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CASE REPORT

Type 1 primary hyperoxaluria: A case report and focus on bone impairment of systemic oxalosis

Hyperoxalurie primitive de type I : description d'un cas et mise au point sur l'atteinte osseuse de l'oxalose systémique

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Summary Primary hyperoxaluria is a rare genetic disorder characterized by oxalate overproduction, leading to kidney failure due to nephrocalcinosis, and is eventually responsible for systemic oxalosis. Bone impairment, secondary to oxalate deposits, is one of the many complications that may occur. Skeletal involvement can be difficult to diagnose because of lack of clinical symptoms and therefore needs to be confirmed by invasive testing, such as transiliac bone biopsy. If confirmed, bone oxalosis is the proof of disease severity and that combined liver-kidney transplantation should be performed.

Introduction

Primary hyperoxalurias (PH) are a group of rare autosomal recessive disorders, primarily defined by the overproduction of oxalate. There are three types of hyperoxaluria: type I hyperoxaluria (PH1) is the most frequent subtype (70—80%) and is caused by the alanine-glyoxylate-aminotransferase (AGT) intrahepatic deficiency, which leads to oxalate overproduction. At least 178 different mutations have been described in the *AGXT* gene (coding for AGT enzyme, localized mostly in peroxisomes of hepatocytes). Oxalate is

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a form of calcium salt, highly insoluble, almost exclusively excreted by the kidney. The estimated prevalence is 1 to 3 cases per million individuals [1]. The excess of oxalate excretion by the kidney in the urinary tract leads to urolithiasis. The crystallization in the renal tubules causes nephrocalcinosis, responsible for chronic kidney disease and progressive renal failure. When glomerular filtration rate (GFR) declines (< 30 ml/min), oxalate accumulation leads to systemic oxalosis and oxalate deposits can be observed in numerous tissues, particularly in the bone [1]. Oxalate overproduction in type II hyperoxaluria (PH2) is caused by a glyoxylate reductase-hydroxypyruvate reductase (GRHPR) deficiency. Over 30 mutations have been identified in the *GRHPR* gene and concern 10% of PH cases. Type III hyperoxaluria (PH3) is caused by the 4-hydroxy-2-oxoglutarate aldolase (HOGA) defect, with 19 different mutations currently known.

Up to this date, no specific treatments are available except vitamin B6 (pyridoxine) supplementation (which usefulness is limited to type I hyperoxaluria) and isolated liver versus combined liver-kidney transplantation (CLKT). The choice of transplantation procedure depends on the type of mutation, pyridoxine sensitivity, and also the severity of excess oxalate storage and its location. Isolated kidney transplantation is associated with a high risk of recurrence of the kidney disease.

The purpose of this case report is to show the importance of bone biopsy in order to determine the bone impairment of systemic oxalosis, and therefore demonstrate that bone biopsy provides help to decide if transplantation is appropriate as well as the type of transplantation needed.

Case report

We report the case of a 29-year-old man, diagnosed at the age of five with type I primary hyperoxaluria. There was no family history of oxalosis. The first symptoms included repeated episodes of monohydrate calcium oxalate urolithiasis, starting at a young age, associated with nephrocalcinosis responsible for progressive renal failure. A composite heterozygous mutation of the *AGXT* gene had been identified during infancy: PGly170Arg exon 4 (inherited from his mother) and pArg36Cys exon1 (inherited from his father) responsible for a pyridoxine sensitive AGT deficiency in liver tissue (PH1).

During childhood, the patient was treated with pyridoxine (vitamin B6) supplementation. The multiple episodes of urolithiasis had been treated with several procedures of extracorporeal lithotripsy, percutaneous nephrolithotomy and ureteroscopy, which had been performed on both kidneys between 2004 and 2008. Multiple coralliform lithiases were removed. However, after a period of follow-up loss, renal disease became terminal at age 25 and the patient underwent hemodialysis during five years.

