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Characteristics and Outcome of Primary Hyperoxaluria Type 1 Patients in Jenin District, Palestine

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Abstract

Background: Primary hyperoxaluria (PH) type 1 is a rare inherited metabolic disorder leading to urolithiasis, nephrocalcinosis and most often end-stage renal disease (ESRD). PH type 1 is the most common and the most severe form of primary hyperoxalurias worldwide. In the developing world, patients with PH type 1 usually have a poor prognosis and short survival time. **Objectives:** We aimed to document the characteristics and outcome of PH type 1 patients in Jenin district, Palestine being the type commonly seen here. **Patients and Methods:** 18 patients were diagnosed with primary hyperoxaluria type 1 in Jenin District (Palestine) between 2005 and 2012. A review of the patients' charts was performed and the following parameters were recorded: sex, age, age at first symptoms, age at ESRD (onset of dialysis), history of conservative treatment, history of parental consanguinity, family history of the disease, and outcome or current status. Some data were obtained directly from physicians and nurses of the kidney unit and/or from patients' families. **Results:** Seven patients were males and 11 were females. Mean age at diagnosis was 3.12 years while the median was 0.42 year (range: 3 months - 20 years). All the patients were from one tribe and the rate of parental consanguinity was 100%. Regarding patients' outcome, 7 children died before initiation of hemodialysis (6 of them during infancy and one at 8 years of age), 2 patients died from complications of liver or combined liver-kidney transplantation procedures, 2 patients died while on hemodialysis, 5 patients were still on conservative treatment at last follow-up, and 2 patients remained on hemodialysis. There was an important heterogeneity in symptoms, age at first symptoms, and age at ESRD. **Conclusion:** The high mortality rate among our patients compared to that found in the literature, may be due to the severity of the disease, shortage of some medical facilities such as absence of pediatric hemodialysis, preemptive liver or combined liver-kidney transplantation operations in Palestine.

Key words: Jenin district; Palestine; Consanguinity; Primary hyperoxaluria type 1.

Abbreviations: AGXT gene: alanine:glyoxylate aminotransferase gene; ESRD: end-stage renal disease.

Introduction

The autosomal recessive inherited primary hyperoxalurias (PH) types 1, 2 and 3 are caused by defects in glyoxylate metabolism that lead to the endogenous overproduction of oxalate. In all forms, urinary excretion of oxalate is markedly elevated which results in recurrent urolithiasis and/or progressive nephrocalcinosis. PH type 1 can induce kidney damage, which is followed by reduced oxalate elimination and consequent systemic deposition of calcium oxalate crystals (i.e. oxalosis) (1). PH type 1 is the most common type of primary hyperoxaluria (2). Early diagnosis is of crucial importance to delay the progression to end-stage renal disease (ESRD) and systemic oxalosis, but diagnosis is too often missed or delayed until ESRD occurs, especially in the infantile form of the disease. This outcome occurs in more than 30% of patients with PH type 1(1). Once the patient reaches ESRD and starts on hemodialysis, prognosis is poor and mortality rate is high which may be explained by sudden arrhythmias and heart block because no dialysis procedure is able to remove adequately the daily production of oxalate (3). Therefore, aggressive dialysis is required to avoid progressive oxalate deposition in established ESRD, and minimization of the time on dialysis may improve both the patient's survival and quality of life (2). Because hemodialysis is not the best treatment option in PH type 1, preemptive isolated liver transplantation should be considered in children who develop the disease during infancy or in those with slowly progressive disease when significant symptoms develop before the occurrence of ESRD, and combined liver-kidney transplantation is suggested for children with ESRD (4). According to a previous study, ESRD occurs by the age of 15 years in 50% of PH type 1 patients and the overall death rate approximates 30% (5). Several cases of PH type 1 have been diagnosed in Jenin District (Palestine) in the last few years. In this study, the characteristics and outcome of all patients diagnosed with this disease in Jenin district during the period 2005-2012 are described.

Patients and Methods

Setting

This study was conducted in Jenin District which includes Jenin city and the surrounding villages with a population of about 300000 persons. This is a retrospective study including all patients diagnosed with PH type 1 from October 2005 to October 2012.The study was conducted in the kidney unit of The Martyr Dr. Khalil Sulaiman Hospital in Jenin city being the only kidney unit in Jenin district where all patients from Jenin district are treated.

