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Original Investigation

Long-term Follow-up Assessing Renal Angiomyolipoma Treatment Patterns, Morbidity, and Mortality: An Observational Study in Tuberous Sclerosis Complex Patients in the Netherlands

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Background: Long-term data from patients with tuberous sclerosis complex (TSC)-associated renal angiomyolipoma (angiomyolipoma) are limited.

Study Design: Retrospective observational study.

Setting & Participants: Adult patients with TSC treated at the University Medical Center Utrecht (the Netherlands) from January 1990 through April 2012.

Predictors: Patient age and angiomyolipoma stage, based on computed tomography lesion count, size, and impact on renal anatomy, with higher stage representing higher angiomyolipoma burden. Patients in stages 3 or higher were considered at high risk for hemorrhage and candidates for selective arterial embolization.

Outcomes: Kidney-related outcomes included hypertension, anemia, decreased kidney function, dialysis, kidney transplantation, nephrectomy, kidney-related blood transfusions, and mortality. Observed mortality was compared to the Dutch National Bureau of Statistics using standardized mortality ratio.

Results: Median follow-up was 15.8 years, of which staging was available for 5.4 years. Of 351 patients with TSC, 244 (69.5%) had confirmed angiomyolipoma; 144 (59.0%) reached stage 3 or higher. Age and angiomyolipoma stage were positively correlated: median age in the none-detected stage was 36.8 years, increasing to 43.6 years for stage 6. Embolization was performed in 117 patients; 57 had 2 or more embolization procedures. Higher stage was associated with hypertension, anemia, decreased kidney function, and transfusion. Hypertension, anemia, and decreased kidney function were more common in patients who underwent selective arterial embolization. 7 patients required dialysis, 7 received a kidney transplant, and 16 underwent nephrectomy. 29 deaths were recorded, most commonly related to renal complications (n = 9 [31%]). Mortality was significantly higher in the study cohort versus the general population (standardized mortality ratio, 4.8; 95% CI, 3.4-6.9).

Limitations: Duration of follow-up with staging was too short to observe stage progression in most patients.

Conclusions: Despite the use of preventive selective arterial embolization, patients with TSC exhibit clinically significant kidney disease and excess mortality, largely because of kidney-related complications.

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INDEX WORDS: Renal angiomyolipoma; selective arterial embolization; kidney-related morbidity; hypertension; anemia; decreased kidney function; blood transfusion; renal hemorrhage; tuberous sclerosis complex (TSC); hamartoma; angiomyolipoma staging criteria; angiomyolipoma progression; mortality; morbidity.

Tuberous sclerosis complex (TSC) is a multisystem disorder characterized by growth of nonmalignant tumors (hamartomas) in various organs throughout the body, including the brain, kidney, lungs, and skin.[1,2] Most patients with TSC have mutations in the *TSC1* or *TSC2* genes, which encode the proteins hamartin and tuberin, respectively.[3] Together, hamartin and tuberin form a tumor suppressor complex that negatively regulates the activity of mammalian target of rapamycin complex 1 (mTORC1), a key regulator of protein synthesis, cell growth and proliferation, angiogenesis, cell metabolism, and cell orientation and migration.[1,3-6] When inhibition of mTORC1 is lost, increased activation of this pathway and formation of nonmalignant tumors characteristic of TSC occur. In the kidney, angiomyolipomas, which are

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composed of abnormal blood vessels, immature smooth muscle cells, and adipose tissue, occur in up to 75% of patients with TSC and are typically multiple in number and located bilaterally.[5] In addition to renal angiomyolipomas, other common renal manifestations of TSC include epithelial cysts (45%) and renal cell carcinoma (2%-3%).[5]

Renal angiomyolipoma is associated with significant morbidity and mortality. Adverse outcomes associated with renal angiomyolipoma can be acute, resulting from the hemorrhage of a lesion, or long term because progressive loss of normal renal parenchyma decreases kidney function and can lead to kidney failure.[1,7-9] Retroperitoneal hemorrhage, also referred to as Wunderlich syndrome, is an acute possibly severe event that can result in death.[7] A medical chart review revealed kidney disease in the form of angiomyolipomas, cysts, or both as the most common cause of death in patients with TSC.[10]

