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Renal and Musculoskeletal Manifestations of Primary Hyperoxaluria in a Girl

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Abstract Primary hyperoxlauria is a rare autosomal recessive disease. This report is of a nine-year-old girl who has suffered from various renal and musculoskeletal manifestations and complications of this disease, which have been well demonstrated by different imaging modalities.

Key words Girl; Hyperoxaluria; Musculoskeletal; Renal

Case Report

The patient was a Pakistani girl born to consanguineous parents. She had uneventful antenatal and perinatal history. She first presented with urinary tract infection (UTI) at four years old. There was no family history of renal disease. Renal ultrasound found a right staghorn stone and left nephrocalcinosis. Percutaneous nephrolithotomy was performed. Biochemical analysis of the retrieved renal stone specimens confirmed the presence of calcium, oxalate and phosphates, with oxalate constituting more than 90% of the organic anions. 24-hour urine test showed a markedly elevated oxalate level up to 1930 mmol/day, around five times the upper limits of the normal range in the patient's age group. 24-hour urine calcium level was normal. Hyperoxaluria type 1 was confirmed. Subsequent genetic analysis found that the patient was homozygous for 364 C>T R122X mutation, a novel non-sense mutation in the alanine: glyoxalate aminotransferase (AGT) gene encoding the hepatic perioxisomal enzyme AGT. Both parents of the patient were heterozygous for the mutation. The patient's young sister did not have the mutated gene.

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Renal function test showed normal serum creatinine level at the time of diagnosis of primary hyperoxaluria type 1 when the patient was five years old. Low oxalate diet, potassium citrate and pyridoxine were prescribed. The patient's mother could not understand Chinese while her father was able to understand both Chinese and English. Treatment plan was explained in the presence of interpreters.

The patient suffered from recurrent urinary tract infection, recurrent urolithiasis and progressive nephrocalcinosis. She underwent repeated extracorporal shockwave lithotripsy (ESWL), percutaneous nephrolithotomy (PCNL) and double J ureteric catheter insertion. Compliance to medical treatment was found to be suboptimal and medical follow-up was defaulted for more than three years. The patient was under medical care again when she was nine years old and was admitted because of recurrent UTI. However, the patient had suffered from end stage renal failure. Patient was then referred to our center for haemodialysis.

Full blown renal and musculoskeletal manifestations were found. Both abdominal radiographs and ultrasound showed bilateral cortical nephrocalcinosis (Figure 1a; Figures 2a-2d). Multiple bilateral renal stones, left hydronephrosis and bilateral small kidneys were evident. Various manifestations of renal osteodystrophy including diffuse osteosclerosis were present. The patient had suffered multifocal intra-osseous lytic lesions and pathological fracture over bilateral femoral neck and proximal humeral diaphyses. Metaphyseal abnormalities were evident over bilateral knees and ankles (Figures 1b & 1c). Skeletal maturation was mildly retarded. Whole body bone scan showed features of metabolic bone diseases (Figure 1d).

