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CASE REPORT

Late Diagnosis of Primary Hyperoxaluria Type 1 Despite Recurrent Kidney Stones and Positive Family History

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Abstract
Primary hyperoxaluria type 1 (PH1) is the most common form of primary hyperoxalurias. It results in increased synthesis and subsequent urinary excretion of the metabolic end product oxalate and the deposition of insoluble calcium oxalate in the kidney and urinary tract. Individuals with PH1 are at high risk for recurrent nephrolithiasis, nephrocalcinosis, and end-stage renal disease (ESRD). A 13 years-old female presented with fatigue, headache, nausea, vomiting, anorexia, renal colic. Initial clinical and laboratory investigations revealed ESRD and the patient was initiated on hemodialysis. Family history of PH1 and a history of recurrent kidney stones for 4 years was elicited. Subsequently, PH1 was confirmed by, physical examination, medical history, family history, laboratory tests, ultrasound imaging, X- ray, CT scanning and renal biopsy. As this disease is no longer rare in Jenin District of Palestine where this patient was seen, delayed diagnosis can not be justified. In conclusion, early diagnosis and effective treatment of PH1 in areas with high prevalence, such as the Jenin District of Palestine, is warranted as it may delay the progression towards ESRD or systemic oxalosis.

Key words: Primary hyperoxaluria type 1, End-stage renal disease (ESRD), Nephrocalcinosis, Nephrolithiasis.

Introduction

Primary hyperoxaluria type 1 (HP1) is the most common form of primary hyperoxalurias (PH). It is an autosomal recessive disorder caused by deficiency of the liver-specific enzyme alanine: glyoxylate aminotransferase (AGT). This results in increased synthesis and subsequent urinary excretion of the metabolic end product oxalate and the deposition of insoluble calcium oxalate in the kidney and urinary tract. As glomerular filtration rate (GFR) decreases due to progressive renal involvement, oxalate accumulates and results in systemic oxalosis (1). PH is a heterogeneous disease with a variable age of onset and a

variable progression into kidney failure. Early diagnosis is mandatory to avoid the damaging effects of systemic calcium oxalate deposition (2). The diagnosis of PH should be suspected in any patient with recurrent kidney stones, normal urinary calcium and uric acid excretion, calcium-oxalate crystals in the urine sediment, and marked hyperoxaluria in the absence of gastrointestinal disease or the ingestion of mega-doses of vitamin C (3). Diagnosis may be established on the basis of clinical and sonographic findings, urinary oxalate with or without glycolate assessment, DNA analysis and, sometimes, direct AGT activity measurement in liver biopsy tissue (1). Concerning ESRD patients, the diagnosis of PH1 must be considered in the differential diagnosis of patients presenting with ESRD with a history of recurrent nephrolithiasis, but the diagnosis of PH1 is more challenging in these patients, for whom urinary oxalate levels are often normal or only moderately increased because of decreased glomerular filtration, and recurrent nephrolithiasis is no longer the dominant clinical feature (4). Although most patients with PH present with renal calculi in childhood or adolescence, the clinical presentation can range from death in infancy in PH1 to asymptomatic cases in adulthood in both PH1 and PH2. This phenotypic diversity, together with the rarity of the disease may account for the delay in diagnosis commonly noted in these patients (5). An unfortunate patient with PH1 with late presentation and poor outcome is presented here to increase awareness about the condition.

