HEPATOBLASTOMA IN A CHILD WITH FAMILIAL HYPOMAGNESAEMIA, HYPERCALCIURIA AND NEPHROCALCINOSIS CAUSED BY MUTATION IN *CLDN16* GENE

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BACKGROUND AND OBJECTIVE

Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC, MIM #248250) is a rare autosomal recessive tubular disorder caused by mutations in the *CLDN16* gene, which encodes protein claudin-16. Claudins are integral membrane proteins are major structural components of the tight junction of all epithelial cells, which crucial for the paracellular flux of ions. Overexpression or downregulation of claudins is frequently observed in epithelial-derived cancers. Hepatoblastoma (HB) is the most common primary liver malignancy in childhood, which has not been reported previously in genetically confirmed FHHNC. We report a case of a young girl with FHHNC presenting initially with bilateral medullary nephrocalcinosis due to hypercalciuria, normal serum Mg level and HB.

RESULTS

This girl was born after an uneventful pregnancy at term from unrelated healthy parents with normal birth parameters. At 7 months of age, she presented with sterile leukocyturia and medullary nephrocalcinosis was revealed. At the age of 19 months the patient was referred to our Clinic. On admission laboratory and imaging tests revealed hypercalciuria (Ca/Cr=3.3 mmol/mmol), increased PTH (149 pg/mL), eGFR 92.5 mL/min/1.73m^2, and bilateral medullary nephrocalcinosis (Fig.1). There was no failure to thrive, imbalance of other serum electrolytes and acid-base status, no rickets, ocular abnormalities or hearing impairment. The girl had elevated serum liver enzyme levels and tumor marker α-fetoprotein (2984 IU/mL). Abdomen ultrasound and computed tomography (CT) showed a growth-like mass of 6.2 x 4.6 cm between right and left liver lobes (Fig. 2, 3). Biopsy of the liver tumor revealed HB without vascular involvement or extrahepatic spread. The girl was treated with courses of chemotherapy according to SIOPEL-3 consisted of carboplatin with lower nephrotoxic potential as alternative to cisplatin and the combination of doxorubicine, farmorubicin and epirubicin. After seven cycles of the chemotherapy, volume shrinkage was observed and a complete resection of the tumor was performed. Annual follow-up during the next 5 years showed normal serum level, abdominal CT did not demonstrate any liver abnormalities, and a stable remission of HB was confirmed.

Fig. 1. Kidney ultrasound shows medullary nephrocalcinosis.

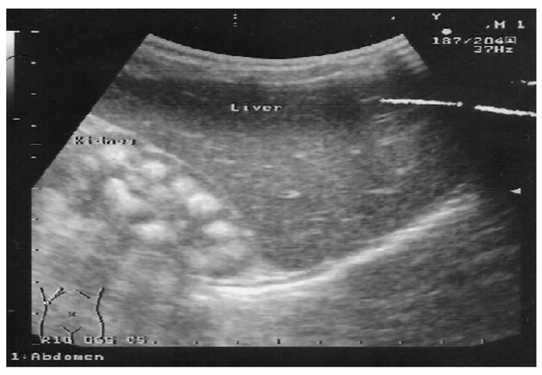


Fig. 2. Liver ultrasound demonstrates HB (arrows).

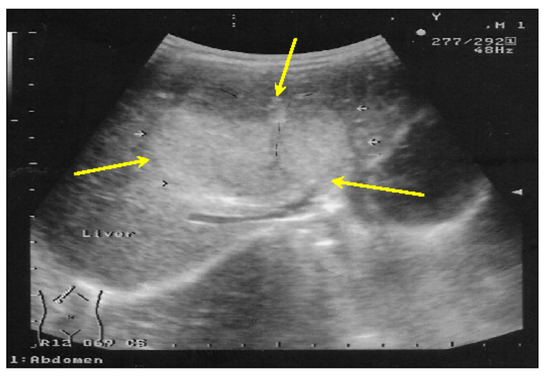


Fig. 3. Abdominal computed tomography scan shows HB (arrows).

