Primary hyperoxaluria type 1: clinical, genetic and biochemical studies
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CHAPTER 03 Primary hyperoxaluria type 1 in The Netherlands: prevalence and outcome

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ABSTRACT

Background. Primary hyperoxaluria type 1 (PH1) is a phenotypically heterogeneous disease. To date the relationship between biochemical parameters and outcome is unclear. We therefore undertook a national cohort study on biochemical and clinical parameters and outcome in PH1.

Methods. Review of medical charts of all Dutch PH1 patients, who were identified by sending questionnaires to all Dutch nephrologists for children and adults.

Results. Fifty-seven patients were identified. The prevalence and incidence rates were 2.9/10^6 and 0.15/10^6/year, respectively. Median age at diagnosis was 7.3 years (range 0-57). Seventeen (30%) patients were older than 18 years at time of diagnosis, of whom 10 (59%) presented with end-stage renal disease (ESRD), in contrast to only nine (23%) of those aged under 18 years. Median age at initial symptoms was 6.0 years (range 0-50). In four of nine patients with infantile PH1, normal renal function was preserved after a median follow-up of 7.7 years (range 0.1-16). Progression to renal insufficiency was associated with the presence of nephrocalcinosis, as assessed by ultrasound (relative risk=1.8; 95% CI, 1.0-3.4) and with pyridoxine-unresponsiveness (relative risk 2.2; 95% CI, 1.1-4.2) but not with age at presentation, the extent of hyperoxaluria, or AGT activity. No apparent nephrocalcinosis was found in five of the 19 patients who presented with ESRD.

Conclusions. Although more than one-half of the PH1 patients have symptoms under the age of 10 years, PH1 can present at any age. In adults, PH1 presents predominantly with ESRD, which may be due to misinterpretation of early symptoms. Although nephrocalcinosis is correlated with development of renal insufficiency, the latter can occur even in the absence of nephrocalcinosis. Pyridoxine sensitivity is associated with better outcome in PH1.
INTRODUCTION

Primary hyperoxaluria type 1 (PH1) is a rare autosomal recessive inborn error of glyoxylate metabolism. It is characterized by a functional defect of the liver specific enzyme alanine:glyoxylate aminotransferase (AGT) which is localized in peroxisomes (1). PH1 is caused either by deficient AGT activity or by mistargeting of the enzyme to mitochondria instead of peroxisomes. AGT detoxifies the metabolite glyoxylate to glycine, using pyridoxal-5-phosphate as a coenzyme. In the absence of functional AGT, oxalate and glycolate are produced in excess, leading to hyperoxaluria and hyperglycolic aciduria. The marked excess of oxalate leads to the formation of insoluble calcium oxalate, resulting in crystalluria, renal stone formation and nephrocalcinosis. In addition to PH1, two other types of primary hyperoxaluria have been described: primary hyperoxaluria type 2 (PH2), which is caused by deficient glyoxylate reductase/D-glycerate dehydrogenase activity, leading to elevated levels of oxalate and L-glycerate in the urine (2) and a type of primary hyperoxaluria that has not been unravelled in terms of biochemical or molecular mechanism: unclassified or atypical PH (3). These other types exhibit the same symptoms as in PH1, albeit somewhat less severe. PH1 shows considerable phenotypic, enzymatic and genotypic heterogeneity (4-7).

Some patients have no symptoms at all or suffer only from recurrent urolithiasis. Other patients develop a chronic renal insufficiency with systemic oxalosis, characterized by oxalate depositions in multiple tissues, such as bone, retina and nerve tissue (8). Even in patients with apparent nephrocalcinosis, conservative treatment with hyper-hydration, citrate and pyridoxine can be successful (9,10).

Unfortunately, the outcome is poor in most patients. Approximately 50% of them have been reported to reach end-stage renal disease (ESRD) at the age of 25 years (4,5,7). Patients with ESRD require intensive dialysis sessions in order to delay systemic oxalate deposition (11). Renal grafts may fail even after a combined liver-kidney transplantation, due to systemic oxalosis (12).

