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*Original Article***Patient referral is influenced by dialysis centre structure in the Diamant Alpin Dialysis cohort study**

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Abstract

Background. Late referral (LR) to the nephrologist of patients with progressing chronic kidney disease (CKD) has numerous deleterious effects and is observed in many countries. The contributing factors associated with LR are controversial and poorly defined. We hypothesized that these factors might be better identified by analysing patients starting dialysis in three distinct European countries within the same area.

Method. The referral and progression of kidney failure patterns were analysed with demographic, clinical and biological data in 279 non-selected consecutive patients starting dialysis in eight centres of three adjacent regions in France, Italy and Switzerland.

Results. Early referral (>6 months before the start of dialysis) was seen in 200 patients (71.6%), intermediate referral (1–6 months) in 42 (15.1%) and LR (<1 month) in 37 (13.3%). However inter-centre variations were between 2 and 19% for LR and 6–50% for combined late and intermediate referral. There were no differences at the national levels, but LR was more frequent in the large city centres than in the private or regional structures, with 31 out of 169 (18.3%), two out of 55 (5.4%) and four out of 55 (7.3%), respectively, of their patients ($P < 0.01$). By multivariate analysis, it appears that, besides the presence of an active cancer and the CKD progression rate, the centre structure and the referring physician (primary care physicians and nephrologists are less responsible for LR than other medical specialists) play a significant role in the practice of LR.

Conclusions. Within a dialysis cohort spread over adjacent regions of three countries, LR has the same

global distribution pattern, indicating that different health and social security systems do not play a major role in inducing or preventing this practice. The contributing factors for LR that were identified are the type of the referring physician and the structure of the dialysis unit. Both factors are potential targets for an educational and collaborative approach.

Keywords: chronic dialysis; end-stage renal failure; epidemiology; late referral; progression of kidney disease

Introduction

Late referral to the nephrologist (LR) has been identified over the last two decades as an important problem in the care of patients with chronic kidney disease (CKD) progressing towards end-stage renal disease (ESRD) [1–8]. LR has now been reported in almost all European and American countries, and may account for up to 50% of the incident patients [5]. Deleterious effects of LR include increased necessity for emergency dialysis and acute vascular access, more frequent and longer hospitalization rates at the initiation of ESRD therapy, and increased short-term mortality and cost [1–8]. More recently, an excess mortality on long-term dialysis [7,9], a suboptimal CKD pre-dialysis quality of care [8,10] and a reduced access to transplantation [11] have also been identified.

In the meantime, the efficacy of therapeutic measures to diminish the progression towards ESRD have been clearly demonstrated [12,13], and several guidelines and

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recommendations to improve the quality of pre-dialysis care have been published [13,14]. So far, however, the LR rates have not diminished, indicating the need for more pro-active preventive measures based on a thorough analysis of the factors that favour LR.

While some of the factors associated with LR have been identified, the study of their specific role usually has been hampered by the varying definitions of LR (from 4 weeks to 6 months), the different periods of observation and the focus on a single centre historical review in most studies [1–9]. A few studies addressed LR either at a regional level within the same country [7,15], and/or in individual tertiary care centres of different countries with varying socio-economic and/or epidemiological backgrounds [16]. The present investigation extended those observations by analysing the referral pattern to the nephrologist and the influence of the progression rate of CKD in order to identify relevant determinants of LR.

Patients and methods

Study design

The Diamant Alpin Collaborative Dialysis Study was set up to investigate prospectively, during a 2 year observation period, the clinical, biological, epidemiological and therapeutic variables among an incident cohort of ESRD patients starting dialysis in a homogeneous Alpine region spread over three different countries in eight dialysis units. The demographic and clinical characteristics of the cohort are described elsewhere [17]. Data relative to the referral pattern were investigated and collected at the time each individual patient started dialysis. The required national, regional or institutional Ethics Committees of all participating units had approved the study protocol.

Centres

This study concerns eight dialysis centres of the adjacent regions of Rhône-Alpes (France), Piemonte and Valle d'Aosta (Italy) and Lausanne (Switzerland). Four centres are large city centres: two university centres (Molinette, Torino and CHU, Lausanne), one a non-profit hospital centre (Bosco, Torino), and one an associative non-profit clinical centre (Tassin); two are regional hospital centres (Annecy and Aoste) and two are private city centres (one non-profit and one for profit) working in synergy with university centres (Aeduc-La Tronche and Cecil Lausanne).