Diagnosis of primary hyperoxaluria

The diagnosis was based on laboratory tests including urine analysis, renal ultrasound, abdominal X-ray, computed tomography (CT) scans in addition to physical examination, medical history, and family history. Urine analysis showed marked calcium oxalate crystals in all the patients. X-rays, kidneys ultrasound, and CT scans showed multi stones or calcium oxalate deposits in the kidneys of all patients. Family history was an important diagnostic tool especially in case of presence of more than one patient in the same family. In five cases, the diagnosis was confirmed by renal biopsies which showed extensive calcium oxalate crystals in both kidneys. Genetic testing was not available in these patients. The information about the diagnostic procedures, the characteristics, and outcome of the patients were obtained from medical records of the patients in the kidney unit, from the physicians and nursing staff of the kidney unit, parents, and the medical records of the hospital.

Statistical analysis

Descriptive statistics such as median and range, mean, standard deviation, and percentage were used to characterize the study data.

Results

Eighteen cases of primary hyperoxaluria type 1 have been diagnosed during the study period. Seven patients were males and 11 were females (male to female ratio 1:1.6). The median age at first symptoms was 0.42 year (range: 3 months - 20 years). The mean age was 3.12 years (standard deviation 5.2 years). Seventy-two percent of patients were diagnosed before the age of 5 years, and 94% were diagnosed before the age of 10 years. The outcome of the cohort of patients is summarized in table 1. A total 11 patients out of 18 (61%) died during the study period. The age distribution at death is shown in table 2. Eleven patients out of 18 (61%) developed ESRD by the age of 15 years and two (11%) developed ESRD after the age of 20 years and 5 patients (28 %) did not reach ESRD stage and are still on conservative treatment. These results are summarized in table 3. Regarding the patients that developed ESRD,

11 out of 13 (85%) developed this by the age of 15 years and only 2 out of 13 (15 %) developed this after age of 20 years, so most of the patients who develop ESRD, reach this stage at a relatively early age before the age of 15 years. The characteristics of each patient included in this study are detailed in table 4 and table 5: age of the patient at first symptoms, diagnostic procedures, age at ESRD, conservative treatment, and outcome at the end of the follow-up. All the patients belong to one tribe (big family) although they are distributed on 10 different small families which are very closely related. There is often more than one affected person in the same family (two or three). The rate of parental consanguinity was 100%, and the parents of all the patients were cousins. To date, no case of primary hyperoxaluria has been diagnosed in other tribes of the Jenin District.

Discussion

The results showed that 61% of our patients died during the study period (7 years) giving an annual mortality rate of 8.7%. This mortality rate is greater than that found in similar studies. For example, in a 15-years study in Switzerland, 7

Table 1. Outcome of primary hyperoxaluria type 1 patients during the period of 2005-2012

Outcome	Number of patients	Percentage (%)
Died before initiation of hemodialysis	7	39
Died after combined liver- kidney transplantation	1*	5.6
Died after liver transplantation	1**	5.6
Died on hemodialysis	2	11
Still on hemodialysis	2	11
Alive and on conservative treatment	5	27.8

** This patient died after 2 years from the operation by Herpes zoster infection due to immunosuppression. This is the second transplantation operation, since 2 years from this operation, this patient received isolated kidney transplantation taken from his uncle and failed after about 2 years.*
*** This patient died after 2 months from liver transplantation (as the first stage of combined liver- kidney transplantation) taken from his mother.*

Table 2. The age distribution of the dead persons from primary hyperoxaluria type 1.

Age interval (years)	Number of patients	Percentage (%)
< 1 year	6	54.5
1 – <5 years	-	-
5 – < 10 years	2	18.2
10 – < 15 years	-	
15 – < 20 years	1	9.1
20 – < 25 years	-	
25-30 years	2	18.2

Table 3. Age at developing end-stage renal disease (ESRD).

Age at developing ESRD	Number of patients	Percentage (%) from total patients
<1 year	6	33.3
4 years	1	5.6
8 years	1	5.6
13 years	2	11.1
15 years	1	5.6
21 years	2	11.1

Table 4. The age of developing first symptom, basis of diagnosis, age of ESRD, documentation of conservative management and outcome in patients who presented in the first year of life*.

