

*Original Article*

**Changing pattern of primary hyperoxaluria in Switzerland**

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**Abstract**

**Background.** The clinical course of primary hyperoxaluria (PH) is greatly variable and diagnosis is often delayed. Little is known about the overall occurrence and current prognosis.

**Methods.** We evaluated all known patients with PH residing and observed in Switzerland during the last 15 years with the help of a survey among Swiss nephrologists.

**Results.** Of the 25 patients observed between 7/79 and 6/94 in Switzerland, 18 were alive in 1994—14 on conservative therapy and four on renal replacement therapy (RRT). Twenty-two patients had PH type 1; the exact type was not determined in three. The estimated prevalence of PH (type 1) is 2 per million population; the minimal incidence is 1 per 100 000 live births. Diagnosis was delayed by 8 years (median) except in infants. Five patients were pyridoxine sensitive. According to life table analysis, 20% of patients were in end-stage renal failure (ESRF) and 10% had died by the age of 15 years, and 50% were in ESRF and 20% dead at 25 years. Prognosis has improved: Five of 13 patients died during the first half of the observation period as opposed to two of 20 in the second part.

**Conclusions.** Overall prognosis appears better than hitherto believed considering the large clinical spectrum of PH. Greater awareness of PH is needed to improve further long-term prognosis.

**Key words:** oxalosis; prevalence; primary hyperoxaluria; survey; Switzerland

**Introduction**

Primary hyperoxaluria (PH), particularly its most common form, type 1, is characterized by increased production of oxalic acid, resulting in recurrent urolithiasis and nephrocalcinosis which often progresses to end-stage renal failure (ESRF) and generalized oxalosis [1,2]. The clinical spectrum of PH is very large and patients are seen at all ages. Little is known

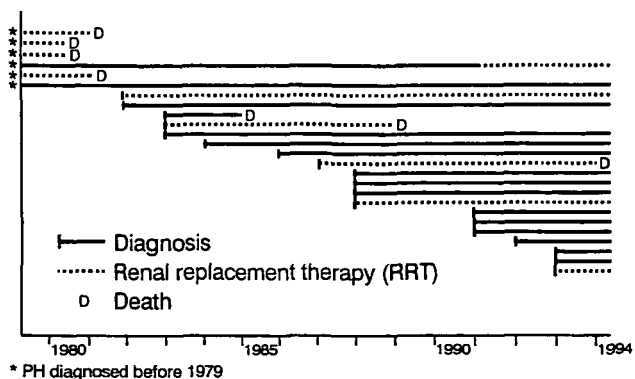
about its occurrence. While reviewing all known patients with PH observed during the last 15 years in Switzerland, we noticed a trend towards more frequent, albeit still considerably delayed, diagnosis of PH and a milder course. PH may be less rare than anticipated and prognosis may be better than hitherto believed.

**Subjects and methods**

Paediatric and adult nephrologists were contacted about all patients with PH residing in Switzerland and treated between 7/79 and 6/94. The total population in Switzerland in 1994 was 7.038 million and the number of children born during these 15 years (1978–1993) was 1.172 million. Diagnosis of PH was based on repeatedly elevated oxalate excretion (normal <0.5 mmol/24 h per 1.73 m<sup>2</sup>), reduced activity of alanine: glyoxylate aminotransferase (AGT) or generalized oxalosis in ESRF after exclusion of secondary hyperoxaluria. Urinary glycolate was measured in 21 patients [3]. The actuarial curves for patient and (native) kidney survival were calculated according to life table methods (Kaplan–Meier). Renal death as the end-point was defined as the age ESRF occurred, i.e. start of dialysis or death from uraemia.

**Results**

Twenty-five patients with PH were observed during the last 15 years; 16 were males (Figure 1). PH was diagnosed in seven patients during the first half of the



**Fig. 1.** Year of diagnosis and subsequent clinical course.

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**Table 1.** Age (years) at first clinical symptoms/signs and at diagnosis of PH

Age group (n)	A 7*	B 12*	C 6
Age at first symptoms/signs (median)	0.3	4.3	24
(range)	(0.1–0.5)	(2–13)	(15–37)
Age at diagnosis (median)	0.6	12	34.5
(range)	(0.1–2.7)	(2.5–38)	(21–62)

\* Less one patient without symptoms detected by family screening.

observation period and in 12 during the second part; in six, diagnosis was known before 1979. Twenty-two patients were classified as type 1 of PH, based on elevated urinary glycolate excretion (19 patients) or diminished hepatic AGT activity (3 patients). The exact type of PH in the remaining three patients could not be established. No case of PH type 2 was diagnosed. As of June 1994, 18 patients were alive; of these, 14 (all with type 1) did not require renal replacement therapy (RRT), suggesting a prevalence of 2 per million population. Renal function was normal or slightly impaired (serum creatinine <100 µmol/l) in 11 of these 14 patients, moderately decreased (serum creatinine <150 µmol/l) in two and severely impaired in one (serum creatinine 200 µmol/l). Diagnosis of PH (type 1) was made 12 times in children born during the study period. The calculated (minimal) incidence is 1 in 98 000 live births.