Patients

Every patient starting a chronic dialysis programme between November 1 1999 and March 31 2001 was considered for enrolment in the study. After oral and written information had been given for the collection of clinical, biological and genetic data, patients had to sign the informed consent form before the fourth dialysis session. Out of a total 296 patients starting dialysis, 279 accepted to be enrolled.

Their pattern of referral to the dialysis nephrologist was defined as early (>6 months before the start of dialysis),

intermediate (between 1 and 6 months) or late (<1 month before starting ESRD therapy). In the absence of a uniform definition of LR, we have chosen the 1 month limit since with a time frame exceeding 1 month, it remains possible to construct a dialysis access that can be used to start dialysis; the 6 months limit was chosen since this time span allows establishment with the patient and their relatives of the long-term confidence needed to inform, decide and plan the different options of the ESRD therapies [14].

Whenever data were available, the evolutive profile of their kidney function during the 12 months preceding the start of dialysis was evaluated by the Cockcroft–Gault estimation of the creatinine clearance [18].

Statistical analysis

Descriptive statistics are reported as frequency and percentage for categorical data or as mean and 2 SEs for continuous data, or median and range when there was non-Gaussian distribution. Percentages were compared with the χ^2 test; continuous variables were compared by ANOVA, with a P -value = 0.05.

The evolution of kidney function was studied by using principal component analysis with the creatinine clearance estimated at T-12, T-6, T-3 and T0. This multivariate descriptive method depicts linear components of initial variables. The first component represents the sum of the different levels of kidney function allowing the differentiation of patients with severely restricted vs less severely restricted kidney function. The second principal component was related to the decrease in creatinine clearance between T-12 and T-6 estimations (positive coefficients) and T-3 and T0 (negative coefficients). Hence, the score on the second principal component was used to separate patients with a low and slow decrease in creatinine clearance (positive score) and patients with a high and rapid decrease in creatinine clearance between T-12 and T0 (negative score).

In order to identify variables that are independently associated with LR, we constructed a logistic regression model with LR as dependent and significant clinical or biological variables (Table 2), and significant organizational and medical factors as independent variables with a manual backward stepwise method. Country and age were also forced into the model.

Results

Timing of referral to the nephrologist could be recorded in all 279 patients starting dialysis. Early referral (>6 months before dialysis) was mentioned in 200 patients (71.7%); 42 (15.1%) had intermediate referral (1–6 months) and 37 (13.3%) were referred late, <1 month preceding the first dialysis session (Table 1). Emergency dialysis was needed for 60 patients (22%); among those, 27 had been referred late (73%) and only six (14%) had been referred early ($P < 0.01$).

Patient factors contributing to LR

To evaluate the progressive nature of the nephropathy, the creatinine clearance estimated at minus 12, 6 and

3 months before the first dialysis session could be recorded in 224 patients. It appears that depending on the progression rate of CKD, two subgroups of patients can be observed, 155 patients being 'slow' and 69 being 'rapid' progressors (Figure 1). In the first subgroup, the estimated creatinine clearance declined over 12 months from a mean of 17 to 12 ml/min, while in the second subgroup it dropped from 32 to 7 ml/min. Among the 69 rapid progressors, 66 had at least doubled their creatininaemia between the T-12 and T0 period; in the remaining three patients, a high initial creatininaemia ($\sim 500 \mu\text{mol/l}$) remained stable at T-6 but showed a very rapid increase between T-3 and T0. In contrast, among the slow progressors group, 26 patients almost doubled

their creatininaemia but were still considered in this group since they had a low creatinine value to start with ($\sim 250 \mu\text{mol/l}$) and a steady increase of this value at a mean of $60 \mu\text{mol/l}$ at each 3 month period. By principal component analysis, they were classified as slow progressors. Globally, the first component explained 70% of the variance and the second component 20%.

The aetiology of the kidney diseases was equally distributed between the two groups except for the vascular nephropathies being more frequent in the slow decline group (34.6 vs 23% in the rapid progressing group). In contrast, smoking was more frequent in the rapid progressing group: 25.6 vs 14.5% ($P=0.04$). Rapid progressors were slightly younger (60.1 ± 31 vs 65.4 ± 25 years; $P<0.01$).

Rapid progressors were observed at each individual centre with an incidence ranging from 18 to 54%. However, this frequency varied depending on the type of structure of the centre: for the large city hospitals, the number was 45 out of 169 (26.6%), for regional centres it was 27 out of 55 (49%), and for private centres it was 18 out of 55 (32.7%) ($P<0.01$).

