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Case report

Congenital hyperoxalosis: a rare metabolic disorder in a term neonate with perinatal autopsy findings

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Abstract

Introduction: Primary hyperoxaluria (PH) is a rare autosomal recessive metabolic disorder resulting from an inborn error of metabolism. It causes renal tubular oxalosis which often leads to renal failure and early foetal demise. Only a few cases of PH detected in the neonatal period have been published in the literature.

Case report: This baby girl was the second child of a 30-year-old woman of a second-degree consanguineous marriage. Maternal gestational diabetes mellitus was diagnosed during the antenatal period. The baby was delivered at 37 weeks + 2 days of gestation following an emergency lower segment caesarean section due to the absence of liquor. A few hours after birth the baby developed respiratory distress and reduced urine output. Investigations revealed high serum creatinine levels. The ultrasound scan was suggestive of acute kidney injury and the baby died on day 2. There was no known family history of renal diseases. During the pathological autopsy examination, there were no definite dysmorphic features. The internal examination revealed bilateral lung hypoplasia and patent ductus arteriosus. The kidneys were of normal size and shape and the microscopy showed numerous, widespread, polarizable oxalate crystals within the renal tubules, in favour of primary hyperoxaluria.

Discussion and conclusion: The extensive renal damage imparted by oxalate deposition may have contributed to the impaired renal function and resulted in obstruction to the urine output, leading to oligohydramnios and pulmonary hypoplasia. Confirmation of the diagnosis of PH requires examination of urine and serum for high oxalate levels and detection of specific genetic mutations. Family screening and genetic counselling are necessary.

Keywords: primary hyperoxaluria, congenital renal diseases, perinatal autopsy

Introduction

Renal tubular oxalosis (RTO) refers to the widespread tubulointerstitial deposition of calcium oxalate crystals, leading to renal failure (1). Secondary hyperoxaluria (SH) can be due to ingestion of substances high in oxalates (e.g. excessive intake of vitamin C, cocoa, spinach, beetroot, ethylene glycol) (2,3). SH can also occur following other pathologies like pancreatic insufficiency, Crohn disease and celiac sprue or after small intestinal bypass surgery. In these cases, fat malabsorption with steatorrhoea occurs, leading to increased oxalate absorption from the small intestine. Furthermore, the presence of oxalate-degrading bacteria like *Oxalobacter formigenes* also contributes to the development of SH (2,3).

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Oxalate is a dicarboxylic acid synthesised by the liver as a by-product of metabolism. Under normal circumstances, the kidneys eliminate most of the oxalate produced in the body. Primary hyperoxaluria (PH) is a rare autosomal recessive metabolic disorder resulting from an inborn error in the glycolate metabolism (1). PH appears to be more common in countries where consanguineous marriages are common (4). The lack of specific liver enzymes in PH results in excessive oxalate accumulation in the body which leads to excreting higher amounts of oxalate in urine (4). PH type I, II and III are caused by mutations in the *AGXT, GRHPR* and *HOGA1* genes, respectively (4). The liver-specific peroxisomal enzyme alanine-glyoxylate aminotransferase, encoded by the *AGXT* gene, is essential for converting glyoxylate to glycine. Deficiency in this enzyme results in an impaired glyoxylate oxidation process, leading to excess oxalate synthesis (4,3). The *GRHPR* gene produces the enzyme glyoxylate reductase-hydroxy pyruvate reductase. PH type II arises when there is a malfunction in glyoxylate reductase which increases the transformation of glyoxylate into oxalate (3,4). The *HOGA1* gene encodes liver-specific mitochondrial enzyme 4-hydroxy-2-oxoglutarate aldolase. The exact role of this enzyme in the production of oxalate is not fully understood (4). So far, over 170 distinct mutations in the *AGXT* gene have been uncovered, which are responsible for PH type I (4). Furthermore, specific genetic mutations of the *AGXT* gene, such as p.G170R, demonstrate an association with a less severe form of the disease or delayed occurrence of kidney failure (4). No definitive genotype-phenotype correlation has been identified in PH type II and III (4).

