Does a late referral to a nephrologist constitute a problem in children starting renal replacement therapy in Poland? – a nationwide study

Anna Jander¹, Michael Nowicki¹, Marcin Tkaczyk¹, Maria Roszkowska-Blaim², Tomasz Jarmolinski³, Ewa Marczak⁴, Ewa Pałuba⁵, Jacek A. Pietrzyk⁶, Grzegorz Siteń⁷, Roman Stankiewicz⁸, Krystyna Szpyrner⁹, Maria Zajaczkowska¹⁰, J. Zachwieja¹¹, W. Zoch-Zwierz¹² and D. Zwołińska¹³

¹Department of Nephrology and Dialysis, Polish Mother’s Memorial Hospital Research Institute, Tódz and Pediatric Nephrology Centres in ²Warszawa, ³Szczecin, ⁴Gdańsk, ⁵Sandomierz, ⁶Kraków, ⁷Rzeszów, ⁸Toruń, ⁹Zabrze, ¹⁰Lublin, ¹¹Poznań, ¹²Białystok, ¹³Wrocław, Poland

Abstract

Background. It is estimated that 20–50% of adult patients start chronic dialysis therapy without prior contact with a nephrologist. The aim of this nationwide study was to assess clinical and metabolic status of children at the start of chronic dialysis in Poland with regard to the timing of the referral to a nephrologist.

Methods. We studied data of 180 children (mean age 14±6 years) undergoing chronic dialysis in 13 (out of 14) dialysis pediatric centres in Poland. Patients were classified as early referrals (ERs) when they entered the dialysis programme at least 1 month after the first referral to a nephrologist or late referrals (LRs) when the dialysis was introduced within 1 month from the first visit.

Results. Seventy-nine percent of pediatric patients were referred early (ER) to the dialysis centre and 21% were referred late (LR) and had to start dialysis within a month. When starting dialysis, LR patients had significantly higher levels of urea and phosphate as well as lower calcium and haemoglobin in comparison with ERs. Hypertension, pulmonary oedema, fluid overload, treatment in the intensive care unit (ICU) and body mass index (BMI) below 10th percentile turned out to be more frequent in the LR group. Peritoneal dialysis (PD) was used as the first method of dialysis in 59% of ERs and 46% of LRs. The majority of ER patients was treated in the predialysis period with calcitriol, phosphate binders and low protein diet (84%, 89%, 92% of all children, respectively), and 20% of them received epoetin. In the up to 3 years observation of our initial cohort, we also found that the patients who were referred late were less likely to receive kidney transplant ($P=0.02$).

Conclusion. The results of the study indicate that the LR to a pediatric nephrologist was associated with poorer clinical and metabolic status of children entering chronic dialysis programmes.

Keywords: children; chronic renal failure; dialysis; late referral; pre-dialysis care

Introduction

Both the clinical status and renal function at the start of dialysis are crucial for both short- and long-term morbidity and survival [1–3]. Late referral (LR) to a nephrologist is related to more severe uraemic symptoms, metabolic acidosis, hypertension, pericarditis, pulmonary oedema and emergency haemodialysis using temporary vascular access [3,4]. LR also hinders the choice between dialysis modalities. Several recent studies have shown that a LR to a nephrologist may significantly contribute to early deaths on dialysis, longer hospitalization and higher treatment costs [4–7]. Early nephrological care and drug interventions result in slower progression of chronic kidney disease and its complications and allow better preparation of patients for dialysis treatment [8]. It is estimated that 20–50% of adult patients commence chronic dialysis without prior exposure to a nephrologist [4,6,7,9]. Only few studies have addressed the timing of the referral to a nephrologist in children with chronic kidney disease but the much lower incidence of end-stage renal disease...
in this population may diminish the scale but not the relevance of the problem [1,2]. The aim of this nationwide study was to assess the clinical and biochemical status of children starting chronic dialysis in Poland with regard to the timing of their contact with a nephrologist.