To analyse the pattern of referral to the nephrologist, the demographic and clinical characteristics of the LR patients were compared with those who were referred early (Table 2). It appears that LR patients have a similar age at the start of dialysis but that their schooling and educational background is less than that of early-referred patients, i.e. less compulsory schooling (8 years of school attendance) and secondary school education. Among the aetiological kidney diseases, nephropathies that were rapidly progressing led more often to LR, whereas familial diseases and glomerulopathies led to earlier referral. LR patients also accumulate more cardiovascular risk factors

Table 1. Number of patients (%) according to the referral category before the first dialysis session in the eight dialysis units

Dialysis centres	Late referral (<1 month)	Intermediate referral (1-6 months)	Early referral (>6 months)	Total
1 F	1 (2.2)	2 (4.4)	42 (93.3)	45 (100)
2 F	3 (8.1)	2 (5.4)	32 (86.5)	37 (100)
3 F	6 (17.1)	7 (20)	22 (62.9)	35 (100)
4 CH	5 (17.9)	9 (32.1)	14 (50)	28 (100)
5 CH	1 (10)	2 (20)	7 (70)	10 (100)
6 I	1 (5.6)	0 (0)	17 (94.4)	18 (100)
7 I	12 (18.8)	11 (17.2)	41 (64.1)	64 (100)
8 I	8 (19)	9 (21.4)	25 (59.5)	42 (100)
Total	37 (13.3)	42 (15.1)	200 (71.7)	279 (100)

1=Agduc-La Tronche, Grenoble, France; 2=Centre Hospitalier, Annecy, France; 3=Centre de Dialyse Tassin, France; 4=CHU Lausanne, Switzerland; 5=Clinique Cecil, Lausanne, Switzerland; 6=Ospedale Regionale, Aosta, Italy; 7=Ospedale Bosco, Torino, Italy; 8=Ospedale Universitario Molinette, Torino, Italy.

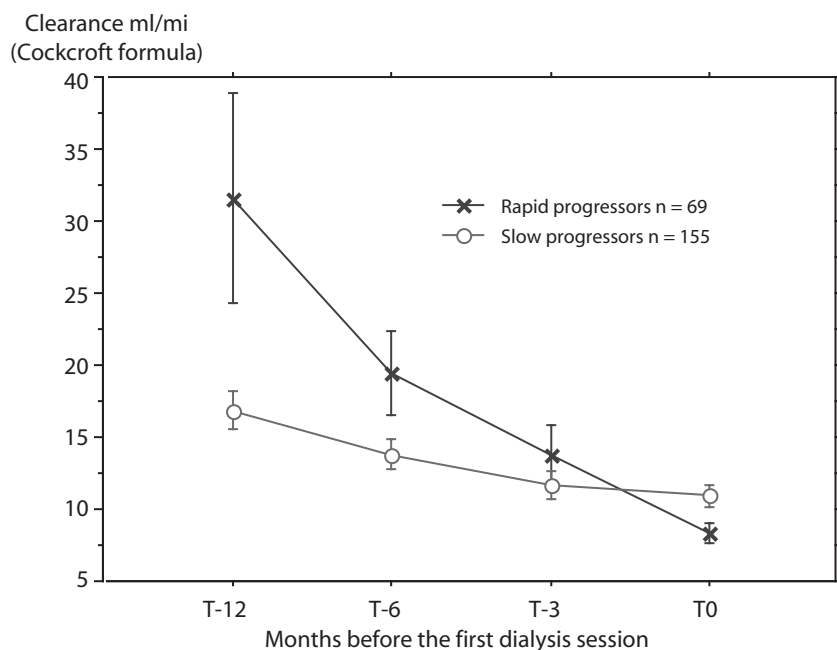


Fig. 1. Evolution of the estimated creatinine clearance according to Cockcroft and Gault [18] during the 12 months preceding the initiation of dialysis therapy depending on the speed of chronic kidney disease progression.