Currently, three clinical subgroups are distinguished within PH1. First, a rare infantile form with early renal insufficiency. Secondly, a rare late-onset form with occasional stone passage in late adulthood and with a good prognosis with respect to renal function. Thirdly, the most common form, with recurrent urolithiasis or nephrocalcinosis and often progressive renal insufficiency (13). However, the relationship between biochemical and clinical parameters on the one hand and outcome on the other remains unclear. Therefore we undertook a multi-centre retrospective study on Dutch PH1 patients to delineate the clinical and biochemical spectrum of PH1, its therapy and its outcome.
SUBJECTS AND METHODS

Sources
The cohort formation was based on two sources. The database of the national Dutch Registry of patients on renal replacement therapy (RENNIE, Rotterdam, The Netherlands). The registry was founded in 1985. All patients on dialysis are included in this database, as registration is obligatory for reimbursement of renal replacement therapy. All physicians of the Dutch Society of Paediatric Nephrology and the Dutch Society of Nephrology received a questionnaire and were personally approached by CSvW or JWG if they did not respond.

Questionnaire
The questionnaires provided individual data about the patients: age, sex, age at first symptoms, age at biochemical diagnosis, symptoms at diagnosis, diagnostic procedures, duration of follow-up, therapeutic strategies and outcome.

Population
All known Dutch PH1 patients who were investigated and/or treated by a nephrologist were included. Prevalence rate was calculated for the most recent follow-up.

Analysis
Patients were diagnosed as type 1 PH if either deficient AGT activity or the combination of hyperoxaluria and hyperglycolic aciduria was demonstrated (ratios in a 24 hour collection of urine exceeding 54 mmol/mol creatinine for oxalate and 140 mmol/mol creatinine for glycolate, as determined in our laboratory). Urinary oxalate and glycolate reference values for small children were derived from data of Reusz et al. (14). For patients in whom urinary oxalate could not be measured because of anuria, highly elevated plasma oxalate levels of more than 20 times the upper limit of the reference range were considered to be caused by PH1 and not by renal insufficiency itself (15). Patients in whom only hyperoxaluria was measured were considered to have PH1 if this was demonstrated in other family members. If these firm diagnostic grounds were not present, we decided to include patients with the following highly suspicious circumstantial evidence for PH1: (i) significant response to pyridoxine therapy (dosage 400-1200 mg/day), defined by a decline of urinary or plasma oxalate levels of more than 30% upon pyridoxine therapy (16); (ii) severe systemic oxalosis. Primary hyperoxaluria type 2 was diagnosed on the bases of elevated urinary levels of oxalate and L-glycerate as well as deficient activities of D-glycerate dehydrogenase and glyoxylate reductase (2). Hyperoxaluric patients who did not fit in any of these categories were grouped as the atypical type of PH (3). Nephrocalcinosis was clinically assessed, based on sonographic or radiological examination. Prevalence and incidence rates were calculated using national demographic data provided by the Health and Welfare Department of Statistics Netherlands. Infantile PH1 was defined as PH1 becoming symptomatic
before the age of 1 year. Follow-up was defined as the period between presentation of initial symptoms or date of diagnosis if no symptoms were present and the date of investigation or date of death of a patient. Renal function was estimated by the Cockroft formula in adults, and the Schwartz formula in children using plasma creatinine values (17,18). Renal insufficiency was defined as a creatinine-clearance of less than 60 ml/min/1.73 m². End-stage renal disease (ESRD) was defined as a creatinine-clearance of less than 10 ml/min/1.73 m².

Five different parameters in relation to outcome were investigated: age at initial symptoms, nephrocalcinosis at diagnosis, level of urinary oxalate at the time of diagnosis, AGT activity and pyridoxine responsiveness (19). For analysis, dichotomous variables were composed according to supposed clinical relevance and related to outcome. For urinary oxalate excretion, the median level of the entire cohort was calculated using all urinary oxalate excretion levels in individual patients measured at the time of diagnosis. Patients with oxalate levels exceeding the median level were compared to those with urinary oxalate levels below the median level with respect to outcome. In the same way, patients with AGT activity lower than 15% of reference activity (normal range 72-166, median 97 nmol/min.mg) were compared to those with AGT activity above 15% (20). Calculation of reference activity was based on measurements of AGT activities in control livers in our own laboratory. We considered pyridoxine therapy successful if urinary oxalate persistently declined by more than 30% (16). Outcome was dichotomized, creating a group of patients with renal insufficiency, and a group without renal insufficiency. Relative risks were calculated for potential prognostic factors.