PH type I, the infantile form, is the most severe and most common of the three types, accounting for about 80% of all cases and results in progressive renal failure (4). PH type II is usually present during childhood, responsible for approximately 10% of cases and has a milder presentation than type I (4). PH type III is rare and milder than PH type I or II (4). The age of onset, progression, severity and specific symptoms that develop can vary greatly even in individuals with the same subtype and even among members of the same family (4).

If untreated, excess oxalate accumulates in the kidneys as calcium oxalate crystals leading to gradual kidney damage and potential renal failure (4). When renal functions deteriorate in PH, the build-up of oxalate in other organ systems, specifically in bones, joints, eyes, heart, and the walls of the blood vessels leads to systemic oxalosis (4).

The diagnosis of PH is based on the patient's history, the urine and plasma oxalate levels and molecular genetic testing for specific mutations (4). Under the microscope, calcium oxalate crystals accumulated in the renal tissue often have a fan-like shape and exhibit birefringence under polarised light.

Case report

A 30-year-old woman who was in a second-degree consanguineous marriage was diagnosed with gestational diabetes mellitus in her second pregnancy and was on oral hypoglycaemic drugs. There was no family history of renal diseases. The first child was a healthy five-year-old girl. The antenatal history of the current pregnancy was otherwise uneventful up to 37 weeks of gestation when oligohydramnios was identified on an ultrasound scan. There was no maternal pyrexia or dribbling. An emergency lower segment caesarean section was performed at 37 weeks +2 days of gestation due to severe oligohydramnios. The baby cried poorly at birth with an APGAR score of 8, 10, 10 and developed respiratory distress and coffee-ground vomitus within seven hours of birth. On Day 1 the baby was admitted to the premature baby care unit and was soon transferred to the neonatal intensive care unit where she received intubation and ventilator support. The chest X-ray revealed an enlarged cardiac shadow and the subsequent 2D echocardiogram revealed a moderate-sized patent ductus arteriosus and severe pulmonary hypertension.

On Day 2, the baby developed convulsions, and the urine output was low. There were alterations in liver function tests. The serum

creatinine and blood urea levels were 106mmol/L and 32 mg/dL, respectively. The subsequent USS of the abdomen revealed increased echogenicity of kidneys and obliteration of cortico-medullary demarcation. Despite the medical management, the baby succumbed to death on Day 2.

A pathological post-mortem was performed. This was a female baby with no definite dysmorphic features, definitive features of Potter facies or any other external abnormality. The body weight was 2600g (50th percentile). The growth parameters were appropriate for the gestational age of 37 weeks. The head circumference was 33 cm (28.5-37.9), the crown-rump length was 32 cm (29.2- 37.0), the crown-heal length was 53 cm (42.7- 52.7) and the foot length was 8 cm (7.2-8.1).
There was no pneumothorax. The trachea and main bronchi were normally formed (Figure 1A). Both lungs were hypoplastic but showed normal lobation. The right and left lungs weighed 11 g and 12 g, respectively (mean 38.7+-22.9). The foetal lung: body weight ratio was <0.012 (0.0087) which was compatible with pulmonary hypoplasia.

The heart was normal with the normal interrelationship of main vessels. There was a patent ductus arteriosus (Figure 1B).

The oesophagus, stomach, small intestine, large intestine, liver, spleen and diaphragm were normally formed and anatomically normal in position.

The kidneys and adrenals were of normal size and present in their normal position. The ureters, bladder and urethra were normal (Figure 2). The uterus, bilateral fallopian tubes and ovaries were normally formed. The brain was anatomically normal.