According to the age at first clinical symptoms, patients were assigned to three age groups: A <2 years, B 2–14 years, and C >14 years. Except for patients in group A who frequently had a severe course, diagnosis was usually considerably delayed, being made almost 8 years (median) after the first clinical manifestations in group B, and even after 10.5 years in C (Table 1, Figure 2). Recurrent urolithiasis was the leading symptom in 83% of patients in groups B and C in contrast to failure to thrive or anaemia due to renal failure in infants.

The symptoms or signs that ultimately led to diagnosis of PH were nephrocalcinosis (7), ESRF (6) and urolithiasis (5). Six of the seven remaining patients

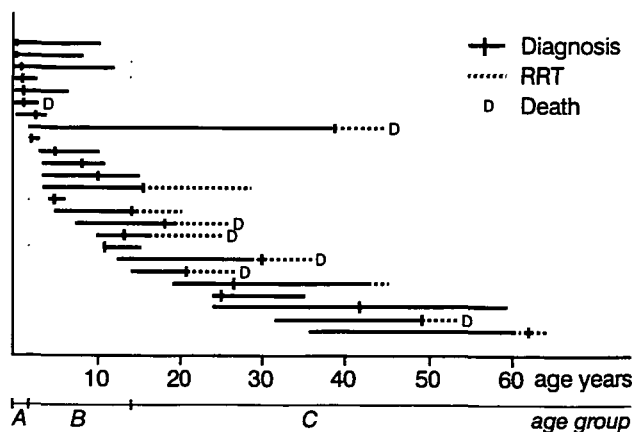
with no obvious symptoms were diagnosed by family screening and one was detected by abdominal ultrasonography performed for other reasons. Fourteen patients had both urolithiasis and nephrocalcinosis, five had stones but no detectable nephrocalcinosis, and another five had isolated nephrocalcinosis. Only one patient, detected by family screening, had normal renal echography.

Altogether there were 15 familial cases belonging to eight families. Seven families had two affected siblings (in 2 instances, only 1 member is included in the study because of death of the sibling before 1979 and residency outside Switzerland respectively). One further family shows apparent autosomal inheritance involving son, mother, and maternal uncle; whereas both adult patients had a concordant clinical course (group C), the son presented with infantile oxalosis (A) [4]. PH is concordant in five of the other seven families (3 × B/B and 2 × C/C) and discordant in one (B/C). Classification is arbitrary in one family because the 8-year-old sister of a patient with infantile oxalosis (A) never had clinical symptoms despite nephrocalcinosis detected shortly after birth. The vast majority of patients (20) were of Swiss origin; four (3 families) came from former Yugoslavia and one from Italy. There was no proven consanguinity.

Five patients were pyridoxine sensitive. Three have been reported previously [4,5]; the other two had reduction of oxalate excretion by nearly one-half. The actuarial survival curves for kidneys and patients run parallel with most losses occurring after the age of 20 years (Figure 3). By the age of 15 years 20% of the patients were in ESRF and 10% had died. By the age of 25 years, half of the patients were in ESRF and 20% were dead. Almost identical data were obtained in the subgroup of 22 patients with documented PH type 1. Of seven patients undergoing isolated kidney transplantation, only one is alive. Two further patients underwent combined liver/kidney transplantation and are alive. General outlook has considerably changed: Whereas five of 13 patients diagnosed before 1986 were dead by then, only two of 20 patients died since 1987.