The overall renal survival was estimated as a function of age by the Kaplan-Meier method, with patient follow-up censored at renal insufficiency. Statistical package used was SPSS 8.0, 1998 and CIA Version 1.0.

RESULTS

The cohort  We obtained a 100% response from all 189 physicians. Fifty-seven PH1 patients from 44 families were identified of whom 15 had been diagnosed by family screening. Consanguinity was reported in five families. Twenty-one of 57 patients had a positive family history for recurrent urolithiasis. Male/female ratio was 27/30. The calculated prevalence rate was 2.9/10⁶ inhabitants and the incidence rate was 0.15/10⁶ per year. The median follow-up time was 12.6 years (range 1-26) in the 15 patients (26%) who were found by family screening, and 11.3 years (range 0-60) in the other 42 patients. Five patients had a different type of primary hyperoxaluria. One patient was diagnosed with PH2 and four presented with an atypical disorder in oxalate metabolism resulting in primary hyperoxaluria that could not be
classified as either PH1 or PH2. As the majority presented with PH1, we decided to analyse only the results of the PH1 patients in our study.

**Diagnosis**

The median age at diagnosis was 7.3 years (range 0-57). Of 57 patients, 17 (30%) were diagnosed after the age of 18. The diagnosis was established on firm grounds in 49. In 44 patients, the diagnosis was based on either AGT deficiency (29 patients), or hyperglycolic hyperoxaluria (15 patients). In four patients it was based on elevated urinary oxalate levels and PH1 in their families and in one patient on the basis of highly elevated plasma oxalate. In addition, another eight patients were included, two of them on the basis of pyridoxine responsive hyperoxaluria and six on severe systemic oxalosis.

**Initial symptoms**

Median age at initial symptoms was 6.0 years (range 0-50). In 10 patients (18%), the onset of symptoms was at adult age. Symptoms and findings at diagnosis are given in TABLE 03.1. Of the 15 patients found by family screening, five were asymptomatic at the time of diagnosis. All other patients had renal symptoms at the time of diagnosis. ESRD was present in 10 out of 17 (59%) patients of those diagnosed at adult age versus 9 out of 40 (23%) of the pediatric patients. Of all 10 adult patients with ESRD at diagnosis, four presented without evident nephrocalcinosis. Renal biopsies in these four patients showed interstitial nephritis with calcium oxalate crystals in destroyed tubules. Nephrocalcinosis was present in eight of nine paediatric patients with ESRD at onset. In retrospect, of the patients in whom PH1 was diagnosed only at the time of ESRD, all nine paediatric patients had suffered from urolithiasis or failure to thrive for 0.2 years (range 0.0-10.7) and eight adult patients diagnosed had reported urolithiasis for 2.5 years (range 0.0-35.8). Two adult patients had neither urolithiasis nor any other symptoms that could be related to PH1 at the time they developed ESRD.
TABLE 03.1  Symptoms and findings of PH1 patients at diagnosis

<table>
<thead>
<tr>
<th>No. of patients (%)</th>
<th>Median age, years (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal insufficiency</td>
<td>57 (100)</td>
</tr>
<tr>
<td>27/57 (47)</td>
<td>10.0 (0.1-50.8)</td>
</tr>
<tr>
<td>● without nephrocalcinosis</td>
<td>3/27 (11)</td>
</tr>
<tr>
<td>or urolithiasis</td>
<td>28.0 (0.1-50.8)</td>
</tr>
<tr>
<td>● with nephrocalcinosis only</td>
<td>9/27 (33)</td>
</tr>
<tr>
<td>● with urolithiasis only</td>
<td>4/27 (15)</td>
</tr>
<tr>
<td>● with both nephrocalcinosis and urolithiasis</td>
<td>11/27 (41)</td>
</tr>
<tr>
<td>● ESRD</td>
<td>19/27 (70)</td>
</tr>
<tr>
<td>Preserved renal function</td>
<td>30/57 (53)</td>
</tr>
<tr>
<td>● no symptoms</td>
<td>7.0 (0.2-57.3)</td>
</tr>
<tr>
<td>● with nephrocalcinosis</td>
<td>5/30 (17)</td>
</tr>
<tr>
<td>● with urolithiasis only</td>
<td>5/30 (17)</td>
</tr>
<tr>
<td>● with both nephrocalcinosis and urolithiasis</td>
<td>12/30 (40)</td>
</tr>
<tr>
<td>● ESRD</td>
<td>18.0 (0.3-50.8)</td>
</tr>
</tbody>
</table>