Methods

We analysed data of children undergoing chronic dialysis in the years 2002 and 2003 in 13 out of all 14 pediatric dialysis centres in Poland. The initial cohort was then observed for up to 3 years. The data were collected using a questionnaire that contained details derived from the available medical files, including causes of chronic kidney disease, the time of diagnosis of renal failure and start of dialysis, the dialysis modality and biochemistry at the start of dialysis therapy, i.e. serum concentration of urea, creatinine, blood haemoglobin, calcium, phosphate, albumin and bicarbonate, residual diuresis and renal function (glomerular filtration rate, GFR, calculated from MDRD equation), dialysis access (temporary vs permanent), presence of hypertension, overhydration, pulmonary oedema and the treatment in an intensive care unit (ICU) at the start of maintenance dialysis therapy. We also analysed pharmacotherapy, i.e. use of active vitamin D, calcium carbonate, erythropoietin, iron and dietary management (low protein diet) of chronic kidney disease prior to the commencement of dialysis.

Patients were classified as early referrals (ERs) or late referrals (LRs) depending on whether they started first dialysis at least 1 month after their first referral to a nephrologist or earlier, respectively [3]. Patients who did not recover their renal function after acute renal failure were excluded from the analysis. Finally, we analysed data of 180 children (101 M, 79 F) at the average age 14±6 years at the time of data collecting.

In a separate analysis, we also calculated in the whole cohort mortality rates in up to 3 years follow-up after starting dialysis and a mean waiting time for first kidney transplantation.

Statistical analysis

Normality of data was evaluated by the Kolgomorov–Smirnov test with Lilliefors's correction. Results were expressed as mean±SD. Statistical comparisons between groups (ER vs LR) were made by two-sided unpaired t-test or Mann–Whitney test. Chi-square and Fisher exact test were applied to compare categorical variables. Linear correlation analyses were used to assess the relation between different variables. P value of less than 0.05 was considered significant.

Results

Thirty-seven of the 180 patients (21%) were classified as LRs and the rest (143, 79%) as ERs. ER patients were referred to a nephrologist on average 48±50 months before starting dialysis. The average age at the diagnosis of chronic kidney disease was significantly lower in ERs than in LRs (7.2±5.4 vs 10.9±7.7 years, respectively; P<0.001), but both groups displayed no differences with regard to the age at starting chronic dialysis (10.8±5.3 vs 11.4±8 years).

We found that the ER/LR ratios in four age categories (0–4, 5–9, 10–14, 15–18 years) were similar (Table 1).

| Table 1. The number of patients starting chronic dialysis by the age categories and referral status |
|---------------------------------|--------|--------|--------|--------|
| Age category (years)            | ER     | LR     | Er     | LR     |
| 0–4                            | 26     | 6      | 35     | 7      |
| 5–9                            | 35     | 7      | 48     | 13     |
| 10–14                          | 48     | 13     | 34     | 11     |
| 15–18                          | 34     | 11     |

In ER patients the percentage of subjects with body mass index (BMI) below 10th percentile at the start of dialysis was 22%, whereas in LR it was 37% (P<0.001). Furthermore, BMI was above 50th percentile in 37% of ER children, but in only 21% in LR group (P<0.001). Nevertheless, the height and body weight in both study groups were comparable (height: 1.31±0.28 m (SDS = −2.28±2.84) in ER vs 1.36±0.29 m (SDS = −1.79±2.91) in LR, P = 0.08; body weight: in ER 35.5±16.0 kg (SDS = −1.66±2.29) vs 38.1±14.9 kg (SDS = −1.44±1.95) in LR, P = 0.19).

The most common causes of chronic kidney disease were chronic pyelonephritis (with or without obstructive uropathy) in 37% of the patients, glomerulonephritis (23%), renal hypoplasia (11%), cystic kidney disease (10%) and congenital nephrotic syndrome (4%). The diagnosis was unknown in 21% of patients in the LR group and in only 1% in ER group (P = 0.03).

At the start of dialysis treatment LR patients had significantly higher serum urea but serum creatinine concentrations were similar. Early referral patients displayed also significantly higher GFR and residual diuresis was greater in ER than in LR (1261±855 vs 901±637 ml; P < 0.05). Haemoglobin levels, calcium, bicarbonate serum concentrations were higher but serum phosphorus was lower in ER than in LR. There were no differences in serum parathyroid hormone concentration and Ca × P product. Mean serum albumin was 3.5 g/l in both groups. The biochemical parameters in LR and ER groups at the start of chronic dialysis therapy are summarized in Table 2.