The vasculature of renal angiomyolipoma is characterized by thick-walled blood vessels that lack normal elastin, making them prone to rupture.[11] Yamakado et al[12] reported that aneurysm size was the most significant predictor of hemorrhage and that angiomyolipoma size and aneurysm size were positively correlated. Similarly, a UK renal registry analysis showed increased risk for hemorrhage in lesions demonstrating serial growth.[13]

Renal angiomyolipoma treatment goals focus on preventing acute events, preserving renal parenchyma, and maintaining long-term kidney function. At the time of this study, approved treatment options in the Netherlands included observation, nephron-sparing procedures (partial nephrectomy, cryotherapy, and radiofrequency ablation), and selective arterial embolization. Historically, embolization was reserved for symptomatic cases in which the angiomyolipoma caused bleeding.[14-16] In the early 2000s, practitioners began to use embolization on an elective basis in patients with large growing angiomyolipomas to prevent hemorrhage and preserve kidney function. This practice was added to the Dutch treatment guidelines in 2006.[17]

Although a number of studies describe the pathophysiology, epidemiology, and treatment of renal angiomyolipomas in patients with TSC, most have small patient samples and short periods of follow-up. The literature documenting long-term follow-up after elective embolization is limited. Consequently, most studies focus on reducing the number of acute events and are not able to report on long-term outcomes, including kidney function. This study was undertaken to evaluate renal angiomyolipoma characteristics, treatment patterns, and associated long-term outcomes in a large cohort of patients with TSC in the Netherlands.

METHODS

Participants

Inclusion criteria for this retrospective analysis were diagnosis of TSC according to the modified Gomez criteria (2 major or 1 major and 2 minor criteria)[18] and aged 18 years or older. From January 1990 through April 2012, patients were treated at the University Medical Center Utrecht (UMCU), where elective embolization is used in patients with TSC with at least one renal angiomyolipoma ≥ 3.5 cm (in longest diameter) that shows serial growth.

Patients or family caregivers could opt out of participation; as a result, data from 2 patients were omitted. This study was approved by UMCU's Institutional Review Board.

Data Sources and Measurement

Data were extracted from UMCU's electronic medical records system and combined with information from older paper-based records and medical charts. Computed tomographic (CT) scans were available from 2000 onward and were generally performed every 2 to 3 years as part of routine follow-up. (Magnetic resonance imaging was not widely available.) When possible, radiologic reports were used when original scans were unavailable. Angiomyolipoma and subependymal giant cell astrocytoma were identified by CT scan, epilepsy was measured by electroencephalography, and other manifestations were determined by clinical examination and history taking. Observations of the treating physician were used to determine the presence of skin lesions and assess cognitive function. Kidney function was measured by calculating estimated glomerular filtration rate using the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) creatinine equation.[19] For this analysis, patients with estimated glomerular filtration rates < 60 mL/min/1.73 m^2 were considered to have decreased kidney function. Renal angiomyolipoma staging criteria developed at UMCU were used as part of the clinical assessment. The criteria (Table 1) are based on 3 factors: number of angiomyolipomas (both kidneys), size of angiomyolipomas, and gross radiologic anatomy of the kidney. Because angiomyolipomas can distort the gross appearance and architecture of the kidney, inspection of kidney anatomy is helpful in ascertaining the extent of disease. Embolization was performed using a combination of

Table 1. Renal Angiomyolipoma Staging Criteria Proposed by University Medical Center Utrecht

Stage	No. of Angiomyolipoma	Angiomyolipoma Size	Description of Kidney Anatomy
None detected[a]	None ≥ 1 cm in longest diameter	—	Normal
1	≤5	<3.5 cm	Normal
2	>5	<3.5 cm	Normal
3	≤5	At least 1 ≥3.5 cm	Kidney intact
4	>5	1-4 ≥3.5 cm	Kidney intact
5	>5	≥5 ≥3.5 cm	Kidney recognizable
6	>5	At least 1 ≥5.0 cm	Kidney not recognizable

[a]Angiomyolipoma not detectable or lesions < 1 cm unidentifiable as angiomyolipoma.