Kidney Involvement in Tuberous Sclerosis Complex: The Impact on Health Care Resource Use and Costs in The Netherlands

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BACKGROUND AND OBJECTIVE

- Tuberous sclerosis complex (TSC) is a rare genetic disorder characterized by malformations throughout the body, such as angiomylipomas (AMLs).
- Renal AMLs are kidney lesions that grow in size, present risk of acute hemorrhage, and may lead to malignant transformation (renal cell carcinoma).
- The literature on the relationship between renal AMLs and CKD is limited, and no previous studies have explored the association between kidney involvement in TSC and health care resource utilization (HCRU), and health care costs.

Hypothesis: To describe the association between renal AML and CKD (including the impact on HCRU and health care costs) using retrospective data from a cohort of Dutch patients with TSC treated at University Medical Center – Utrecht (UMCU), prior to the introduction of everolimus.

METHODS

- Data:
  - Medical chart data from patients with TSC primarily treated at a single center in the Netherlands: UMCU.
  - Combine patient demographic information with records from scans, surgical procedures, specialist visits, medications, and other types of HCRU.
- CKD Stage:
  - Kidney function was measured prior to any surgical procedure or embolization.
- Time period:
- While recent advances have led to the use of everolimus for the treatment of renal AML, the current study focuses on the period prior to any renal AML treatment.
  - Only patients opted-out.
- Study was approved by UMCU’s institutional review board.

Study design:
- Descriptive, longitudinal open cohort study (see Figure 1).

Statistical analysis:
- Patients were classified into longitudinal open cohorts based on:
  - CKD stage 1 (through stage 5).
  - Determined through estimated glomerular filtration rate (eGFR), calculated from serum creatinine levels using the CKD-EPI formula4,5
  - Patient observation time and utilization placed in CKD stage 1 cohort until first serum creatinine measurement.
  - Number of AMLs in both kidneys.
- Renal AML size:
  - >3.5 cm or ≥3.5 cm.
- Gross radiological anatomy of the kidney
  - Patients with <1 cm AML who did not have a CT scan were placed in AML<3.5 cm cohort.
- Patients could contribute to multiple cohorts due to changes in their CKD stage and renal AML size.
- Average eGFR and the proportion of patients reaching CKD stages were compared with those presenting a reference population of Dutch patients with TSC:
  - Linear regression of mean eGFR vs. age was used to assess the age trend in mean eGFR.
  - Recent study

RESULTS

- P value for HCRU and cost differences were estimated by non-parametric bootstrapping to account for the cross-sectional study design and non-normality of health care costs.

Table 1: eGFR by patient age

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients</th>
<th>Mean eGFR (SD)</th>
<th>Median eGFR</th>
<th>25th percentile</th>
<th>75th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 year</td>
<td>14</td>
<td>55 (28.0)</td>
<td>51 (28.0)</td>
<td>44.5 (27.0)</td>
<td>64.0 (30.0)</td>
</tr>
<tr>
<td>1-5 years</td>
<td>43</td>
<td>60 (25.0)</td>
<td>58 (25.0)</td>
<td>53.0 (23.0)</td>
<td>66.0 (30.0)</td>
</tr>
<tr>
<td>6-10 years</td>
<td>63</td>
<td>68 (25.0)</td>
<td>66 (25.0)</td>
<td>61.0 (26.0)</td>
<td>76.0 (30.0)</td>
</tr>
<tr>
<td>11-20 years</td>
<td>68</td>
<td>72 (25.0)</td>
<td>70 (25.0)</td>
<td>64.0 (26.0)</td>
<td>80.0 (30.0)</td>
</tr>
</tbody>
</table>

Table 2: HCRU and health care costs by CKD stage

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Number of Patients</th>
<th>HCRU Rate (95% CI)</th>
<th>Health Care Costs (€)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>354</td>
<td>0.001 (0.000–0.003)</td>
<td>87 (66–118)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>138</td>
<td>0.002 (0.001–0.004)</td>
<td>204 (180–243)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>54</td>
<td>0.003 (0.002–0.005)</td>
<td>424 (297–587)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>0.004 (0.003–0.006)</td>
<td>657 (367–1,182)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>0.005 (0.004–0.006)</td>
<td>797 (287–1,182)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Figure 1. Study design

- Number of renal AMLs

Figure 2. eGFR by patient age

- Number of renal AMLs

Figure 3. HCRU rates by CKD stage

- Number of renal AMLs

Figures 4. HCRU rates by CKD stage

- Number of renal AMLs

Figure 5. Overall health care costs by CKD stage

- Number of renal AMLs

Table 3. Overall health care costs by CKD stage

<table>
<thead>
<tr>
<th>CKD Stage</th>
<th>Cost PPPY (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>58 (43–74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>138 (120–160)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>3</td>
<td>548 (350–720)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>1,421 (707–2,500)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>5</td>
<td>1,540 (707–2,500)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

- Number of renal AMLs

LIMITATIONS

- Small sample size for select sub-groups and missing data limit the precision and generalizability of the results and preclude more detailed analyses.
- Results do not have a causal interpretation, due in part to confounding by indication.

- This study was based on a single-center, single-center design.

CONCLUSIONS

- Patients with TSC tend to develop kidney impairment more frequently, and at an earlier age, than patients without TSC.
- CKD in patients with TSC is associated with renal AML severity, HCRU, and health care costs.
- CKD was associated with the presence of numerous small renal AML as well.
- CKD was more prevalent in patients with CKD stage 2 or higher.
- There is a need for routine kidney function monitoring and early intervention in patients with TSC.
- Treatments that slow the rate of kidney function decline in patients with TSC may substantially reduce the HCRU and costs associated with renal AML in this patient population.

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