Systemic symptoms

- Bone disease 12/57 (21)
- Retinopathy 5/57 (9)
- Failure to thrive 6/57 (11)
- Other symptoms (neuropathy, malaise, chronic diarrhoea) 20/57 (35)

Infantile PH1
Nine patients (16%) were symptomatic during infancy. Five patients had symptoms due to renal insufficiency (failure to thrive) and one had urolithiasis. Three patients were found by family screening. Two of them had a reduced renal function and were diagnosed shortly after birth by screening, because PH1 had been found in an older sibling who died of PH1. The third patient found by screening had been known to have haematuria and nephrocalcinosis since 3 months of age.

Time between initial symptoms and renal insufficiency
There was no relationship between age at onset of symptoms and age at start of dialysis.

Outcome
Of the 27 patients with renal insufficiency at presentation, 19 had ESRD. Of the other eight patients with renal insufficiency, four developed ESRD. In two patients, renal function has remained stable throughout the follow-up period, being 4 years. In two patients, who were followed up for 7.5 and 13 years, respectively, renal function improved to normal values. Of 30 patients with a normal renal function at first examination, eight developed renal insufficiency leading to ESRD in five. Overall, 33 of 57 patients developed renal insufficiency, of whom
28 had ESRD at the end of the study. Of these 33 with renal insufficiency, 24 (73%) demonstrated nephrocalcinosis at diagnosis (TABLE 03.2). FIGURE 03.1 shows the Kaplan-Meier survival curve of renal function in relation to age, with end-point at renal insufficiency. Fifty per cent of the patients had reached renal insufficiency at a median age of 30.0 years (range 22.2-37.7). Eleven patients (19%) died as a consequence of PH1 or its therapy at a median age of 18.0 years (range 0-55). Renal insufficiency occurred in four (27%) of the 15 patients found by family screening. Of 17 isolated kidney transplantsations, performed at a median age of 31.2 years (range 11.1-55.4), eight were successful. The median survival of the kidney grafts was 2.7 years (range 0-26). Transplant failure was always caused by deposition of calcium oxalate. The only patient who received a liver transplant without a renal graft died from complications of the liver graft. Of three combined liver/kidney transplantsations, performed at the ages of 1.7, 3.9 and 16.6 years, respectively, one was successful, one needed a second liver graft and one a second renal graft.

**TABLE 03.2 Outcome in relation to initial symptoms (%)**

<table>
<thead>
<tr>
<th>Initial symptoms</th>
<th>No. of patients (%)</th>
<th>Renal insufficiency</th>
<th>ESRD (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrocalcinosis</td>
<td>14 (25)</td>
<td>9/14 (64)</td>
<td>7/14 (50)</td>
<td>4/14 (29)</td>
</tr>
<tr>
<td>Nephrocalcinosis with urolithiasis</td>
<td>19 (33)</td>
<td>15/19 (79)</td>
<td>13/19 (68)</td>
<td>5/19 (26)</td>
</tr>
<tr>
<td>Urolithiasis</td>
<td>16 (28)</td>
<td>6/16 (38)</td>
<td>6/16 (38)</td>
<td>1/16 (6)</td>
</tr>
<tr>
<td>No nephrocalcinosis, no urolithiasis</td>
<td>8 (14)</td>
<td>3/8 (38)</td>
<td>2/8 (25)</td>
<td>1/8 (13)</td>
</tr>
<tr>
<td><strong>Total number (%)</strong></td>
<td><strong>57 (100)</strong></td>
<td><strong>33 (58)</strong></td>
<td><strong>28 (49)</strong></td>
<td><strong>11 (19)</strong></td>
</tr>
</tbody>
</table>