Age at developing first symptoms	ESRD and (its age of onset)	Conservative treatment**	Age at the end of the study (years) / and outcome
6 months	Yes (13 years)	**Yes**	13 years (on hemodialysis).
6 months	Yes (8 years)	**Yes**	Died at age of 8 years before hemodialysis
4 months	Yes (4 years)	**Yes**	Died at age of 6 year
5 months	Yes (5 months)	**No**	Died at age of 7 months before initiation of hemodialysis
4 months	Yes (4 months)	**No**	Died at age of 4 months before initiation of hemodialysis
3 months	Yes (3 months)	**No**	Died at age of 4 months before initiation of hemodialysis
4 months	Yes (4 months)	**No**	Died at age of 6 months before initiation of hemodialysis
3 months	Yes (3 months)	**No**	Died at age of 4 months before initiation of hemodialysis
3 months	Yes (3 months)	**No**	Died at age of 4 months before initiation of hemodialysis
4 months	No	Yes	Age is 7 years (on conservative treatment)
4 months	No	Yes	Age is 10 years (on conservative treatment0
4 months	No	Yes	Age is 13 years (on conservative treatment)

** Basis of the diagnosis is these patients were medical history (MH), family history (FH), kidney ultrasonography (US), plain abdominal radiography (AXR), computed tomography (CT), urine analysis (UA) , plasma biochemistry.*

*** conservative treatment: vitamin B6, high fluid intake, dietary restriction.*

Table 5. The clinical and disease characteristics [age of developing first symptom, basis of diagnosis, age of ESRD, documentation of conservative management and outcome in patients who presented after the first year of life

Age at developing first symptoms	Diagnostic basis*	ESRD	Age of onset of EASD (years)	Conservative treatment**	Age at the end of the study (years) and outcome
2 years	MH, FH, AXR, US, CT, Lab, UA.	No	-	Yes	4 years (on conservative treatment)
6 years	MH, FH, AXR, US, CT, Lab, UA, RBx	No	-	Yes	11 years (on conservative treatment)
7 years	MH, FH, AXR, US, CT, Lab, UR, RBx.	Yes	15	Yes	Died at 15 years old after 2 months from liver transplantation
8 years	MH, FH, AXR, US, CT, Lab, UR, RBx.	Yes	21	Yes	Died at age 30 years after 2 years of combined liver- kidney transplantation
9 years	AXR, US, CT, Lab, UR, RBx	Yes	13	No	Died at age of 13 years after 2 months from hemodialysis
20 years	MH, AXR, US, Lab, UR, RBx	Yes	21	Yes	Died on hemodialysis at age 30 years

**Basis of the diagnosis: medical history (MH), family history (FH), kidney ultrasonography (US), plain abdominal radiography (AXR), computed tomography (CT), urine analysis (UA), renal biopsy (RBx).*

*** conservative treatment: vitamin B6, high fluid intake, dietary restriction*

out of 25 patients died during the study period giving an annual mortality rate of 1.9% (6). The annual mortality rate in our patients is also higher than in a study in northern Israel, in which 12 out of 36 patients (33.3%) died during 10 years giving an annual mortality rate of 3.3% (4). The overall death rate in our patients is around twice of that found in the literature (about 30%) (5).The high mortality rate in our patients compared to other countries may be due to several reasons including frequency of infantile oxalosis, disease severity and shortage of some medical facilities such as pediatric hemodialysis, combined liver-kidney transplantation or preemptive liver transplantation

procedures which are not available in Palestine. Six of the patients who develop initial symptoms in the first year of life were in ESRD at diagnosis. These young patients were in poor conditions and urgently needed hemodialysis but since pediatric hemodialysis is unavailable in Palestine and their families were unable to treat them in Israel because of the financial burden of treatment, they died before initiation of dialysis. Regarding transplantation procedures, only 2 out of 18 patients (11%) underwent combined liver-kidney transplantation performed in Jordan. This proportion is lower than reported in a previous study from northern Israel where 9 out of 36 patients (25%) received combined liver-kidney transplantation (4). No preemptive liver transplantation was performed in Jenin District in comparison to 3 cases out of 36 (8%) in northern Israel (4). The shortage of liver transplantation operations in Jenin District as compared to Israel may also be due to other reasons such as weakness of Palestinian economy. Other important causes are lack of specialized physicians and staff, and lack of the culture of preemptive liver transplantation operations by the families which may be due to family unawareness and/or poverty. Many parents are unaware of the nature of the disease and its complications. This may be due to non-clarification of the disease and its prognosis by some physicians. Some families are aware of the disease and its complications (because they have an experience with other cases in the same family or in the relatives) but financial burden, patient's age, or the fear from complications of the surgical procedure may prevent them from accepting the operation for their children. Parental consanguinity was evident in all patients. This is slightly greater than the rate found in Tunisia, where the prevalence of primary hyperoxaluria type 1 is high, according to a recent study in which a family history of consanguinity was noted in 90% (7).

