Carbonic anhydrase deficiency: Three Siblings

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INTRODUCTION

The carbonic anhydrase II (CA II) deficiency syndrome is a rare autosomal recessive disorder associated with osteopetrosis, renal tubular acidosis (RTA), and cerebral calcification . Other features include visual and auditory impairment, short stature, a large cranial vault, history of multiple skeletal fractures, developmental delay and cognitive defects, anemia,splenomegaly and secondary erythropoiesis.

We report here, three siblings of carbonic anhydrase II deficiency syndrome presenting with short stature, distal renal tubular acidosis and cerebral calcification. This is the first report of the disease occurring in three successive generations with a novel homozygous mutation on 8q22.

CASES

Two sisters (aged 16,5 years and 13.5 years, respectively) were referred to pediatric endocrinology department due to the history of recurrent long bone fractures (sister 1 1: 3 fractures, sister 2: 2 fractures).

They were born to third degree consanguineous parents. Their 3 years old brother was invited for medical examination as the parents had reported him to have develeopmental delay.

Birth lengths and weights of the three siblings were within normal ranges, but growth parameters of two sisters were below the 3rd percentile after 1 year of age. Motor milestones and speech development were also delayed for all of them.

At presentation, the height age and bone age of sister 1 were 11 years and 16 years and of sister 2 were10.3 and 12 years, respectively. Their brother's height (92 cm, 25 p) and weight (14,5 kg, 50 p) were in normal ranges at presentation.

They all had a broad head with prominent forehead, a long bulbous nose, a relatively thin upper lip, dental carries, dental malalignment and malocclusion. Denver II Developmental Screening Test of the third child was abnormal.

The laboratory investigation of all revealed renal tubular acidosis with metabolic acidosis associated with hypokalemia, hyperchloremia and persistently positive urine anion gap without renal failure and the urinary pH of >5.5 indicating distal renal tubular acidosis .

Skeletal surveys showed hyperdensity of bones compatible with osteopetrosis .

Hematological workups, liver function tests, serum PTH and acid phosphatase levels of the children were in normal ranges.

Renal ultrasound scans revealed urolithiasis in sister 1 and in the brother.

Brain CT scans showed symmetric calcifications of the subcortical white matter, basal ganglia, thalami and cerebellar hemispheres.

Other hormonal causes of short stature were ruled out.

The presence of osteopetrosis, cerebral-cerebellar calcifications and distal renal tubular acidosis suggested the diagnosis of carbonic anhydrase II deficiency in these three siblings.

The patients were found to be homozygous for the mutation in CA II gene and parents were heterozygous for the same mutation.

They were started on potassium chloride and sodium bicarbonate.

Discussion

- Renal tubular acidosis is the most likely cause for growth retardation and alkali and potassium supplementation should be started early in the disease course to delay further complications.
- CA II deficiency should be considered in children presenting with osteopetrosis without anemia and thrombocytopenia.
- Prenatal diagnosis could be offered either from cultured amniocytes or from chorionic villus biopsy.