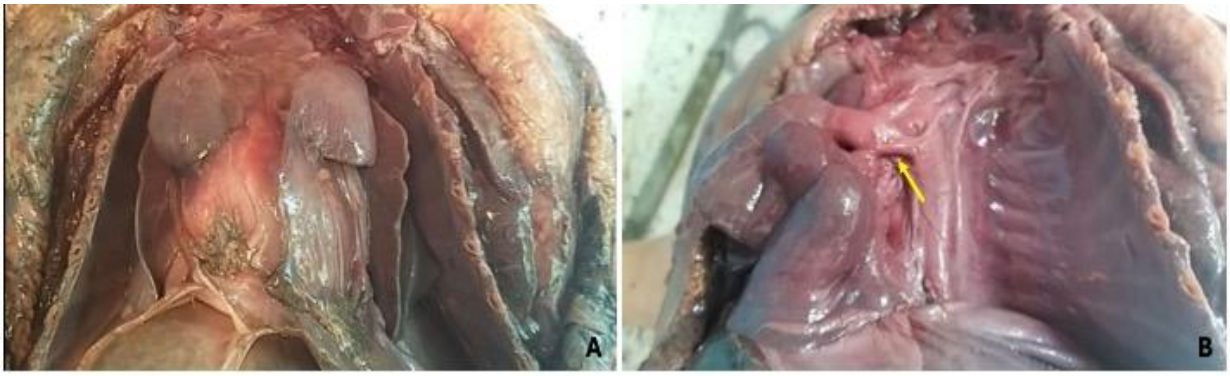

Figure 1: Thoracic cavity: **A.** bilateral lung hypoplasia **B.** patent ductus arteriosus (arrow)