**FIGURE 03.1 Cumulative survival of renal function in relation to age with patient follow-up censored at renal insufficiency (creatinine clearance less than 60 ml/min/1.73 m²).**
Outcome of infantile PH1

Median follow-up was 7.7 years (range 0.1-16) in nine patients. Five developed ESRD. The three patients who were found by screening showed complete recovery from initial symptoms, improvement of renal function and/or decrease of nephrocalcinosis upon conservative treatment. All three were sensitive to pyridoxine therapy. The two index patients had developed ESRD and died before the age of 6 months. One other patient with a follow-up of 10 months, presenting with infections and urolithiasis, was pyridoxine sensitive and preserved renal function.

Determinants of outcome

Relative risks were calculated for different parameters (TABLE 03.3). One patient had a full response on pyridoxine therapy (i.e. normalization of urinary oxalate levels) and three patients had a urinary oxalate reduction of more than 80%. Eight of 24 (33%) patients who were responsive to pyridoxine developed renal insufficiency, resulting in ESRD in five of them. Of the 11 patients who were pyridoxine-resistant, eight (73%) developed renal insufficiency, resulting in ESRD in six of them.

**TABLE 03.3** Calculated relative risks for different parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>No. of patients&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relative risk for renal insufficiency</th>
<th>(95% CI)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urinary oxalate above the median level</td>
<td>18/37</td>
<td>1.1</td>
<td>(0.5-2.2)</td>
</tr>
<tr>
<td>AGT &lt; 15% of reference value</td>
<td>19/29</td>
<td>0.45</td>
<td>(0.3-1.8)</td>
</tr>
<tr>
<td>Pyridoxine non-responsive</td>
<td>11/35</td>
<td>2.2</td>
<td>(1.1-4.2)</td>
</tr>
<tr>
<td>Nephrocalcinosis</td>
<td>33/57</td>
<td>1.8</td>
<td>(1.0-3.4)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Number of patients/number of patients for whom information could be obtained

**DISCUSSION**

In this study we performed a thorough search in The Netherlands for all PH1 patients by using data from multiple sources, including patients on renal replacement therapy as well as patients with preserved renal function. Despite the limitations of such a retrospective study, we feel that we acquired a complete overview of Dutch PH1 patients: we were able to contact all nephrologists nationwide who are in charge of treatment of PH1 patients. Probably due to the methods used for patient retrieval, the prevalence rate we found for PH1 in The Netherlands (2.9 per 10<sup>6</sup>) is higher than those reported by Cochat *et al.* (1995) (5) in France (1.05 per 10<sup>6</sup>) and by Kopp and Leumann (1995) in Switzerland (2 per 10<sup>6</sup>) (21). Since the calculated incidence for PH1 in
The Netherlands was not higher than reported in those other European countries, the higher prevalence has to be explained by the longer period for patient retrieval we used. Nevertheless, we believe that the observed prevalence rate is still an underestimation of the true prevalence, since the heterogeneous phenotype and the vague initial symptoms can easily result in a delay of screening for PH1 or no screening at all. For instance, 26% of the patients in our study were found by screening in families with one or more known PH1 patients, and 66% of them already had renal symptoms that were at that time not linked to PH1: urolithiasis, haematuria and recurrent urinary-tract infections. The low prevalence of PH2 as observed in our study may also be explained by the mild symptoms in this disorder, resulting in a failure to diagnose the underlying metabolic disease.

Symptoms in the Dutch PH1 patients, whether presenting at infantile, pediatric or adult ages, are comparable to those described in previous studies (4,5,7,21,22). While most infantile patients present with a-specific symptoms such as failure to thrive, older patients have symptoms that are often related to the urinary tract. In our study, ESRD was present in 10 (59%) of 17 patients diagnosed at adult age versus in nine (23%) of 40 patients presenting at pediatric age. The high prevalence of ESRD in adults, and the fact that in this study ESRD is reported to occur even in the absence of a history of urinary stones is remarkable. This seems to contrast with the presumption that in adults PH1 presents predominantly with a mild phenotype. However, it may well be that in these patients mild signs and symptoms prior to the development of ESRD were not adequately understood, and that therefore the opportunity for a timely diagnosis was missed. This stresses the importance of a search for hyperoxaluria in all patients with otherwise unexplained mild renal symptoms. In view of our finding that ESRD may occur as the first presenting sign of PH1, even in the absence of reported previous symptoms like urolithiasis, we believe that screening for PH1 should be performed in all patients with ESRD of unknown origin.

