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CASE IMAGE

Unusual cause of cerebral calcifications in an 8-year-old girl

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Key Clinical Message

Genetic counseling and genetic screening for hyperoxaluria should be recommended for children with urinary lithiasis for early management to avoid progression to oxalosis especially if there is a family history of lithiasis.

Primary hyperoxaluria type 1 (PH1) is caused by a deficiency of the liver peroxisomal enzyme alanine–glyoxylate aminotransferase (AGT) resulting in overproduction of calcium oxalates. In its later stage, a systemic deposit of calcium oxalates is observed. We present the case of an 8-year-old girl with exceptional neurological involvement secondary to this disease.

KEYWORDS

alanine–glyoxylate aminotransferase, children, end-stage renal disease, Nephrocalcinosis, nephrolithiasis

1 | BACKGROUND

Primary hyperoxaluria type 1 (PH1) is caused by a deficiency of the liver peroxisomal enzyme alanine–glyoxylate aminotransferase (AGT) resulting in overproduction of calcium oxalates. This will lead to urinary supersaturation of calcium oxalate and crystal formation. Deposition of calcium oxalate crystals in the kidney parenchyma leads to a condition termed oxalate nephropathy characterized by nephrocalcinosis associated with nephrolithiasis. In its later stage, a systemic deposit of calcium oxalates is observed. We hereby present the case of an 8-year-old patient with exceptional neurological involvement secondary to the disease.

2 | CASE PRESENTATION

An 8-year-old girl presented to the pediatric emergency department with headache and visual acuity decline for the past 1 month. The parents are first cousins, and a previous history of urolithiasis in the maternal uncle was reported. On examination, she had delayed growth, pallor, and blurred vision. Biological tests showed severe anemia, hypothyroidism, and end-stage renal

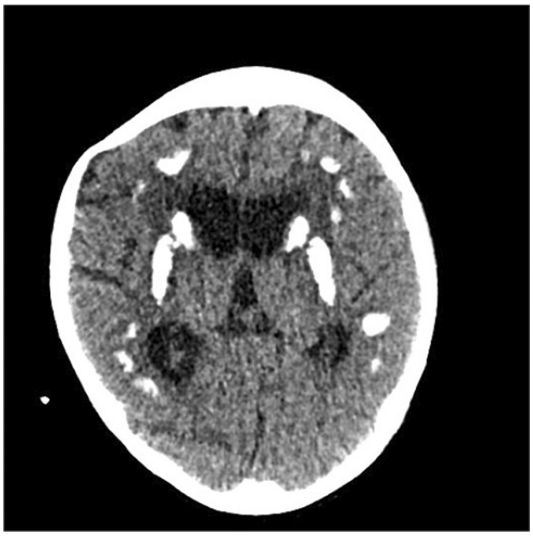

FIGURE 1 Bilateral multiple cerebral macrocalcifications on the cerebral CT scan.

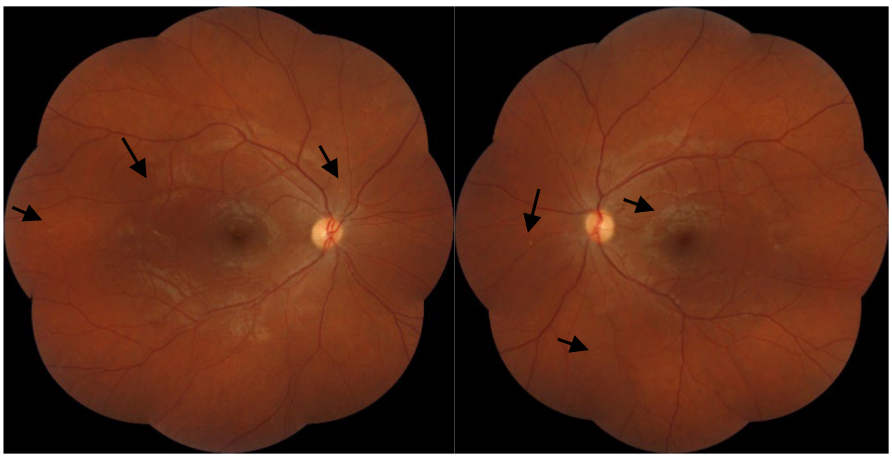

FIGURE 2 Fundus photographs showing bilateral retinal crystalline deposits located at the posterior pole and the periphery.