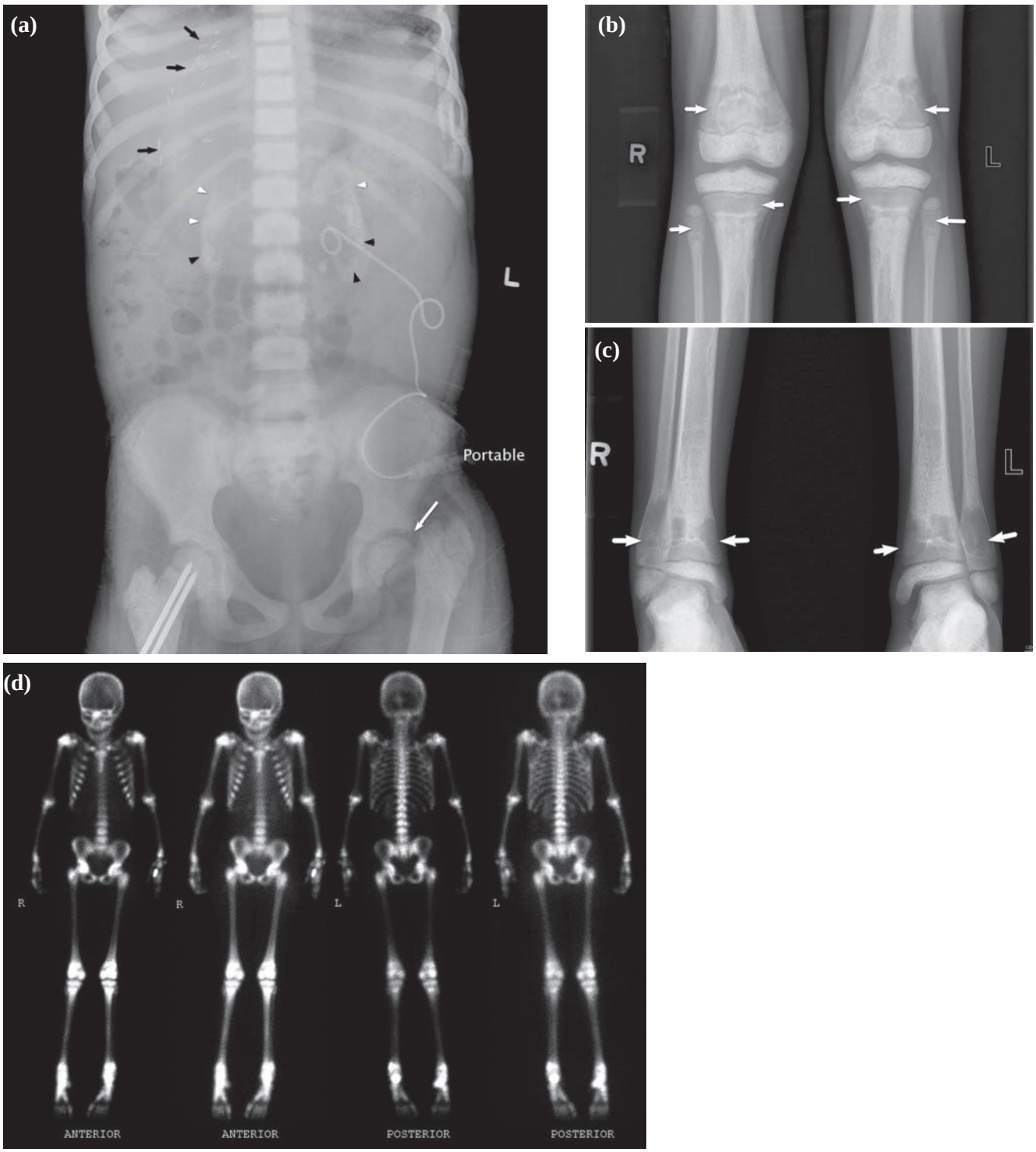

Figure 1 (a) An abdominal radiograph showed markedly increased densities of both kidneys (white arrowheads), multiple bilateral renal stones (black arrowheads) and a displaced pathological fracture over the left femoral neck (white arrow). Surgical clips over the right upper quadrant of the abdomen (black arrows) were due to liver transplant. A left percutaneous nephrostomy tube and two fixation pins over the right femoral neck were in-situ. Generalised increased in bone densities with osteosclerosis along the vertebral column were also evident. (b & c) Conventional radiographs of bilateral lower limbs showed symmetrical, wide and translucent metaphyses of bilateral distal femurs, proximal and distal tibias and fibulas (white arrows). The diaphysis of these bones showed markedly increased densities and coarsened trabeculation. (d) Whole body bone scan images in anterior and posterior projections showed markedly increased tracer uptake in the whole skeleton, especially over the periarticular regions of peripheral long bones. Renal and soft tissue activities were reduced. No activity in urinary bladder was detected.

