18) A novel mutation in the AVPR2 gene in a Palestinian family with nephrogenic diabetes insipidus

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Abstract

Background: Nephrogenic diabetes insipidus (NDI) is a clinical disorder characterized by a urinary concentrating defect resulting from resistance of the collecting duct to the antidiuretic action of vasopressin (AVP).

NDI is classified into hereditary and acquired causes.

X-linked recessive NDI is caused by mutations in the gene encoding the V2 vasopressin receptor (V2R) and is the most frequent genetic cause of the inherited NDI.

Here we describe a novel mutation in the AVPR2 gene in a Palestinian family with NDI.

Clinical Data: A male infant, born to a non consanguineous Palestinian family, presented in the neonatal period with failure to thrive, vomiting, irritability & fever. Blood sodium was high up to 170mmol/L, blood osmolality raised over 330mOsm/kg while urine osmolality remained low between 45-135mOsm/kg, urine output was 7cc/kg/hr & positive family history of a brother diagnosed previously to have NDI suggesting X-linked inheritance of the disease.

Molecular Data: Sequencing the AVPR2 gene revealed a novel mutation (C82Y) in affected patients in exon 2 of the gene, predicting Cysteine to Tyrosine substitution at the 82 amino acid residue of the AVPR2 gene, while the mother being carrier for the mutation and healthy brother and father does not have the mutation.

Conclusion: We describe a novel mutation in the AVPR2 gene in a Palestinian family with NDI, allowing early diagnosis to prevent severe dehydration and complications in addition to genetic counseling.

19) Molecular diagnoses of Tyrosinemia Type II following Identification and Characterization of Tyrosine Aminotransferase (TAT) Gene Mutations Among Suspected Patients

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Tyrosinemia Type 11, also called Richener- Hanhart syndrome (RHS) is a rare autosomal recessive disorder. It is caused by deficiency in tyrosine aminotransferase (TAT), resulting in elevated tyrosine levels in plasma and urine, and leading to painful palmoplantar hyperkeratosis, pseudodendritic keratitis and variable mental retardation.

Sizteen different mutations have been reported in the TAT gene worldwide. Although the clinical complications of tyrosinemia type 11 were described in patients from the Middle East, the molecular basis has been identified only in a limited number of Tunisian and Palestinian patients. Molecular genetic analysis represents the most reliable and accurate approach to identity heterozygote (carrier) and homozygous (patients) genotypes among suspected individuals since TAT is not expressed in chorionic villi or animosities. This investigation involves the molecular characterization of TAT gene mutations in

seven Palestinian RHS patients (tyrosinemia type 11) diagnosed based on serum tyrosine levels and other clinical manifestations of the disease. DNA sequence analysis and BLAST were used to search for abnormality in the TAT gene after sequencing the 12 exons and exon-intron boundaries included within the gene. Two mutations were identified; a nonsense mutation (R417X) in two RHS patients (previously reported in a French Patient), and a splicing mutation (T408T) (previously reported in two Palestinian brothers) in the other five patients. Moreover, six polymorhisms could be identified, three were previously identified including IVS11 +143 a > g, IVS8 +113 t > c, and S103S and three new ones that include g→t @-17, IVS7+84 c > g, IVS7-73 g > t. The T408T splicing mutation appears to be specific to the RHS Palestinian families as none of these nucleotide transversions were reported in other populations. These results provide the bases for implementing molecular genetics analysis for precise diagnoses of patients and carriers of the disease in and provides a strong tool for genetic counseling programs within the population. It also provides a powerful tool for prenatal diagnoses of fetuses for parents who are carriers of the disease. These results also provide the bases for selection of specific intron-exon sequences in the analysis process among RHS suspected patients who are referred to the various medical centers and clinics for diagnoses and treatment.

20) Optimizing Chelation Therapy in Thalasemia patients; Bridging Clinical Data and Patient Management

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Abstract

Patients with thalassemia major who receive regular blood transfusions are likely to develop iron overload. This will result following saturation of the iron carrying capacity of transferrin, which generally takes place after 20 transfusions. Consequently, excess plasma iron (labile iron) is cleared rapidly by the liver, heart and endocrine tissues at a rate that exceeds 200 times normal uptake of transferring-bound iron. Excess labile iron within cells will destroy the structure and function of mitochondria, lysosomes, lipid membranes, proteins and DNA. The clinical consequences can include liver cirrhosis and fibroses, cardiomyopathy, diabetes and other endocrine disorders. With proper control of body iron at all times in patients, these effects are preventable but only some are reversible once tissue damage has occurred.

The primary rate of iron chelation therapy is to bind and remove iron from the patient body at a rate either equal to or greater than the rate of iron uptake of transfused iron. Complete chelation should aim to achieve both iron balance and iron detoxification. In patients who accumulated dangerous tissue iron levels, removal of this iron is also highly desirable. Several iron chelators have been developed to help achieve these objectives. The recent introduction of the effective oral chelator deferasirox provides chelation coverage and significant control of LPI levels over the entire 24 hour period. Evidently, administration of the drug at a dose of 20-30 mg/kg/day significantly controls iron levels in plasma, liver and myocrdiocytes in thalassemi a major patients. Accumulating clinical data from key studies indicate that thalassemia patients can lead a happy and enjoyable normal life similar to normal individuals if their treatment is performed right and they receive the proper clinical attention from the medical staff.

Definitely, chelation therapy requires close monitoring of patients vital organ status and the treatment protocol should be adjusted accordingly. Long term treatment with iron chelation highlights the importance of titrating the dose of the drug for each patient according to individual rates of iron intake from continued blood transfusion, current iron storage levels, safety markers (renal function for example) and target body iron content desired.