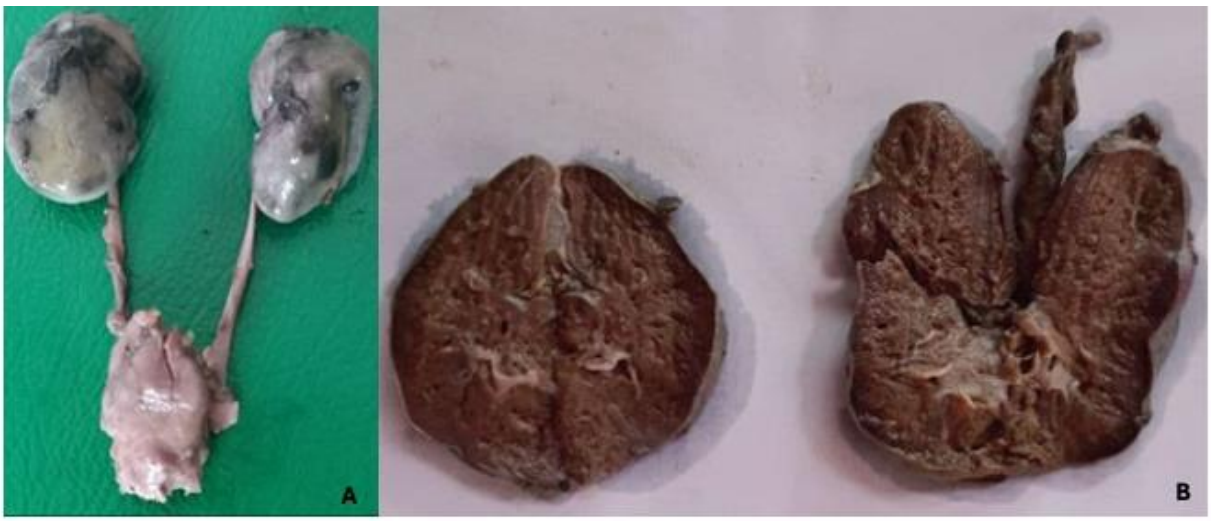

Figure 2: A and B (B) Normally formed kidneys, ureters and bladder

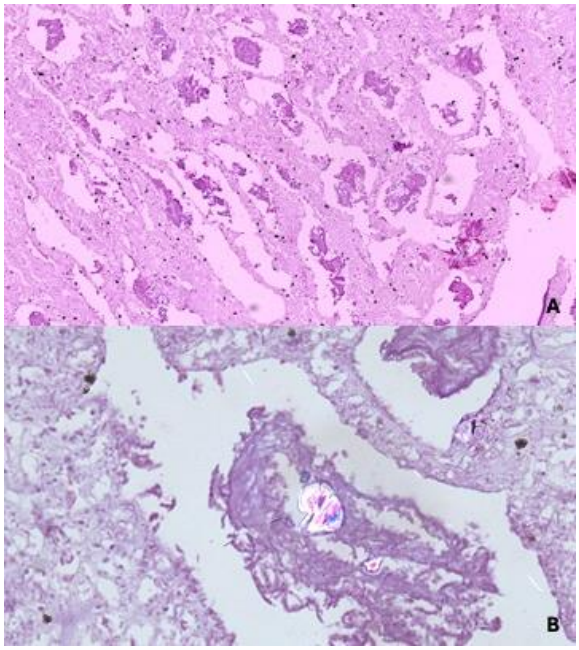

Figure 3 : A. Renal oxalate crystals (H&E x40)
B. With polarization (x 200)

Microscopically, all organs showed variable degrees of autolysis. The renal cortex showed preserved architecture. There was no tubular or glomerular cyst formation. Both kidneys showed polarisable oxalate crystals occluding the tubular lumina.
The lung tissue showed the alveolar stage of development. There was no evidence of pulmonary haemorrhage, hyaline membrane formation or pneumonitis.
The heart muscle, brain tissue, liver, spleen, suprarenal glands and pancreas showed no significant pathology.
Polarisable crystals were not found in tissues other than kidneys.

Discussion

The clinical findings and radiological evidence were compatible with acute kidney injury and the autopsy findings of polarised oxalate crystals in the renal tissue favoured hyperoxaluria. The age of the patient and the severity of renal involvement were in favour of PH type I, which has been reported in neonates (8,9). The earliest reported signs and symptoms of PH type I disease include cyanotic episodes, hypotonia, unexplained tachypnoea and tachycardia in a baby of five hours of age who also had renal calcinosis and middle cerebral arterial infarct. He had a known family history of PH type 1 in siblings and an uneventful antenatal history (9). A 25-day-old baby girl with a similar family history and uneventful antenatal history presented with respiratory distress, acute renal failure, metabolic acidosis, and hypertension, passed away from the illness within one week (8).

According to a study conducted by Neveen A. et al., 35.3% of infants diagnosed with PH progressed to end-stage renal disease (5). In another study carried out by Manel J et al., It was noted that children with infantile PH and end-stage renal disease are at a high risk of early death. (6).

Polarisable crystals were not found in the other organs of this baby, excluding the possibility of systemic oxalosis, similar to the other two cases of neonatal PH type 1, where no systemic involvement was identified (8,9). In a study carried out in Egypt, 2/26 patients demonstrated extrarenal manifestations of oxalosis (10).

The widespread deposition of oxalate crystals resulting in renal damage is the most likely contributory factor for the impaired renal function and obstruction to urine output leading to oligohydramnios in this baby. Reduced amniotic fluid volume limits the foetal lung expansion, which affects the normal growth of lung tissue, leading to pulmonary hypoplasia (7,11). Lungs in oligohydramnios-related conditions are usually symmetrically small, with normal lobation (11).

Significant pulmonary hypoplasia leads to respiratory insufficiency shortly after birth resulting in respiratory distress. These babies are difficult to ventilate and often succumb to respiratory insufficiency (11). Persistent pulmonary hypertension occurs when pulmonary vascular resistance fails to decrease during the perinatal transition. The deoxygenated blood shunts from right to left through the patent ductus arteriosus, leading to persistent foetal circulation after birth. The causes of persistent pulmonary hypertension

include respiratory distress syndrome and pulmonary hypoplasia (7).

The diagnosis of PH requires examination of urine and serum for increased oxalate levels, and detection of the specific genetic mutations, which were not possible in this case. Therefore, genetic counselling and family screening were arranged.

The management options for other patients with PH include dietary modification, and medical management with medications such as potassium citrate, thiazides or magnesium (4). Treatment with pyridoxine/vitamin B6 is effective in specific AGXT mutations, whereas it may not work for patients with different AGXT mutations (4). Lithotripsy is an effective intervention for patients with a high stone burden. End-stage kidney disease requires dialysis, and a liver or renal transplant or a combined liver-kidney transplant (4). Targeted gene therapy with RNA interference includes treatment with lumasiran (4). Hepatocyte cell therapy is a developing treatment option (4).

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