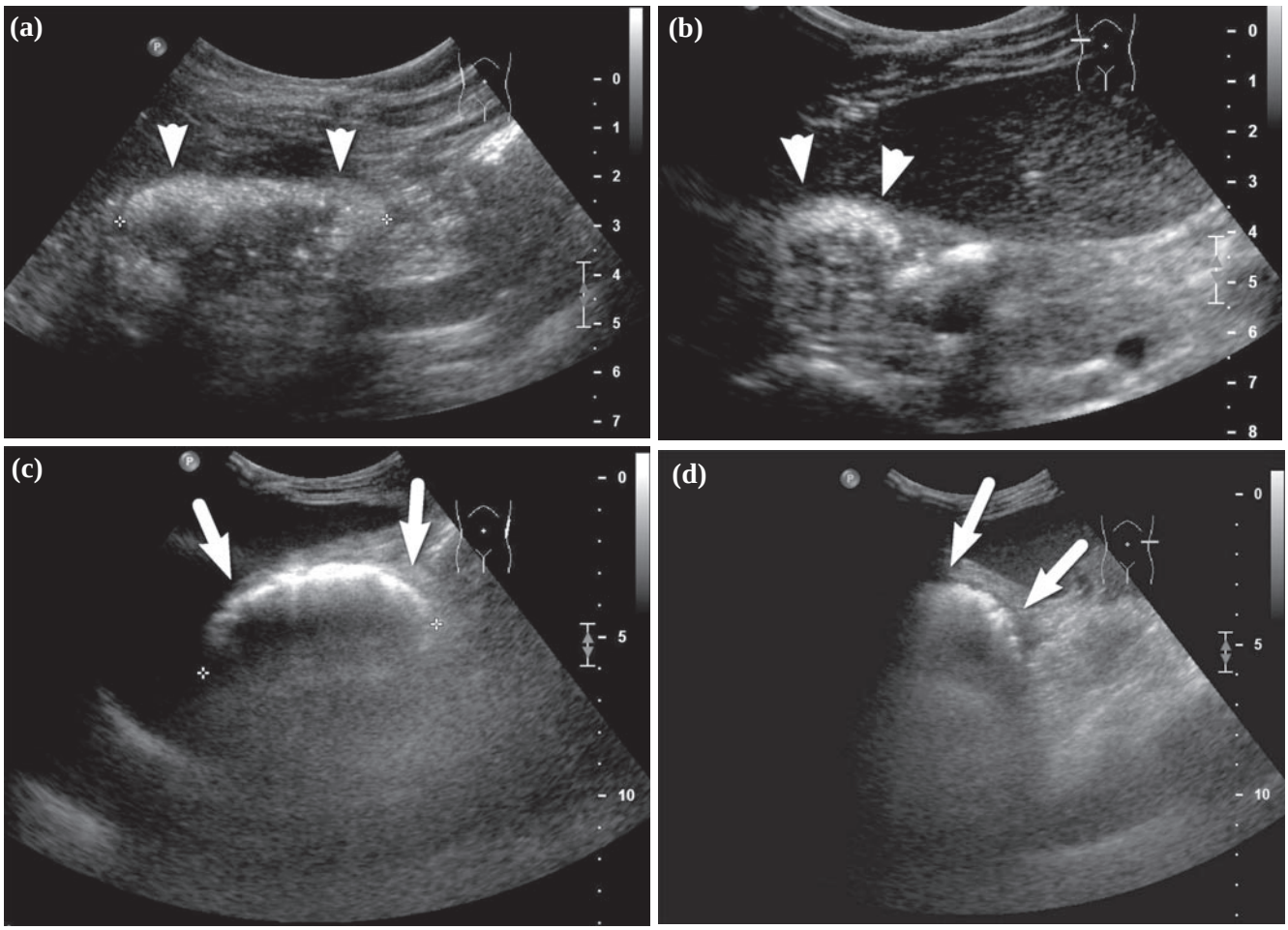

Figure 2 Longitudinal and transverse ultrasound images showed small right (a & b) and left (c & d) kidneys, markedly echogenic renal cortices (white arrowheads for right kidney; white arrows for left kidneys) and posterior acoustic shadowing. Findings were suggestive of bilateral cortical nephrocalcinoses.

The patient finally received liver transplant from a deceased donor at ten years of age. She is now still having haemodialysis in our center and has been on the list for renal transplant.

Discussion

Primary hyperoxaluria is a rare autosomal recessive disease. It can be classified into two types, depending on the underlying chromosomal abnormalities. Type 1 primary hyperoxaluria is caused by mutation of the alanine glyoxalate aminotransferase (AGT) gene on chromosome 2q37.3, which results in deficiency of the enzyme AGT. The enzyme AGT is present in the perioxisomes of the liver. Type 2 primary hyperoxaluria is due to deficiency of the glyoxlate reductase enzyme. The involved gene is on the chromosome 9q11. Both forms will cause excessive endogenous production of oxalate.