LR patients were in a worse general clinical status at their first dialysis. More patients in the LR group had blood pressure higher than 95th percentile for sex, age and height. Pulmonary oedema and fluid overload were found more frequently in LR. Significantly higher number of LRs was treated in an ICU (Table 3) and high percentage of LR started dialysis with a temporary vascular access (67.6% vs 21.7%; P < 0.001). The average time of the temporary access use, however, did not differ between the groups (53 and 56 days, respectively).

PD as the first method of dialysis was chosen in 59% of ER and 46% of LR but that difference was not
Biochemical and haematological parameters at the start of dialysis

<table>
<thead>
<tr>
<th></th>
<th>ER (mean ± SD)</th>
<th>LR (mean ± SD)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum urea (mmol/l)</td>
<td>28.4±9.3</td>
<td>38.8±27.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>689±778</td>
<td>865±601</td>
<td>NS</td>
</tr>
<tr>
<td>Haemoglobin (g/dl)</td>
<td>9.3±1.6</td>
<td>8.4±5.9</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Haematocrit (%)</td>
<td>28±5</td>
<td>25±7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.3±0.5</td>
<td>1.9±1.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Serum phosphate (mmol/l)</td>
<td>1.9±0.6</td>
<td>2.5±1.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Ca x P product (mmol²/l²)</td>
<td>4.3±1.8</td>
<td>5.0±2.6</td>
<td>NS</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>243±337</td>
<td>373±264</td>
<td>NS</td>
</tr>
<tr>
<td>Bicarbonate (mmol/l)</td>
<td>20.1±4</td>
<td>15.3±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>GFR (ml/min/1.73 m² BSA)</td>
<td>12.1±7</td>
<td>8.7±7</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

NS = not significant.

Clinical status of the patients at the start of chronic dialysis

<table>
<thead>
<tr>
<th></th>
<th>Hypertension (%)</th>
<th>Fluid overload (%)</th>
<th>Pulmonary oedema (%)</th>
<th>ICU treatment (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>57</td>
<td>32</td>
<td>6</td>
<td>0.7</td>
</tr>
<tr>
<td>LR</td>
<td>76a</td>
<td>68a</td>
<td>30a</td>
<td>24a</td>
</tr>
</tbody>
</table>

*aSignificantly different vs ER patients, P < 0.05.

Many authors define the LR as a need to refer patients to a nephrologist 1–6 months and even 12 months before start of chronic dialysis [3,4,8,9]. We applied a very restrictive definition of the LR which has been very recently named as ultralate referral, i.e. 1 month or less of contact time with a nephrologist before starting dialysis [10]. Using this definition 21% of children started chronic dialysis in Poland as LRs. Surprisingly, this percentage is not much different from the adult patients in our country (17%) [11]. Similar data in pediatric populations in other countries are not available, but according to a very recent analysis carried out in the United States about 7.3% of the children commence dialysis at a GFR of less than 5 ml/min/1.73 m², and another 50% at less than 10 ml/min/1.73 m² BSA [1]. Our results may be surprising, because the primary pediatric care is satisfactorily developed in Poland and out- and inpatient specialist nephrological care is available in most Polish cities. Furthermore, there are 14 pediatric dialysis centres in our country, whose population reaches about 38 million [12], and similar to other European countries [13], 10–12 children per million in Poland are diagnosed with end-stage renal disease [12].

We could only hypothesize that a lack of nationwide standards in Poland up to 2002 and relatively low awareness of renoprotective strategies among other specialists (urologists, neurologists and primary care pediatricians) might have resulted in a high percentage of LRs. However, there may be still several other factors to blame for the high percentage of LR including lack of sufficient medical education or communication, low patients' awareness and compliance or health-system related reasons, as described elsewhere [5].