disease (ESRD). Renal ultrasound revealed grade 3 nephrocalcinosis associated with urolithiasis. The diagnosis of primary hyperoxaluria (PH) was suspected. Computerized tomography (CT) scan of the head revealed bilateral macrocalcifications of the caudate and lenticular nuclei, the pineal gland, and the frontal, parietal, occipital, and temporal subcortical white matter. Calcifications of the vermis and cerebellar hemispheres were also observed (Figure 1). Ophthalmologic assessment found bilateral retinal crystalline deposits located at the posterior pole and at the periphery (Figure 2, arrow). Primary hyperoxaluria type 1 (PH1) was confirmed by Sanger sequencing identifying homozygous mutation NM_000030.3:c.731C > T p. (Ile244Leu). Extra renal replacement therapy by peritoneal dialysis was started. There was no indication for combined liver-kidney transplantation at this stage of the disease. Unfortunately, the child died 1 month later due to a worsening of his neurological condition related to diffuse cerebral calcifications.

3 | DISCUSSION

PH1 is a rare congenital metabolic disorder of the glyoxylate pathway,[1] which manifests with nephrocalcinosis, urolithiasis, and ESRD. In countries with high consanguinity rates, such as North African and Middle Eastern populations, the prevalence of the disease is higher than Europe, the United States and Japan, and its real frequency remains largely unknown.[1] The decline of the glomerular filtration rate (GFR) results in systemic oxalate deposition throughout the body, including joints, bones, eyes, and skin.[2] Other manifestations include refractory anemia secondary to bone marrow replacement, hypothyroidism due to damage to the thyroid gland, myocardial deposition with conduction defects or cardiomyopathy, retinopathy, vasculopathy, and cerebrovascular infarction.[3–6] To the best of our knowledge, cerebral calcifications have never been reported in the literature. Treatment is based on Adequate hydration (3 L/m2/day), pyridoxine, and anti-crystallization therapy with orally administered potassium/sodium citrate. Combined or sequential liver and kidney transplantation has been considered for a long time as the gold standard treatment for PH1 management. Actually, Lumasiran, an investigational RNA interference (RNAi) therapeutic agent, reduces hepatic oxalate production by targeting glycolate oxidase could be considered as the future cornerstone treatment for patient with PH1.[7,8] Unfortunately, this last treatment is not yet available in the majority of developing countries. More than 160 mutations are actually described in PH1, which four (c.508G > A (p.G170R), c.33_34insC (p.K12QfsX156), c.731 T > C (p.I244T), and c.454 T > A (p.F152I)) account for more than 50% of PH1 alleles and form the basis for diagnostic genetic screening for PH1.[9,10] c.731 T > C (p.I244T) is the most frequent pathogenic variant in North African PH1 patients; its pyridoxine sensitivity is variable.

Although ethical concerns remain a major issue related to PH1 in developing countries, genetic counseling and genetic screening for hyperoxaluria should be recommended for children with urinary lithiasis for early management to avoid progression to oxalosis.

AUTHOR CONTRIBUTIONS

Abir Boussetta: Conceptualization; investigation; methodology; writing – original draft; writing – review and editing. **Manel Jellouli:** Supervision; visualization. **Rym Maamouri:** Conceptualization; visualization; writing – review and editing. **Tahar Garagah:** Supervision; validation.

ACKNOWLEDGMENTS

All authors contributed to the elaboration of this article.

CONFLICT OF INTEREST STATEMENT

The authors declare that no conflict of interest exists.

DATA AVAILABILITY STATEMENT

All data underlying the findings are fully available.

ETHICAL APPROVAL

No ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals. Informed consent was obtained from the patient included in this study.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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