A 23-year-old man presented with right upper abdominal pain and vomiting. He was found to have gallstones, mental retardation and dysmorphic features, and referred to the Medical Genetics Clinic. He was born of a non-consanguineous marriage. Delivery was normal and there were no perinatal complications. A right corneal leukomatosus opacity, ciliary staphyloma, myopic changes in the left fundus, with posterior dislocation of the lens were diagnosed at the age of 8 years, when he underwent a herna surgery. He left school in third grade because of learning difficulties. His hair colour had become lighter since the age of 12 years.

One sister had mental retardation and seizures, and died at the age of 8 years (Fig. 1). A brother who was unable to walk died at the age of 2 years.

His weight was 60 Kg, height was 169 cm and arm span was 179 cm. He had a marfanoid body habitus (without arachnodactyly), pallor, sparse light-colored hair with a high forehead, malar flush and high arched palate. Right eye showed corneal clouding, and left eye had an irregular pupil with dislocated lens. He had dark pigmented palmar creases, and diffuse pigmentation of arms and legs. The liver was palpable 3 cm below the right costal margin. Other organ systems were normal. Clinical features and family history were suggestive of homocystinuria.

Investigations: hemoglobin 11.5 g/dL, mean corpuscular volume 97.2 fL, serum vitamin B₁₂ 240 pg/mL (normal 200-950), folic acid 7.0 ng/mL (3-17) and serum ferritin 518.3 ng/ml (20-320). Lipid profile, and liver and thyroid functions were normal. USG abdomen showed an enlarged, diffusely-hypoechoic liver and cholelithiasis. ECG showed occasional premature ventricular complexes. Serum and urine homocystine levels were high 322.5 (normal 0-15) and 2775 (5-15) μmol/L were both high, confirming the diagnosis of homocystinuria. He underwent laparoscopic cholecystectomy; the gallbladder was thick-walled, had multiple mixed stones, and showed chronic cholecystitis with xanthogranulomatous reaction at histology. Stone analysis, cystathionine-beta-synthase (CBS) levels, plasma methionine and genetic studies were not done.

He was treated with pyridoxine (vitamin B₆), folic acid and vitamin B₁₂ supplementation. The family was counselled regarding autosomal recessive mode of inheritance.

Homocystinuria, an inborn error of sulphur-containing aminoacid metabolism, leads to increased urine homocystine levels. Reduced activity of CBS causes classical homocystinuria. Sometimes, deficiency of methylenetetrahydrofolate reductase or methionine synthase may be responsible.

Main findings in classical homocystinuria include mental retardation, ectopia lentis and/or severe myopia, skeletal abnormalities such as excessive height and limb length, vascular abnormalities characterized by thromboembolism and a clinical suspicion of Marfan syndrome. Plasma and urine homocystine levels are markedly increased. Major long-term complications include thromboembolism, coronary artery disease, osteoporosis, fatty infiltration of liver and pancreatitis.

Gallstones have not been reported in classical homocystinuria. In a study among Japanese healthy elderly subjects undergoing routine medical checkup, those with gallstones had higher plasma homocystine levels; it was unclear whether this association was causative, though increased oxidative stress on gall-bladder by elevated homocystine levels was proposed. In another study, antioxidants were shown to prevent gallstone formation, though plasma homocystine levels were similar in patients with cholesterol stones and controls. Also, oxidative stress in gallbladder mucosal scrapings of patients with gallstones.
has been reported. Further studies may help determine the role of homocysteine in gallstone formation.

Eddy Tjandrajana · Sunil Agarwal* · Sumita Danda
Clinical Genetics Unit,
Department of Gastrointestinal Sciences, and
*Surgery Unit-2,
Christian Medical College,
Vellore 632 004, India

Dr. S. Danda (✉)
e-mail: sdanda@cmcvellore.ac.in

References

Generalized convulsions due to sorafenib-induced hypocalcemia

A 77-year-old man was admitted to our department with generalized convulsions of 10 minutes duration. The patient had been diagnosed to have advanced hepatocellular carcinoma (HCC), 4 months prior based on histology. He was being treated with sorafenib (Nexavar® Bayer, Leverkusen) 400 mg twice a day for the last 3 months. The patient also had a history of epileptic seizures secondary to cerebral stroke, and he was being treated with acetyl-salicylic acid 100 mg and valproic acid 500 mg twice daily without recurrence of seizures during the last 3 years. On admission, he was conscious with normal neurological examination except from the presence of tonic convulsions. Valproic acid 1200 mg was given intravenously over 20 min and the convulsions were terminated. CT scan of the brain showed the presence of pre-existing cerebral infract. Laboratory tests revealed normal glucose levels (115 mg/dL), and low serum calcium (total: 6.5 mg/dL, ionized: 3.8 mg/dL); all the other electrolytes (Na, K, P, Mg), albumin and serum levels of valproic acid were normal. Clinical examination revealed the presence of Trousseau’s and Chvostek’s signs. The patient received calcium gluconate 2 g intravenously over 10 min followed by a slow infusion of calcium. Vitamin D, parathyroid hormone and calcitonin levels were normal and did not reveal any known factor for hypocalcemia.

Although both acetyl-salicylic acid and valproic acid have been associated with hypocalcemia,1 the patient was under these regimens for a long period. Since sorafenib was the only recently introduced drug, it appears to be the cause of hypocalcemia in our patient. To our knowledge, hypocalcemia with seizures has been described previously in only one patient with leukemic involvement of the CNS treated with dasatinib.5 This is probably the first case report of convulsions due to sorafenib-induced hypocalcemia in a patient with HCC. The pathogenesis of hypocalcemia after sorafenib administration remains uncertain, but a non-specific effect on calcium homeostasis could be considered as possible mechanism.6

In conclusion, hypocalcemia should be suspected in patients with HCC under sorafenib who developed seizures, particular in patients with a history of epilepsy.

Evangelos Cholongitas · Chrysa Georgousaki · Simos Spyrou · Maria Dasenaki
Department of Internal Medicine,
General Hospital of Sitia, Greece

E. Cholongitas (✉)
e-mail: cholongitas@yahoo.gr

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