Type 1 primary hyperoxaluria, being more common, is more heterogenous in presentation. It occurs in one in 60 000 to 120 000 live births.[1,2] It can be sub-divided into three forms, depending on the clinical presentation. The neonatal form is also known as the malignant form. It is rare but severe. Fifty percent of patients were reported to suffer from end stage renal failure at the time of diagnosis.[3] The infantile form has a milder clinical course in terms of speed of progression to the ESRF. It can be diagnosed by screening of the family members of the patients. The median age of presentation is reported to be five years and around

half of the patients suffered from ESRF by the age of 25.[4] The late childhood form is rare and it can be discovered during the workup of urolithasis through biochemical analysis of the renal or ureteric stones.

While renal and musculoskeletal manifestations are most easily detected by imaging, oxalate deposition can actually occur in multiple other organs including the central nervous system, eyes, skin, nerves, blood vessels and even the intestine. However, exact diagnosis of primary hyperoxaluria requires demonstration of excessive urinary excretion of oxalic acid and genetic studies. Determination of glyoxlate reductase or alanine:glyoxalate aminotransferase enzyme deficiency in the liver tissue is also a recognised means.

For renal manifestations, bilateral cortical nephrocalcinoses and recurrent urolithasis in a paediatric patient should prompt further investigation of possible primary hyperoxaluria. Ultrasonography, without involving ionising radiation, is sensitive in detection of nephrocalcinosis in early stage when the finding cannot be visualised on abdominal radiographs. Medullary nephrocalcinosis is calcium deposition in the distal convoluted tubules in the loops of Henle. It accounts for more than 95% of nephrocalcinoses.[5] Cortical nephrocalcinosis is the calcium deposition of renal cortex. While there are more than 30 causes of medullary nephrocalcinosis, only a few differential diagnoses of cortical nephrocalcinosis in native kidneys exist in paediatric patients. They include oxalosis, acute cortical necrosis and Alport's syndrome.

The composition of the renal or ureteric stones is usually calcium oxalate, which renders them to be visualised on conventional radiographs. Hydronephrosis and pyelonephritis, well known complications of urolithasis, can be detected by grey scale and power Doppler renal ultrasound respectively.

Kidney damage can be caused by nephrocalcinosis, infection secondary to urolithasis, and oxalate deposition. Renal failure will cause failure of excretion of oxalic acid. Extra-renal deposition of the highly insoluble oxalate crystals will then occur and systemic oxalosis ensues. Musculoskeletal system is a common site of involvement. Conventional radiographs are most commonly used and the most widely available modality to demonstrate the musculoskeletal manifestation. The bone changes can be secondary to oxalosis itself or renal osteodystrophy, which are sometimes difficult to be distinguished. Irregular transverse sclerotic bands observed in the metaphyseal segments of tubular bones are well known findings.[6] Intra-osseous or periosteal bone lesions secondary to calcium oxalate deposition might be found.[7] Wide translucent metaphyseal zone with sclerosis adjacent to the diaphysis were also reported.[8] Features due to renal failure and secondary hyperparathyroidism including Rugger Jersey spine, diffuse osteosclerosis, subperiosteal resorption, soft tissue and vascular calcification, can be demonstrated radiographically. However, these findings are also seen in patients suffering from renal osteodystrophy secondary to other causes. Retarded skeletal maturation, pathological fractures with slow healing and epiphyseal displacement have great impact on the growth and development. These are important radiographic features to look for in the paediatric patients.

The role of bone scan in the diagnosis of oxalosis is unclear. Features of metabolic bone diseases may be shown. They include diffuse increase in bone activity, particularly along the axial skeleton, over the calvarium, costochondral junctions and sternum. Increased metaphyseal and peri-articular activity, increased bone-to-soft tissue ratio and little renal activity are also possible bone scan findings of metabolic bone diseases. The underlying causes of these findings include renal osteodystrophy, secondary hyperparathyroidism due to renal failure and osteomalacia. Therefore, these bone scan findings are not specific for oxalosis. Rapid resolution of abnormal bone uptake and extra-osseous abnormalities have been described in a young patient suffering from primary hyperoxaluria after combined liver and renal transplantation.[9] Further studies are necessary to verify if bone scan may be used to monitor the response of treatment.