Physical examination revealed no clinical symptoms other than those related to hemodialysis. There was no bone or joint pain, no skin involvement, no neurological abnormalities. Cardiopulmonary examination was normal.

Creatinine level was 848 μmol/l, calcium level was 2.48 mmol/l (2.20—2.70), phosphorus level was 2,56 mmol/l (0.87—1.50), sodium was 141 mmol/l (135—145), potassium was 4.4 mmol/l (3.5—5.0), C-reactive protein was 8.3 mg/l (< 4.0), albumin was 44 g/l (35—50), there was no major anemia or other cytopenia (hemoglobin was 11.7 g/dl). Liver function tests where normal (AST = 12 UI/L (15—40), ALT = 16 UI/L (10—49), ALP = 97 UI/L (41—117), GGT = 41 UI/L (8—70)). There was no hyperparathyroidism: PTH 1-84 was 45 pg/ml (11—54 pg/ml). 25-OH vitamin D was 23.8 ng/ml (30—40 ng/ml). Oxalate levels were stable during hemodialysis.

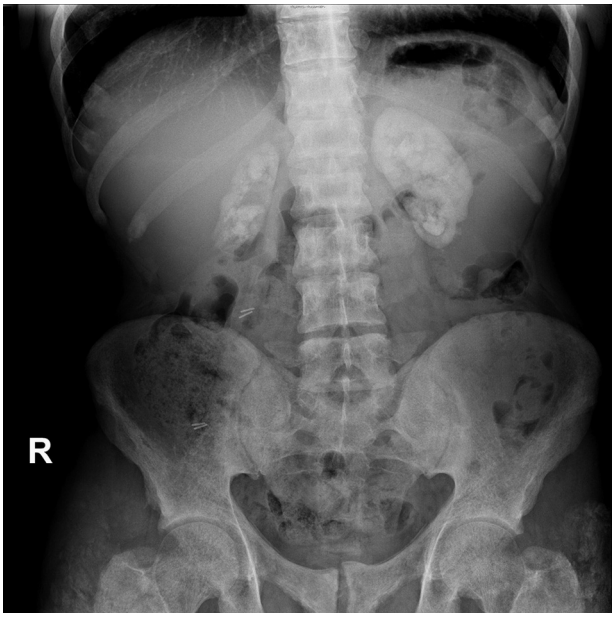

Figure 1 Abdominal X-Ray showing bilateral nephrocalcinosis.

Spinal X-Rays showed a normal bone structure, without any vertebral fracture. Coralliform lithiases were identified in both kidneys (Fig. 1). Dual Photon Absorptiometry (Hologic device, Delphi, Hologic Bedford, MA, USA, with white male as referent population) performed at the lumbar spine was 0.822 g/cm^2 (*Z*-score −2.4) and Bone Mineral Density at the total hip was 0.697 g/cm^2 (*Z*-score: −2.8) and was 0,707 g/cm^2 at the femoral neck (*Z*-score: −2.3).

At age 29, there was no proof of systemic oxalosis, and moreover no clinical, biological, or radiological abnormalities suggesting a possible bone damage. Even if isolated kidney transplantation is associated with a high risk of kidney disease recurrence, our patient expressed the preference for isolated kidney transplantation versus a CLKT. As the possibility of asymptomatic bone impairment was suspected, a transiliac bone biopsy after simple tetracycline labeling was performed to investigate potential oxalate bone deposits, in order to confirm the suspected disease severity. The iliac bone sample was fixed in 70° ethanol, then dehydrated in absolute ethanol and embedded in methyl methacrylate, without decalcification. Sections (8 μm in thickness) were obtained using a heavy duty microtome and stained with Goldner's trichrome. Microradiography was done on 100 μm thick slabs.

Histological analysis showed a very dense trabecular bone, containing numerous hematopoietic cells. Numerous blood vessels, connective cells and adipocytes were identified. More importantly, numerous oxalate crystals were

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