Chronic renal failure and its treatment in tuberous sclerosis

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Abstract

Background. Chronic renal failure is rare in tuberous sclerosis, but its precise frequency is not known and treatment modalities have not been evaluated.

Methods. A questionnaire was addressed to the 260 French dialysis centres and the characteristics of 65 patients with tuberous sclerosis and chronic renal failure were analysed.

Results. In France the approximate prevalence of tuberous sclerosis with end-stage renal failure is 0.7 cases per million and that of end-stage renal failure in tuberous sclerosis 1 per 100. Tuberous sclerosis with chronic renal failure was more frequent in females (63.1%) and was diagnosed at a mean age of 29 years. Renal impairment was the first manifestation of tuberous sclerosis in about half the cases. Renal tumours were frequent, with angiomyolipomas in 15 cases (23.1%), cysts in 12 cases (18.5%), and both in 35 cases (53.8%). Malignancies were associated in nine cases (13.8%). Nephrectomy was done before dialysis in 21 cases (32.3%), and after the start of dialysis in six cases (9.2%). All but one of the 48 patients with end-stage renal failure were treated by dialysis; 20 were transplanted, with good results.

Conclusions. Tuberous sclerosis with end-stage renal failure is rare. These patients require dialysis and renal transplantation, but we recommend binephrectomy after starting dialysis and before transplantation, given the risk of cancer and bleeding related to angiomyolipomas.

Key words: angiomyolipomas; renal cell carcinomas; renal cysts; chronic renal failure; tuberous sclerosis; adenoma sebaceum

Introduction

Tuberous sclerosis (TSC) is an autosomal dominant hereditary disease characterized by a high rate of spontaneous mutations and genetic heterogeneity involving at least two loci [1,2]: TSC1 (9q34) and TSC2 (16p13). The prevalence of TSC is about 1/14,000, but is probably underestimated as poorly symptomatic forms may not be taken into account [3–5]. Vogt's classical triad of 'epilepsy, mental retardation and adenoma sebaceum' is no longer sufficient to define this phacomatosis, which associates various neurological, ocular, cutaneous, osseous, and visceral disorders [6]. The kidney is the most frequently involved organ (40–80%) with angiomyolipomas, renal cysts, and more rarely cancers [7–9]. Renal failure mainly affects those patients who survive neurological disorders, which are the main cause of death.

The aim of this study was to assess the prevalence of TSC with renal failure, together with the features and management of renal failure in this setting, according to a French nationwide survey and a review of the international literature.

Subjects and Methods

This survey was based on a questionnaire sent to the 260 adult and paediatric dialysis centres listed in the French dialysis directory.

Study population

The diagnosis of TSC was based on the presence of typical skin lesions such as adenomas sebaceum and ungual fibromas; neurological manifestations such as seizures, subependymal calcifications and/or gliosis nodules; renal angiomyolipomas; and a suggestive familial history. All known cases of TSC with chronic renal failure were analysed. For statistical evaluation, we only analysed TSC with end-stage renal failure, as the need for dialysis or transplantation minimized the risk of underestimation.

Questionnaire

The following information was recorded in each case: diagnostic evidence, gender, familial history of TSC, age at diagnosis, age at onset of renal failure, age at onset of dialysis, age at transplantation, current health status and, if relevant, age of death and its cause.

The following clinical aspects were recorded: cutaneous manifestations, neurological disorders with the results of CT scan and/or magnetic resonance imaging, and ocular, cardiac, pulmonary or bone involvement. Close attention was paid
to renal manifestations, including initial signs (haematuria, proteinuria, renal failure), radiographical results, cause and outcome of renal failure, histological findings when biopsy or nephrectomy was performed, and treatment with drugs, dialysis or transplantation. The rate of reply to the questionnaire was high (93.1%). We noted the characteristics of 65 patients with TSC and renal failure, 40 of whom were still receiving treatment for end-stage renal failure. Seventeen of the 23 French countries (74%) had at least one patient with TSC and renal failure.

Results

Forty of the 65 patients in this survey were still receiving treatment for end-stage renal failure (dialysis in 22 cases and successful transplantation in 18). On the basis of these 40 cases, the prevalence of TSC with end-stage renal failure is approximately 0.7 per million in France (58 million inhabitants).

In all there were 41 females and 24 males. At the time of diagnosis the average age was 29.2 ± 14.2 years; at the onset of renal failure it was 35.7 ± 10.4 years. Among the 47 patients who had undergone dialysis, average age at the start of treatment was 39.1 ± 10.7 years. Age at transplantation (20 patients) was 38.9 ± 9.5 years.