Table 2. Characteristics of the patients referred to a nephrologist either late (<1 month) or early (>6 months before the first dialysis session)

	Late referral (<i>n</i> = 37)	Early referral (<i>n</i> = 200)	<i>P</i>
Age (years)	67 ± 23	63 ± 28	NS
Compulsory schooling	62.2%	81%	<0.04
Certificate of secondary school education	13%	25.5%	0.09
Glomerular nephropathy	2.7%	16.5%	<0.03
Vascular nephropathy	40.5%	29%	NS
Familial nephropathy	2.7%	16%	<0.03
Coronary disease	37.8%	18.5%	<0.02
Two atheromatous lesions	32%	12.5%	<0.03
Active cancer	21.6%	8.5%	<0.02
Rapid progressors	59%	28%	<0.001
Hb (g/l) at dialysis start	86.9 ± 31	98.7 ± 35	<0.01
Serum albumin (g/l) at dialysis start	32.6 ± 12	35.5 ± 11	<0.01
Emergency dialysis	73%	14%	<0.01
Temporary central venous catheter	44.4%	12%	<0.0001
Peritoneal catheter	13.9%	13.5%	NS

Patients classified as 'intermediate referral' are not included in the table.

(atheromatous lesions evidenced in the coronary arteries or elsewhere), an effect apparently independent of age.

As expected, LR patients more often need emergency dialysis and transient central venous access: 25% of the patients needed a temporary central venous catheter for the first dialysis session in the 'rapid' progressing subgroup *vs* 12% in the 'slow' subgroup (*P* < 0.05).

Our study did not confirm, however, that LR patients more often choose haemodialysis instead of peritoneal dialysis: 13.9 *vs* 13.5%.

Organizational and medical factors contributing to LR

Globally, the referral pattern appeared homogeneous among the three countries; however, it should be noted that large inter-centre differences were observed, with LR ranging from 2 to 19%, and combined late and intermediate referral from 6 to 50% per centre (Table 1). These differences do not appear to be related to national regulations or practices but are favoured mostly by local structural characteristics. Indeed, LR was high and comparable in the large city centres of all three countries but much lower in the other units: the former were faced with 84% of the LR patients, private units with 5% and regional hospitals with only 11% (*P* < 0.01). In contrast, early referral was made for 40% in large city centres, for 35.5% in private units and for 24.5% in regional hospitals.

Concerning the referring physician, primary care physicians or nephrologists are less responsible for LR than other medical specialists: 12 LRs among the 138 patients referred by generalists (8.7%), none out of 13 referred by other nephrologists *vs* 25 out of 128 (19.5%) sent by other specialists (*P* = 0.01). The latter specialists

Table 3. Regression analysis of LR probability for the whole patient cohort (*n* = 279)

	Odds ratio	95% CI	<i>P</i> value
Country			
France	1		
Italy	0.8	0.3–2.5	NS
Switzerland	0.95	0.25–3.8	NS
Centre structure			
Regional	1		
Private	1.1	0.15–7	NS
Large city	7.3	1.8–30	<0.01
Referring physician			
Generalist or nephrologist	1		
Other specialists	2.8	1.2–6.4	0.02
Active cancer			
No	1		
Yes	3.6	1.2–11.5	0.03
Progression of kidney failure			
Slow	1		
Rapid	7.1	2.9–16.7	<0.01
Primary glomerular disease			
Yes	1		
No	6.2	0.8–50	0.08 (NS)
Obligatory school education			
Yes	1		
No	3	1.2–7.7	0.02
Age	1.03	0.99–1.06	NS

All the clinical, biological and organizational variables that were significant in univariate analysis have been considered (primary glomerular disease was left in the model as its *P*-value was near 0.05). In addition, country and age were forced into the model. The backward stepwise method was used for analysis.

belonged to the following specialities: general internal medicine (for *n* = 50 patients), diabetology (*n* = 12), urology (*n* = 12), cardiology (*n* = 10) and others (*n* = 7). For the additional 37 cases, a speciality other than nephrology or general medicine was indicated but not specified.

By multivariate analysis, the factors favouring LR were investigated (Table 3). While the country in itself (i.e. social and health structures) does not play a role, it appears that the type of centre is the most important discriminating factor. In addition, a rapid progression of CKD, an aetiological kidney disease other than glomerulopathy, the presence of an active cancer, a low level of patient education and the type of referring physician are also factors leading to LR in this analysis.

Discussion

Although LR to the nephrologist of patients with CKD has been recognized as a worldwide problem, its causes are not yet clearly defined. If indeed some cases are unavoidable due to the acute progression of CKD, most of them are due to other factors that potentially can be prevented [3,5].

LR for non-medical reasons is also frequent in our Alpine region: despite the very strict definition of our

time limit (<1 month), LR was observed in 13.3% of the whole cohort population, only two out of three patients were referred early, notwithstanding the attention devoted to this problem in our region over a long time [19].

