at 90th percentile per weight and height. The new cystourythrography revealed no vesicoureteral reflux. Urologic studies did not reveal anatomic obstruction and the upper tract changes were attributed to ''functional'' obstruction secondary to the passage of large urine volumes[5]. In addition, these children may have maintained high bladder sphincter pressures in an attempt to stay dry[6].

Discussion

More than 200 different disease-causing AVPR2 mutations have been identified in X-linked NDI families; yielding about 50 % missense mutations, 27 % small deletions/insertions, 9 % nonsense mutations, and 8 % large or complex deletions[7]. In addition to mutational analysis of NDI patients, detailed functional characterization of the altered AVPR2 proteins is an important part of molecular characterization.

The incidence of NDI in Greece has not been fully addressed.

Different mutations are reported which cause amino acid substitution in V2 vasopressin receptor with other functional effects[8].

The known R337 stop mutation is responsible for the disease in the patient[9]. The mother of the patient carried two different mutations in the AVPR2; R337X and a 12 bp-deletion ΔR247-G250. Allelic separation showed that the mutations were located on different alleles. The sister was heterozygous for the 12 bp-deletion mutation. Additionally, mutational analysis of family was extended to the AQP2 gene. All three family members shared a recurrent, silent mutation in exon 2 (S167(TCC>TCT), rs426496) and three common SNPs (rs410837, rs371777 and rs403201) in the third intron of the AQP2 gene. The patient and his mother had an additional heterozygous mutation (rs3741559) in the first intron, close to the splice donor site. However, no functionally relevant mutation was identified in the AQP2 gene.

The genetic status of this family is interesting as the mother presents with the known stop mutation R337X but also with 12bp inframe deletion in the second X chromosomal allele. The 12bp deletion causes a 4-amino acid deletion (Arg-247 to Gly-250) in the 3 intracellular loop of the V2 vasopressin receptor. This mutation has been previously found and it was claimed that it does not cause effects on receptor function[10]. Having one X chromosomal allele affected in a female, it can cause mild symptoms (polyuria and polydipsia without hypernatremia). Such cases are attributable to skewed X chromosome inactivation. The patients sister also suffered from polydipsia, polyuria and when a d DAVP (1-deamino-8-D-arginine vasopressin) test was performed, her urinary osmolality remained unchanged. ΔR247-G250 has no negative effects on ligand binding and cAMP accumulation in *in vitro* assays. Further, the sequence of the deleted region in the ICL3 and its length are evolutionary not conserved. The cause of the mild polyuria observed in the sister of patient remains unclear.

Symptoms and signs of mild or partial NDI in a patient with deletion of Arg-247 to Gly-250, force us to reconsider if the above deletion has no effect on V2 vasopressin receptor. In contrast to what has already been published, we believe that this deletion can cause some functional effects. According to this 50% of the male children of a mother affected with the Arg-247 to Gly-250 deletion will suffer from mild NDI.

This study reports the clinical and laboratory characterization of NDI and reiterates the importance of the genetic basis that underlies the disease diagnosis and genetic counseling.

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