TSC was revealed by a renal impairment in half the cases, by skin manifestations in 22 cases and by neurological disorders in 10. A family history of TSC aided the diagnosis in only two cases, although it was recorded in 29 observations: 10 times in ascendants, nine times in descendants, six times in siblings, and four times variously associated.

Cutaneous manifestations were present in 90.8% of cases and included adenomas sebaceum, ungual fibromas, hypomelanotic macules, café au lait spots, shagreen patches, mollusca pendula and nail dystrophy. Of the six cases without cutaneous disorders, two were diagnosed at the onset of renal failure and two after starting dialysis. Polycystic kidney disease was the initial diagnosis in these four cases.

Seizures (most often in the patient's past history) and/or mental retardation were found in only 47.9% of cases. All but two of the patients had either subependymal calcifications on CT scan or nodules of gliosis on magnetic resonance imaging, four patients had a cerebral tumour (2 hamartomas and 2 gliomas). In 18 patients without clinical neurological disorders, TSC was only diagnosed at the onset of renal failure in 12 cases and later in six cases.

Other manifestations were ocular in 6.2% of cases, pulmonary in 4.6%, and osseous (cysts) in 10.8%. No cardiac involvement was observed.

Renal tumours

Angiomyolipomas and cysts (Figure 1) were present in 95.4% of the patients. Nine patients had malignancies, eight were removed: three clear-cell tumours, two hypernephromas, two non-papillary tumours and one oncocytoma. None of these eight patients had metastases, but the cancer was bilateral in two cases. One patient had an enormous renal tumour which had not been operated on because of the presence of pulmonary metastases. These malignancies were associated with angiomyolipomas in three cases, cysts in three, and both in three.

In the six cases in which a renal biopsy was performed, glomerulosclerosis associated with tubulointerstitial damage was found in four, membranoproliferative glomerulonephritis in one and nephrocalcinosis in one. Nephrectomy was done before dialysis in 21 cases: it was bilateral in eight cases, but separated in time; binephrectomy was done after the beginning of dialysis in six cases (after transplantation in two). The indications were severe haemorrhage in six cases, malignancies in eight and angiomyolipomas in 13.

At the time of the survey, 17 patients (26.2%) had mild or moderate renal impairment, 22 (33.8%) were on dialysis (haemodialysis in 19, CAPD in 3), 18 (27.7%) had a functional transplant and 8 (12.3%) had died. Six deaths occurred during haemodialysis, and were due to infectious, neurological or pulmonary causes. One severely retarded patient died of uraemia (dialysis was withheld), another died of septic shock 4 years after transplantation. Only one patient returned to dialysis after early graft rejection. Among the 20 transplanted patients (2 living donors), 18 still have a correctly functioning graft (16 with creatininemia below 150 μmol/l), with an average follow-up of 7.2 ± 3.9 years; one died and one returned to dialysis (Table 1). No malignancies occurred after transplantation, and neurological disorders did not deteriorate.

Discussion

TSC with renal failure is characterized by late diagnosis (about 29 years in our series and previous case reports) and by a predominance of females: 63.1% in this series and 72.5% in the literature [10–14]. TSC was revealed by renal failure in 50% of our patients and 75% of reported cases [10–14]. Skin involvement was not influenced by the presence or absence of renal failure, whereas neurological manifestations were slightly more frequent and severe in patients with renal failure: 37.5% of our patients had epilepsy, compared to 50% of patients in previous reports; similarly, often mild mental retardation was present in 10.4% of our patients
Chronic renal failure and its treatment in tuberous sclerosis

Cases Age at 
manifestations are absent and neurological disorders 20 of STB can be difficult, particularly when cutaneous and 23% of previously reported cases. The diagnosis 11 10 16 15 14 11 distinguished from TSC cysts. dying before it develops. It is difficult to appreciate the reasons. First, the response rate to our questionnaire 19 18 17 16 15 14 was only of 93.1%. Secondly, diagnosis of TSC with 1/14.500 [3, 5], which would mean that end-stage renal failure occurs in approximately one per 100 patients with TSC. According to the Mayo Clinic series [3], after neurological involvement, renal impairment is the second cause of death in TSC (renal failure or tumoral complications, retroperitoneal haemorrhage, and metastases of renal cell carcinoma). Among the patients with TSC and renal failure in our series, one died of renal failure and another seven died of complications of dialysis or transplantion.