Seventy two percent of patients have reached ESRD during the study period. Of these, 85% developed ESRD by the age of 15 years and 15% after the age of 15 years. This proportion is greater than that was described in the literature where ESRD is reached by the age of 15 years in 50% of patients (5). This may be due to a particular severe form of primary hyperoxaluria type 1 in Jenin District (namely severe infantile form) since 12 cases presented with symptoms and were diagnosed a few months after birth and 6 cases died after one or two months from disease onset. The median age at presentation (5 months) is much younger than that found in Saudi Arabian children (5 years). Moreover, 94% of our patients were diagnosed before the age of 10 years in comparison to 80% in Saudi Arabia (8). This suggests that primary hyperoxaluria type 1 in our patients may be more severe than that in the Saudi Arabian children. The relative heterogeneity in symptoms, age at disease onset, and age at ESRD in our patients may be explained by differences in disease severity due to variation in the levels of other enzymes in the oxalate synthesis pathway, dietary intake of oxalate precursors, absorption of dietary oxalate, hydration, pyridoxine intake and type of mutation. Conservative treatment by diet restriction of oxalate precursors, hyperhydration, and pyridoxine intake (vitamin B6) has shown positive effects in some patients in postponing the development of ESRD. However, since many patients were diagnosed with ESRD due to PH type 1 within a few months after birth, it is possible that more than one mutation in the *AGXT* gene may be found in our patients. Genetic studies are therefore needed to determine the location and type of mutations. Primary hyperoxaluria type 1 has been found only in one tribe in Jenin District. It is obvious that marriage among relatives (especially cousins) is the cause of the high incidence of PH type 1 in this tribe, this phenomenon is not recent but exists through generations in this tribe. This disease and its complications cause physical and psychological suffering to the patient and his family. In addition, the family suffers financially because of the cost of treatment. It is possible to prevent or decrease the incidence of this disease in our community. Preventative and effective measures should be put in place to aceive this goal. The foremost preventive measure to decrease the incidence and the burden of PH is avoiding consanguineous marriage, especially between cousins.

In conclusion, the overall prognosis of PH type 1 is poor in Jenin district, Palestine. Majority of patients with primary hyperoxaluria type 1 in this cohort suffered from the severe infantile form of the disease, but since other patients are diagnosed at an older age and because of heterogeneity of disease presentation more than one mutation in the *AGXT* gene might be involved in our patients and genetic studies are therefore warranted.

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References

1. Hoppe B. An update on primary hyperoxaluria. Nat Rev Nephrol 2012;8(8):467-75.
2. Cochat P, Liutkus A, Fargue S, Basmaison O, Ranchin B, Rolland MO. Primary hyperoxaluria type 1: still challenging! Pediatr Nephrol 2006;21(8):1075-81.
3. David-Walek T, Niederstadt C, Rob PM, Fricke L, Latta K, Steinhoff J, et al. Primary hyperoxaluria type 1 causing end-stage renal disease in a 45-year-old patient. Nephron 2001;87(1):80-4.
4. Shapiro R, Weismann I, Mandel H, Eisenstein B, Ben-Ari Z, Bar-Nathan N, et al. Primary hyperoxaluria type 1: improved outcome with timely liver transplantation: a single-center report of 36 children. Transplantation 2001;72(3):428-32.
5. Cochat P, Gaulier JM, Koch Nogueira PC, Feber J, Jamieson NV, Rolland MO, et al. Combined liver-kidney transplantation in primary hyperoxaluria type 1. Eur J Pediatr 1999;158Suppl 2:S75-80.
6. Kopp N, Leumann E. Changing pattern of primary hyperoxaluria in Switzerland. Nephrol Dial Transplant 1995;10(12):2224-7.
7. Gargah T, Khelil N, Youssef G, Karoui W, Lakhoua MR, Abdelmoula J. Primary hyperoxaluria type 1 in Tunisian children. Saudi J Kidney Dis Transpl 2012;23:385-90.
8. Sanjad SA, Al-Abbad A, Al-Sabban E. Primary hyperoxaluria type 1: an underestimated cause of nephrocalcinosis and chronic renal failure in Saudi Arabian children. Ann Saudi Med 1999;19(1):4-7.