The management of primary hyperoxaluria can be classified into supportive measures, urologic therapy and organ transplantation. Supportive measures should be commenced as soon as possible once the diagnosis is made to decrease oxalate production and increase urinary solubility of calcium oxalate. Dietary restriction of food and drink rich in oxalate, increase in fluid intake, use of various calcium-oxalate crystallisation inhibitors such as citrate and magnesium can help to decrease stone formation.[10] Pyridoxine, a cofactor of AGT, is found to be sensitive in around 10% to 40% of patients. Response to pyridoxine may delay the progression to ESRF.[11] Good compliance to medical treatment is necessary although the symptoms may be mild early in the course of the disease. Possible constraints include limited medical resources and resulting long interval follow-up, lack of engagement in the management and understanding of the disease process

by the parents. For the patient in this case, language barrier may also be another culprit. Patient has been diagnosed to have primary hyperoxaluria at her age of four when her renal function was not significantly impaired. However, due to lack of compliance to treatment and defaulted follow up for four years, systemic oxalosis took place and various renal and musculoskeletal manifestations and complications occurred. Co-operation of specialist center and primary health-care team and regular visits by community nurses may be considered for the patients diagnosed to have primary hyperoxaluria to ensure the compliance to treatment. Special attention to the patients of minority racial groups with enhancement of the service of interpreters in the healthcare system has to be considered.

Urologic therapy is required to tackle the urolithasis and its complications, especially urinary tract obstruction and infection. Percutaneous nephrostomy, which involves placement of a drainage catheter through the skin into the collecting system, can be performed under ultrasound guidance and aseptic technique. Patients are in prone position in this procedure, which can be performed with local anesthesia and sedation even in paediatric patients. This procedure is valuable in decompression of acutely obstructed or infected and obstructed pyelocalyceal system. The latter condition is known as pyonephrosis. Through dilatation of the tract from the skin into the pyelocalyceal system, various surgical instruments (e.g. forceps and nephroscope) may be inserted through the tract to remove and break down the renal and upper ureteric stones. These procedures are known as percutaneous nephrolithotomy, which is useful to tackle large (>2 cm) stones not amenable to extracorporeal shock wave lithotripsy.

However, when oxalosis ensues and end-stage renal failure develops, organ transplantation is the only curative treatment. Different transplantation strategies have been adopted and there is no uniformly accepted guideline. Combined and synchronous liver-kidney transplantation appears to be the best solution, with simultaneous correction of the enzyme defect of alanine glyoxalate aminotransferase and restoration of the renal function. Shortage of donated organs and absence of expertise in performance of the combined liver-kidney transplantation operation are major obstacles. Metachronous approach may be another solution. This involves liver transplantation, then dialysis until sufficient oxalate clearance from the body, which is followed by kidney transplantation.[12] Isolated liver transplantation may be considered in patients without advanced renal failure. However, the exact renal function in terms of glomerular filtration rate that allows isolated liver transplantation remains unknown at the present stage. Renal transplantation alone has yielded poor results in the past, with 1-year graft survival rates of only 26%.[13] It cannot be recommended as the underlying enzyme defect could not be corrected and continued oxalate overproduction will cause loss of the renal graft.

With known genetic defects, gene therapy appears to be a possible therapy. AGT transfection into the hepatocytes has been successful in vitro.[14] However, its potential use in humans is not yet established at the present stage and lots of researches are required to determine its feasibility and safety.

In summary, a paediatric patient who had full-blown renal and musculoskeletal manifestations of primary hyperoxaluria and oxalosis has been reported. Manifestations and complications of oxalosis are readily demonstrated by imaging, especially conventional radiographs and renal ultrasonography. Cortical nephrocalcinosis in a paediatric patient should prompt a physician to investigate for possible primary hyperoxlauria, especially in the presence of renal stones. Early detection and good compliance to medical treatment are essential to the optimal management of primary hyperoxlauria, to prevent or deter the systemic deposition of oxalate, its renal and musculoskeletal complications. Co-operation of specialist center and primary health-care team, visits by community nurses, special attention to the patients of minority racial groups with enhancement of the service of interpreters in the healthcare system can be helpful.

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