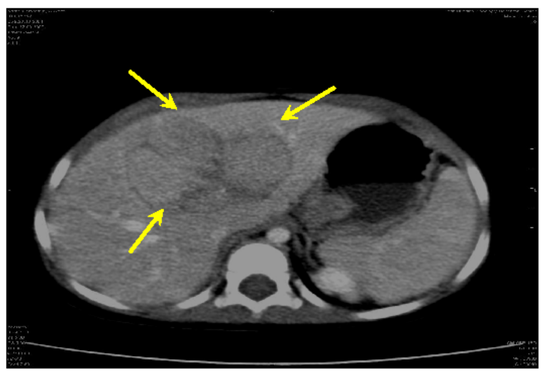
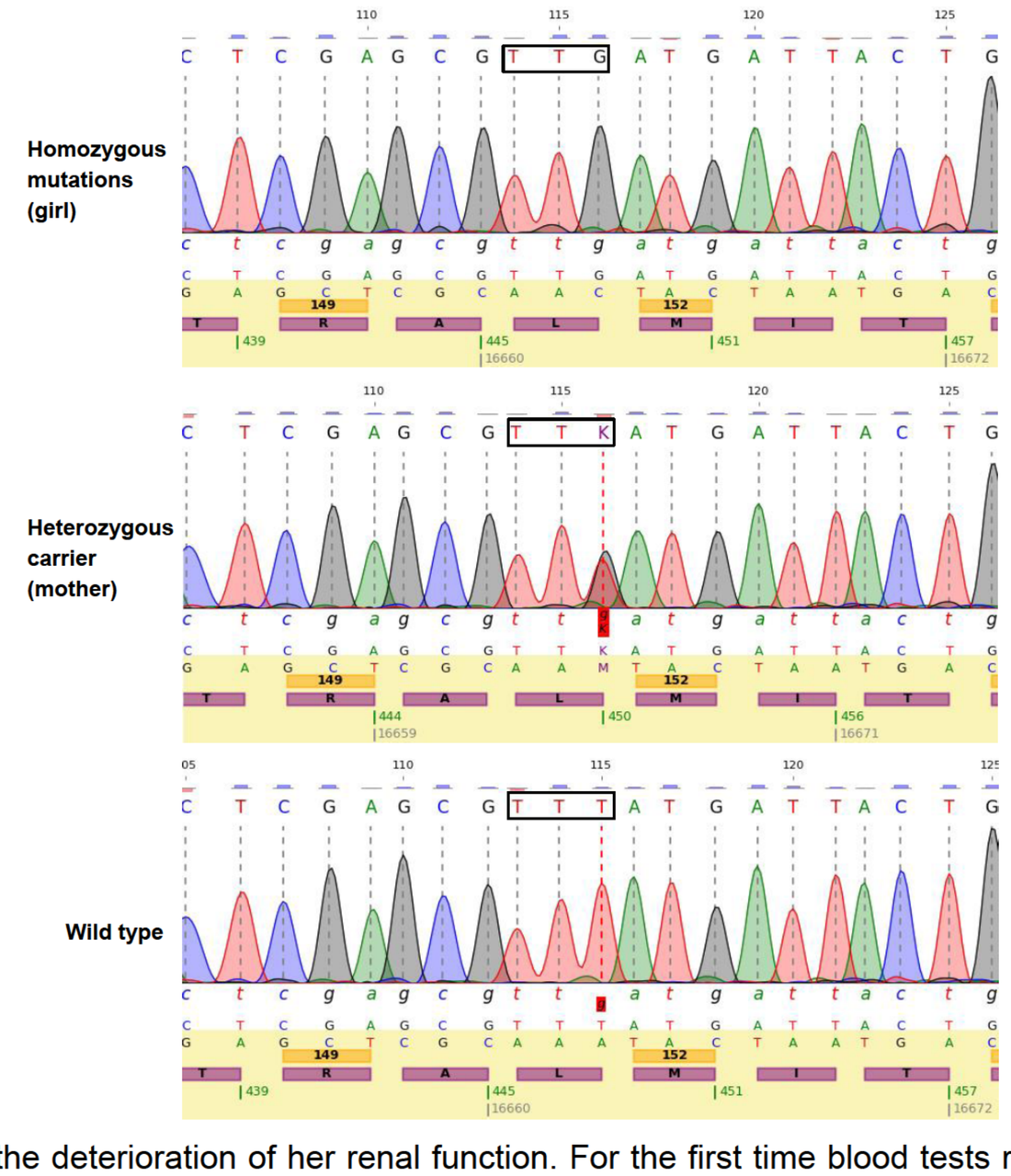


Fig. 4. DNA sequence chromatograms: the codon position 151 with the mutation p.L151F(TTG>TTT) in *CLDN16* and wildtype.



At 8 years of age the girl was admitted to our clinic repeatedly because of the deterioration of her renal function. For the first time blood tests revealed hypomagnesemia (0.63 mmol/L) with elevated serum creatinine level (115 μmol/L) and eGFR 55.4 mL/min/1.73 m^2, increased serum PTH level (105.5 pg/mL), and hypercalciuria (Ca/Cr 1.6 mmol/mmol). Calculated fractional excretion rate of Mg was elevated (11.9%). Renal US revealed worsening of nephrocalcinosis and signs of urolithiasis. Sequence analysis of *CLDN16* gene revealed a homozygous mutation in exon 3 (c.453G>T), which resulted in a Leu151Phe substitution affecting the first extracellular loop confirming the diagnosis of FHHNC (Fig. 4). The same heterozygous mutation was also found in her mother who had normal serum Mg and creatinine levels, urinary excretion of Ca and Mg, and renal US. Treatment with hydrochlorthiazide was started in an attempt to reduce hypercalciuria, oral Mg and citrate substitutions. During the 12-months follow-up, Mg supplementation did not normalize the serum Mg level (0.57 mmol/L), while hydrochlorothiazide mildly reduced hypercalciuria, but nephrocalcinosis showed no significant improvement. At the last control at the age of 9 years, she had elevated serum creatinine level (147 μmol/L) and decreased eGFR to CKD stage 3a (45.3 mL/min/1.73 m^2), respectively.

CONCLUSION

We presented the first case of FHHNC caused by mutation in the *CLDN16* associated with HB which might be related to the altered expression patterns of claudin members. We speculated that used potential nephrotoxic chemotherapy for HB can be responsible for rapid progression of renal failure in index case.

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