Case presentation

A thirteen year-old female was admitted to the emergency unit of The Martyr Dr. Khalil Sulaiman Hospital in Jenin city of Palestine on 1/10/2012 suffering from fatigue, headache, nausea, vomiting, anorexia and renal colic. She had had a 4 year history of recurrent kidney stones. Laboratory tests showed hemoglobin 9g/dl, red blood cells 3.53 m, white blood cells 4.8 k/Ul, urea 155.4 mg/dl and serum creatinine 21.6 mg/dl. Urinalysis showed 3+ proteinuria and 1+ hemoglobinuria. Microscopic examination of urine sediment showed many white blood cells (packed field), 10-12 red blood cells and 8-10 epithelial cells. Depending on these laboratory findings, clinical investigation, and medical history (recurrent kidney stones), the patient was diagnosed initially as ESRD as a result of recurrent kidney stones and she was initiated on hemodialysis 3 times weekly after 3 sessions in the initial 3 days from diagnosis. Abdominal ultrasound showed that both kidneys to be 10 cm in length with marked increase in echogenicity obliterating corticomedullary differentiation. Partial hydronephrosis of the left kidney was also seen with no evidence of solid renal masses identified. On both sides and at positions corresponding to renal papillae there were calcification of medium and large size in keeping with calcified papillae, 4 cm cystic space was noted in the upper pole of left kidney. Review of the history revealed that the patient suffered from renal colic about two months before developing ESRD (on 11/8/2012). A urinary tract ultra sound was done which showed multiple left renal stones with the largest one being about 1.5 cm in size, there was a partial dilatation of the upper calyceal group of the left kidney (partial hydronephrosis) due to a stone about 1 cm in size which caused incomplete obstruction of this group. Concerning the right kidney, there were 3 stones , the largest one about 1 cm in size, there was no hydronephrosis. Urinary bladder was normal. Unfortunately, the patient was not duly followed by physicians and family after this US imaging findings (for example urea and creatinine tests were not done) until the patient developed end-stage renal disease on 1/10/2012. Kidney X-Ray and CT scan images were performed on 6/10/2012. X-Ray and CT scan showed multi stones and calcium oxalate deposits in both kidneys. Depending on ultrasound images, X- ray, CT scan, physical examination, medical history of recurrent kidney stones without a history of secondary hyperoxaluria or medication, strongly positive family history (two cousins were known to have hyperoxaluria type 1 and many other relatives known to have died from this disease), the patient was diagnosed as a patient of primary hyperoxaluria type 1. The diagnosis was confirmed by renal biopsy which showed extensive oxalate crystals deposition in both kidneys. The concentrations of urea and creatinine before dialysis (on 1/10/2012) were 155.4 mg/dl and 21.6 mg/dl respectively. After three sessions of dialysis (on 5/10/2012), the concentrations of urea and creatinine improved to 88 mg/dl and 12.1 mg/dl respectively. The previous history revealed the appearance of renal stones since 2008 which was interpreted by her physicians. The patient and family were inappropriately *reassured* that "she had few renal stones which will be eliminated via the urinary tract with no ill effect on her kidneys" her father confirmed. Passing some stones from time to time was not viewed ominously by the father!. The patient succumbed to his disease shortly after the presentation with ESRD. The patient died in 23/11/2012 within two months from treatment by hemodialysis.

Discussion

Despite the personal history of recurrent kidney stones for 4 years and family history of PH1, recognition of the sad case

was delayed till the patient developed ESRD. Although she had bilateral multiple kidney stones and nephrocalcinosis for long time, she was not screened for PH over the years 2008-2012. This misdiagnosis (i.e. inability to distinguish common types of kidney stones from recurrent kidney stones caused by PH) reflects the difficulty that is faced by some physicians in making a confident diagnosis of PH. This may be due to limited experience in this field, but ignoring family history by the physicians must have contributed to this miss-diagnosis. The patient is from a family with a history of PH (2 maternal cousins died from complications of PH1 and many persons from the patient's own tribe are either suffering or died from the same disease).There are several reports in the literature in which a delay in the diagnosis of PH for many years occurred and sometimes until ESRD has developed (2,6-9). Furthermore, in some reports, the diagnosis of PH was only reached after failed kidney transplantation (10,11). The patient's family on many occasions, play an important role in the progression of the patient's case towards ESRD. Parents must seek second opinion, they should not leave their child's case of recurrent kidney stones without adequate explanation. This may have been a definite contributing factor in our case.

In conclusion, due to the difficulties that face some physicians or nephrologists in the diagnosis of PH due to rarity of the disease, lack of some medical facilities or limited experience, delay in the diagnosis of the disease may occur. However, in some areas or certain groups physicians must have a high index of suspicion when dealing with increased risk such as the patient's tribe in Jenin district which has a history of PH. All patients with history of recurrent kidney stones from this tribe must be screened for PH. Therefore, family history remains an important tool in our practice with this regard. Because of the heterogeneity of PH and because it may appears in infancy, some times since birth or after few months from birth, every case of kidney stone in the kids must be explored to find an etiology, family history must always be ascertained and documented.

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