Besides the deleterious effects of LR on dialysis initiation, our study also confirms that the quality of pre-dialysis care is less optimal in LR patients: their haemoglobin is at 86.9 *vs* 98.7 g/l and their serum albumin is at 32.6 *vs* 35.5 g/l when compared with patients who were referred early. Those latter values are better but still not optimal; indeed, several reports have emphasized that pre-dialysis care presently is not optimal, even when delivered by a nephrologist [8,20].

Due to its design, the present study allowed us to investigate in a homogeneous manner which epidemiological, individual patient, medical or organizational factors (reimbursement rates, specialist access or social security system related) are at work in adjacent regions spread over three different countries.

Patient factors

Interestingly, there were no differences in the distribution of aetiological kidney diseases within the three regions of our studied population. In contrast to some other reports [2,8], LR was not more frequent among the elderly. It appears that previous personal and medical history plays a role: patients with a longer and higher education, and those with a glomerulopathy or a familial CKD were referred earlier.

In addition to the deleterious effect of a rapidly progressing CKD, it also appears that independently of their age, patients with more vascular lesions are referred later. This observation was also made by others [3,9]. An explanation could be that patients with vascular lesions have a more rapid progression of their CKD, but in fact the reverse was observed: no relationship was found between vascular lesions and the rapid progression of CKD. Interestingly, in the group of rapid progressors, the patients were younger and more active smokers, again emphasizing the deleterious role of smoking on the progression of CKD. It has been suggested recently that smoking cessation should become a primary objective in the management of patients with CKD [14].

Medical and organizational factors

At the national level, the homogeneous referral pattern in France, Italy and Switzerland observed in our study indicates that different health care and social security systems are not playing a role in the LR practice. However, the pattern of referral to the nephrologist has shown interesting inter-centre variations. While LR was frequent in metropolitan areas, it was much less frequent in two different categories of dialysis units, i.e. large centres located in the vicinity of university hospitals with which they work in synergy (Lausanne Cecil and Agduc-LaTronche) and regional hospitals of

less populated or more isolated regions (Annecy and Aosta). In this context, it is worth noting that the LR problem has been reported so far almost exclusively by tertiary care or large city hospital dialysis units [1–9].

It might be argued that the complex and worsening clinical condition of LR patients makes their referral to a large city hospital centre more logical. However, while this is expected to occur more frequently in elderly patients, there is no age difference among the different referral categories; co-morbidity factors were not more frequent in the patients referred to large city hospitals. In addition, clinically more complex situations are generally treated by haemodialysis before the condition is stabilized, but in our study peritoneal dialysis is chosen as first therapy in the same percentage of both early and late referred patients. It has to be noted that because sometimes communication is difficult within our region for geographic reasons, a selective transfer to large city centres remains exceptional and, in fact, no secondary transfer from the large city centres to the regional hospitals was noted.

Since no demographic or epidemiological differences were observed, two hypotheses concerning medical factors may be put forward: (i) when nephrological teams are smaller, they are easily identifiable and usually known on a personal basis by the other medical specialists; and (ii) the smaller medical communities in isolated regions could be a factor favouring early referral; in contrast, when in a more competitive medical situation, a chronic patient becomes a source of income, an early referral may put the physician at risk of losing that patient [19].

Interestingly, the type of medical specialization seems to play a role in the referral practice: while no nephrologist was responsible for LR, primary care physicians referred their patients earlier than other medical specialists, in particular general internal medicine specialists. A similar observation has been made in parts of Belgium and France [5,9]. This could be partly attributed to the fact that primary care physicians are more used than other specialists to refer their patients for specialized care by virtue of their previous medical education and their more strenuous daily workload. This again stresses the importance of medical demography and its financial constraints. It has been claimed repeatedly in the three countries of the present survey that too many specialists but insufficient numbers of primary care physicians are available. Our observations are in line with those comments.

Taken globally, the present study shows that among a homogeneous ESRD population spread over three countries, LR has deleterious effects on pre-dialysis care and dialysis initiation, independently of age or progression rate of CKD. LR has the same supra-national distribution pattern, indicating that different health and social security systems do not play a major role in causing or preventing this practice. For the first time, this study demonstrates that the structure of the dialysis unit plays a role in the LR pattern, probably

through the medical density in any given region and the interpersonal relationship between primary care physicians and nephrologists. Among the referring physicians, primary care physicians and nephrologists are less responsible for LR than other specialists. These observations underline the need for a more diversified educational and collaborative approach in LR prevention.

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