A potential shortcoming of our study could stem from the fact that we were able to analyse only data of children undergoing chronic dialysis at the time of the data collection. Children who had died or had been transplanted prior to the analysis were not included in this study. This former source of bias in our analysis is probably of minor importance since according to the 2003 report on renal replacement therapy in Poland mortality rate among children on maintenance dialysis in our country continues to be very low (about 3% annually) [12]. On the other hand, however, the transplanted patients (about 30/year) who were not included in our database because of earlier transplantation were probably in better general condition and were more likely ERs. Therefore, if the data of such patients had been included, it could have made the proportion of LRs lower than we found. We could not also include patients who were transplanted prior to start of dialysis but according to our knowledge only 7 children received kidney transplant before dialysis in
years 2001–2002 or during dialysis (about 30 patients per year) [12].

In the analysed population haemoglobin and haematocrit were higher in ER patients. That was in agreement with an earlier study [14]. Interestingly, at the time of data collection only 20% of the analysed children were treated with epoetin in the predialysis period. That was caused mainly by the lack of appropriate and uniform reimbursement policy for epoetin in our country. Epoetin in predialysis period had not been available in Poland before 2002 and even now is not fully reimbursed.

The secondary hyperparathyroidism is the major risk factor for the development of renal osteodystrophy [15]. In our study patients classified as LRs had lower serum calcium and higher phosphate serum concentrations than those referred to a nephrologist earlier. Our results are similar to those found in the adult chronic dialysis population [4,9].

Malnutrition and growth disturbances are of major importance in children suffering from chronic kidney disease. The main causes of malnutrition are inadequate calorie intake, uraemic toxins, hormonal disturbances and acidosis [15]. In patients in the LR group, serum bicarbonate levels were significantly lower, but we did not observe significant differences in serum albumin. The reason for that finding is unclear. Our observations may also suggest that early referral to a pediatric nephrologist, monitoring of nutritional status and adequate energy and protein intake can prevent growth retardation and that notion was supported by our finding of significantly lower proportion of ER compared with LR children with BMI below the 10th percentile.

The general clinical status was worse in LR patients since the majority of them had uncontrolled hypertension and more frequently they were diagnosed with pulmonary oedema, fluid overload or were treated in the ICU. Those observations are similar to the findings of the recent West European survey in adult patients [3,4]. Most of our LR patients started dialysis in emergency conditions using a temporary vascular access with an increased risk of infections and hospitalizations, as was also reported by others [4,7,14]. Many reports have indicated that ERs are treated with PD as the first modality of dialysis treatment more often than LRs [16]. It could be due to the fact that the choice of PD requires longer preparation time and patients’ education. In contrast, Winkelmayer et al. found that LR was not related to an initial dialysis modality choice after adjusting for demographic and clinical parameters [17] and we also observed no difference in the proportion of PD and haemodialysis (HD) patients in both groups. Yet, it is worth noticing that studies done in adults and children are not comparable in this regard since PD is traditionally considered as a modality of choice in a child population and HD is less often applied to infants and small children due to technical difficulties.

Another relevant, however not unexpected, finding from our study is that children who are referred earlier to the nephrologist have a greater chance to be transplanted within 3 years from starting dialysis but the 3-year mortality rates were similar in ER and LRs. The lack of the difference may be explained by a very low mortality in our cohort.

To conclude, our survey shows that the LR to a nephrologist in children beginning chronic dialysis treatment in Poland is also a problem as in the adult population. Children who are not treated by nephrologists in the predialysis period are in a worse clinical condition and have more advanced biochemical and clinical signs and symptoms of uraemia and its complications. Our point is that, for the time being, every effort should be made to improve collaboration between primary pediatricians and pediatric nephrologists. This has recently become adopted as the main goal of the Polish Society of Pediatric Nephrology.

Acknowledgements. The authors express their appreciation to Aneta Czuprynia, Anna Kalużyńska (Lódz), Beata Leszczyńska, Jarosław Sołyński (Warszawa), Irena Makulska, Katarzyna Kilis-Petrusińska (Wrocław), Katarzyna Zachwieja, Dorota Dróżdż, Monika Miklaszewska, Teresa Smolnik (Kraków), Krystyna Schramm and Irena Balasz (Gdańsk) for cooperation in collection of the data for this study and to Anna Kamińska for secretarial assistance.

This study was financed by the grant from the Polish Ministry of Science. No. KBN GTME: 02925

Conflict of interest statement. None declared.

References

Received for publication: 13.3.05
Accepted in revised form: 11.11.05