Renal failure in TSC is related to nephronic reduction owing to tumour invasion and sometimes to surgery; cysts in particular [3,12] cause hyperfiltration of the remaining glomeruli, creating focal glomerulosclerosis [10,11,13]. The tumours are essentially angiomylipomas and cysts, which are often both present. Angiomyolipomas are frequent, usually multiple, bilateral, and large. They are often silent [3,7–9,15,16] but can manifest by a tumoral or haemorrhagic syndrome (haematuria, intratumoral or retroperitoneal haemorrhage) [18], which partly explains the large number of nephrectomies (41.5% of our patients). Nephrectomies done before the start of dialysis (32.3% in our series) are an important cause of renal deterioration, so angiomyolipomas should be treated as conservatively as possible. Cysts [3,7–9,12,15–17] can be single or multiple and bilateral, mimicking polycystic kidney disease in the absence of angiomyolipomas [15,19,20]. TSC can remain undiagnosed, especially when cutaneous and neurological manifestations are mild. Renal failure seems to be accelerated by the presence of cysts, given their potentially high growth rate [7,12,19], whether they are isolated or associated with angiomyolipomas.

Malignant tumours [8,15,16,21] are more frequent (4.4%) than in the general population; their high frequency (13.8%) in our survey was probably due to our patients’ more advanced age. The mean age was 28 years in the literature [21] but 39 years in our survey, with a distinct predominance of women: 81% [21], and 87.5% in our survey. We found bilateral lesions in 25% of cases, compared to 43% [21]. Three deaths out of 16 were due to metastases [21], whereas none of our patients died of metastases, even though one patient had pulmonary metastases. The development of renal cell carcinoma appears to be due to epithelial proliferation in cysts rather than angiomyolipomas [7], but this could not be confirmed in our series.

End-stage renal failure requires dialysis or renal transplantation, given the young age of these patients and the mild neurological manifestations, with the exception, in our series, of one patient with severe debility. Dialysis raises no specific problems apart from

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**Table 1. Characteristics of the 20 patients transplanted in our series**

<table>
<thead>
<tr>
<th>Cases</th>
<th>Age at transplantation</th>
<th>Sex</th>
<th>TSC involvement</th>
<th>Duration of dialysis (years)</th>
<th>Binephrectomy</th>
<th>Kidney donor</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>M</td>
<td>+ +</td>
<td>2</td>
<td>–</td>
<td>Cadaver</td>
<td>Alive at 8 years (creat:100 μmol/l)</td>
</tr>
<tr>
<td>2</td>
<td>66</td>
<td>F</td>
<td>– –</td>
<td>1</td>
<td>in 2 times</td>
<td>Cadaver</td>
<td>Alive at 1 year (creat:110 μmol/l)</td>
</tr>
<tr>
<td>3</td>
<td>28</td>
<td>M</td>
<td>+ +</td>
<td>2</td>
<td>–</td>
<td>Cadaver</td>
<td>Alive at 8 years (creat:112 μmol/l)</td>
</tr>
<tr>
<td>4</td>
<td>43</td>
<td>F</td>
<td>+ –</td>
<td>1/3</td>
<td>in 2 times</td>
<td>Living</td>
<td>Alive at 10 years (creat:100 μmol/l)</td>
</tr>
<tr>
<td>5</td>
<td>35</td>
<td>F</td>
<td>+ +</td>
<td>7</td>
<td>1 kidney</td>
<td>Cadaver</td>
<td>Alive at 9 years (creat:300 μmol/l)</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>M</td>
<td>+ +</td>
<td>4</td>
<td>in 2 times</td>
<td>Cadaver</td>
<td>Alive at 7 years (creat:114 μmol/l)</td>
</tr>
<tr>
<td>7</td>
<td>30</td>
<td>F</td>
<td>+ –</td>
<td>5</td>
<td>–</td>
<td>Cadaver</td>
<td>Alive at 6 years (creat:139 μmol/l)</td>
</tr>
<tr>
<td>8</td>
<td>30</td>
<td>F</td>
<td>+ +</td>
<td>1/2</td>
<td>in 2 times</td>
<td>Cadaver</td>
<td>Alive at 4 years (creat:110 μmol/l)</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>F</td>
<td>+ +</td>
<td>1</td>
<td>–</td>
<td>Cadaver</td>
<td>Alive at 3 years (creat:105 μmol/l)</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>F</td>
<td>– –</td>
<td>2</td>
<td>–</td>
<td>Cadaver</td>
<td>Alive at 1 year (creat:108 μmol/l)</td>
</tr>
<tr>
<td>11</td>
<td>57</td>
<td>F</td>
<td>+ +</td>
<td>1</td>
<td>–</td>
<td>Cadaver</td>
<td>Alive at 4 years (creat:110 μmol/l)</td>
</tr>
<tr>
<td>12</td>
<td>28</td>
<td>M</td>
<td>– –</td>
<td>1/3</td>
<td>in 2 times after transplantation</td>
<td>Cadaver</td>
<td>Alive at 14 years (creat:105 μmol/l)</td>
</tr>
<tr>
<td>13</td>
<td>15</td>
<td>F</td>
<td>+ +</td>
<td>1</td>
<td>–</td>
<td>Living</td>
<td>Alive at 6 years (creat:102 μmol/l)</td>
</tr>
<tr>
<td>14</td>
<td>31</td>
<td>M</td>
<td>+ +</td>
<td>1/2</td>
<td>–</td>
<td>Cadaver</td>
<td>Dead at 4 years (sepsis)</td>
</tr>
<tr>
<td>15</td>
<td>36</td>
<td>F</td>
<td>+ +</td>
<td>2</td>
<td>–</td>
<td>Cadaver</td>
<td>Alive at 7 years (creat:140 μmol/l)</td>
</tr>
<tr>
<td>16</td>
<td>37</td>
<td>F</td>
<td>+ –</td>
<td>2</td>
<td>–</td>
<td>Cadaver</td>
<td>Alive at 5 years (creat:100 μmol/l)</td>
</tr>
<tr>
<td>17</td>
<td>45</td>
<td>M</td>
<td>+ –</td>
<td>1</td>
<td>–</td>
<td>Cadaver</td>
<td>Returned to dialysis (after 5 months)</td>
</tr>
<tr>
<td>18</td>
<td>35</td>
<td>M</td>
<td>+ –</td>
<td>2</td>
<td>–</td>
<td>Cadaver</td>
<td>Alive at 7 years (creat:110 μmol/l)</td>
</tr>
<tr>
<td>19</td>
<td>45</td>
<td>F</td>
<td>+ –</td>
<td>4</td>
<td>in 2 times</td>
<td>Cadaver</td>
<td>Alive at 7 years (creat:116 μmol/l)</td>
</tr>
<tr>
<td>20</td>
<td>35</td>
<td>M</td>
<td>+ –</td>
<td>2</td>
<td>–</td>
<td>Cadaver</td>
<td>Alive at 7 years (creat:110 μmol/l)</td>
</tr>
</tbody>
</table>