## Discussion

The aim of this study was to record all patients with PH seen during 1.5 decades in one country, so as to eliminate bias by selection. Urologists were not contacted, since paediatric stone patients in Switzerland



**Fig. 2.** Age at first clinical manifestation and clinical course. Time of diagnosis is indicated by vertical bar.

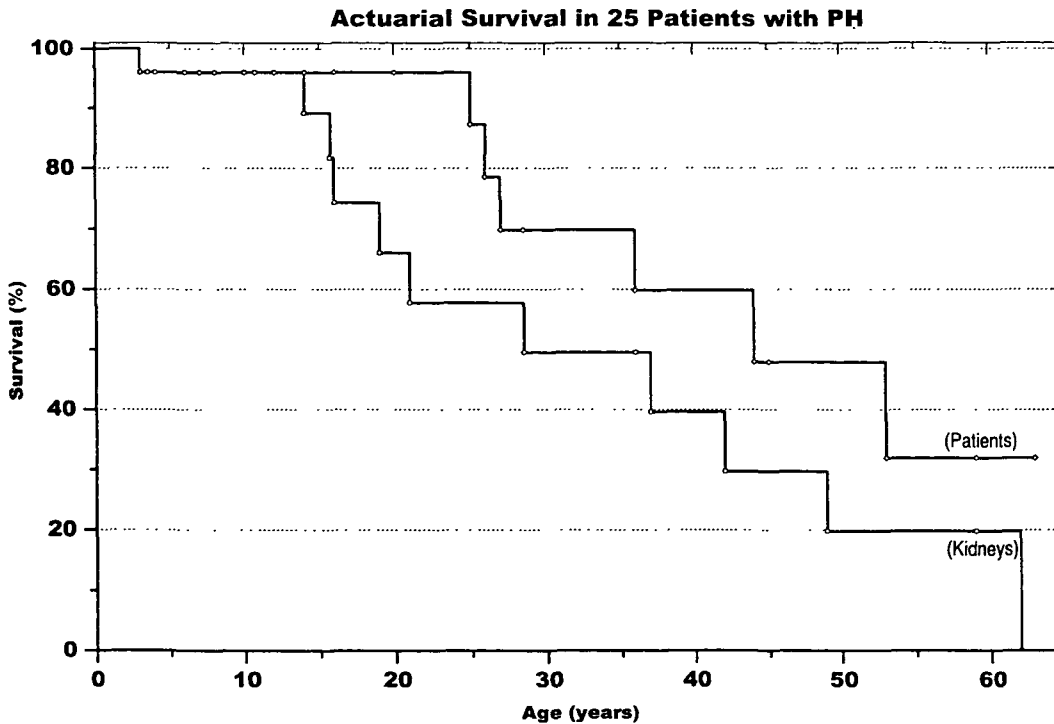


Fig. 3. Actuarial survival in 25 patients with PH. End-points are age at renal death and age at death of the patient.

are seen by paediatric nephrologists and adult patients with a metabolic stone disease are referred to nephrologists. However, it is likely that not all patients with PH were detected. Indeed, diagnosis of PH was established thanks to family screening—and not on clinical grounds—in almost one-quarter of all patients, who otherwise would have been missed. The estimated prevalence rate (2 per million for type 1) therefore is a minimum figure. The same applies to the estimated incidence (calculated per live births) since there is little doubt that diagnosis of PH has not yet been made in every patient born during the study period. Comparatively more patients were diagnosed in the last few years, possibly thanks to greater awareness of PH.

Published data concerning the prevalence of PH are scarce. In a recent survey in France (1988–1992), a prevalence rate of 1.04 per million was calculated for PH type 1 [6]. The Swiss figure is almost twice as high. Only 17 patients were observed in Scandinavia during 10 years (1967–1976); 10 were alive at the end of that period [7].

The very large clinical spectrum of PH (primarily type 1) has again been demonstrated and may be one reason why diagnosis was so often delayed. Indeed, six patients were already in ESRF when PH was diagnosed. The clinical heterogeneity is not sufficiently explained by remaining activity of the peroxisomal enzyme AGT or by mitochondrial mistargeting; other factors (e.g. episodes of dehydration) are important as well [1]. Initial symptoms may be very vague (e.g. intermittent abdominal pain), and a high level of suspicion is needed.

Much progress has been made unravelling the molecular basis of PH type 1 [1], but clinical assessment still runs far behind. Normal urinary oxalate/creatinine ratios for different age groups are available for screening purposes [3,8].

The prognosis of PH has to be reassessed in the light of this study. Whereas 50% of children were reported to reach ESRF before age 15 [2], this was the case in only 20% of our patients according to life table analysis. However, the actuarial data must be interpreted with caution because of the low number of older patients. It is likely that previous studies (see [2]) were biased towards patients with serious and early clinical manifestation. Furthermore the general outlook seems to have improved, thanks to greater awareness of PH, leading to earlier diagnosis and intervention. Renal failure may thus be prevented or delayed [5,9,10], at least as long as renal function is not seriously compromised. Such conservative measures are far more economical and simpler than combined liver–kidney transplantation, at present the best form of renal replacement therapy in PH type 1 [11].

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