In our study, progression to renal insufficiency was not statistically associated with the level of urinary oxalate or with AGT activity (TABLE 03.3), which is in agreement with other observations (6). Apparently, the *in vitro* activity of the AGT enzyme does not adequately predict the *in vivo* metabolism of glyoxylate. In contrast, progression to renal insufficiency was statistically associated with the presence of nephrocalcinosis, detected by ultrasound, and with non-responsiveness to pyridoxine (TABLE 03.3). In this study, we assessed the effectiveness of pyridoxine on the reduction of urinary oxalate levels in PH1. According to the suggestion of Latta to define pyridoxine responsiveness by a 30% reduction in urinary oxalate levels (16,23), 69% of the Dutch PH1 cohort is responsive to pyridoxine treatment. Our results demonstrate that
response to pyridoxine therapy predicts outcome of renal function (TABLE 03.3). Therefore, a 30% decrease of urinary oxalate upon pyridoxine administration is a clinically relevant value to evaluate this therapy in individual PH1 patients. Furthermore, early recognition of PH1 as the cause of renal insufficiency is of the utmost importance because pyridoxine may reverse the course of the renal disease, as demonstrated by our study. Good outcomes can be achieved by pyridoxine treatment, even in infantile cases. Three of nine infantile patients in our study recovered from severe symptoms present at the time of diagnosis after the start of pyridoxine and one other infantile patient preserved renal function upon pyridoxine administration. This effect of pyridoxine on the course of renal insufficiency in infantile PH1 patients has only been reported so far in exceptional cases (23).

Although progression to renal insufficiency was statistically associated with the presence of nephrocalcinosis, nephrocalcinosis was not found by renal ultrasound in five of 19 patients presenting with ESRD. Interestingly, in four of those five patients, calcium oxalate depositions were visible on kidney biopsy specimens. In one of these five patients, renal biopsy was not performed.

It is unlikely that in these patients nephrocalcinosis was missed on ultrasound, as sonography appears to be a sensitive and reliable method for the detection of nephrocalcinosis (24). Apparently, calcium oxalate deposition as seen on renal biopsy can occur without nephrocalcinosis as detected by ultrasound. The role of oxalate in the destruction of renal parenchyma is uncertain. It has been generally assumed that the destruction of the renal parenchyma in PH1 is caused by the diffuse deposition of calcium oxalate in the kidneys, visible as nephrocalcinosis on ultrasound studies (25). Alternatively, it has been suggested that a high oxalate concentration can be toxic by enhancing the production of free radicals, thereby destroying renal tubular cells, resulting in renal insufficiency (26). Whatever the precise mechanism of renal destruction in PH1 may be, these findings clearly demonstrate that the absence of nephrocalcinosis as detected on renal ultrasound studies does not exclude PH1 and evolution to ESRD. Since the combination of nephrocalcinosis and urolithiasis in children is highly suspicious for PH1 (27), we therefore recommend a diagnostic work up for hyperoxaluria in all patients with unexplained chronic renal insufficiency or recurrent urinary tract symptoms at all ages.

One-third of the patients in this Dutch PH1-cohort had already developed ESRD before PH1 was diagnosed. There are several explanations for this late detection. First, metabolic assessment is not a routine procedure in patients with recurrent urinary tract symptoms. Secondly, the diagnostic procedure of PH1 can be cumbersome; even small
violations of the protocol of urine collection for oxalate measurement can cause false-negative results and, as we have demonstrated in this paper, progression to ESRD is possible without apparent nephrocalcinosis on renal ultrasound. Extensive family screening of patients with demonstrated PH1 may reveal asymptomatic patients as well as patients with renal disease not yet attributed to PH1. If adequate metabolic screening strategies are applied, early treatment of these patients is possible, which may prevent (further) loss of renal function.

We thank all the physicians nation-wide who agreed to provide detailed information on PH1 patients.

REFERENCES