and 23% of previously reported cases. The diagnosis of STB can be difficult, particularly when cutaneous manifestations are absent and neurological disorders are moderate; renal failure is sometimes related to polycystic kidney disease, which cannot readily be distinguished from TSC cysts.

Renal failure is rare in TSC, the majority of patients dying before it develops. It is difficult to appreciate the precise frequency but TSC with end-stage renal failure has an apparent prevalence of 0.7 per million in France, which is probably underestimated for the following reasons. First, the response rate to our questionnaire was only of 93.1%. Secondly, diagnosis of TSC with renal failure is difficult when cutaneous and neurological manifestations are mild. Thirdly, the rarity of TSC in adults explains the lack of diagnostic experience.

The prevalence of TSC in literature is estimated at 1/14.500 [3, 5], which would mean that end-stage renal failure occurs in approximately one per 100 patients with TSC. According to the Mayo Clinic series [3], after neurological involvement, renal impairment is the second cause of death in TSC (renal failure or tumoral complications, retroperitoneal haemorrhage, and metastases of renal cell carcinoma). Among the patients with TSC and renal failure in our series, one died of renal failure and another seven died of complications of dialysis or transplantion.
Renal transplantation in TSC has only been reported in 14 cases (Table 2 [17,22–27]). If we compare these data with our 20 cases, average age at the time of transplantation was respectively 29.2 years and 38.9 years and the proportion of women 71.4 and 60%. Cutaneous manifestations, present in every reported case, were absent in two of our cases. Neurological disorders were minor in both series. The kidney donor was familial in four reported cases and two of our cases. Outcome was good, with only one death in each study [17]. The transplant was functioning well in 11 of the 14 reported cases for which data are available (follow-up of up to 14 years), and in 18 of our 20 cases, with an average follow-up of 7.2 years. The discovery of a renal malignancy does not contraindicate transplantation at distance of nephrectomy; indeed, in four cases [16,22,23], including one in our series, no metastasis had occurred 1.5, 3.5, 4 and 9 years after transplantation. One patient of the four with cerebral tumours was transplanted after removal of a cerebral glioma while on dialysis. There is no evidence that neurological disorders worsen after transplantation.

Long-term follow-up of the 18 patients with a functional transplant revealed no bleeding complications or cancers. Most of the 12 patients who had not undergone bifunectomy before transplantation had renal cysts, sometimes associated with angiomyolipomas. However the three cancers reported in the literature [16,22,25] among the 14 transplanted patients, the four cancers (2 metastatic) in the Mayo Clinic series [21], and the nine malignancies in our survey suggest that the native kidneys should not be kept, apart from the risk of bleeding associated with angiomyolipomas. If the native kidneys have not been removed before transplantation, they should be checked yearly by computed tomography; nephrectomy should be done at the slightest suspicion of cancer and should be discussed if angiomyolipomas are diagnosed, unless selective embolization is preferred.

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