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Association between the growth rate of renal cysts/angiomyolipomas and age in the patients with tuberous sclerosis complex

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Abstract
Purpose Renal manifestations of tuberous sclerosis complex (TSC) occur with a high frequency and a wide range of severity. The onset and complications of each affected organ depend on the age. This study aimed to investigate the associations between comorbidities, frequency, and size of cysts/angiomyolipomas of TSC and the patients in the different ages.
Methods We performed a systematic evaluation of patients with TSC at integrated clinics for TSC. The patients were diagnosed with TSC according to Roach's clinical diagnostic criteria. All the patients underwent a systematic evaluation with a medical history review, recording of cutaneous manifestations, magnetic resonance imaging of the brain, chest computed tomography scan, and cardiac echography. Each patient was routinely evaluated with renal magnetic resonance imaging.
Results Of the 57 patients with TSC, renal lesions or manifestations were observed in 38.5 % at preschool-age group (<6 years) that increased to 75.0, 85.7, and 100 % in school-age group (6–18 years), young adulthood group (18–30 years), and middle-aged group >30 years, respectively. Renal complications or interventions were found in 72.7 % of patients >30 years. There was a strongly positive association between the size of renal lesions and age ($p < 0.001$). Comorbidities of TSC were significantly correlated with pulmonary lymphangiomyomatosis ($p < 0.001$) and seizure remission ($p = 0.018$).
Conclusions The results indicate a positive association of progressively growing renal lesions in patients with TSC with increasing age. It is mandatory for clinicians that monitor the high-risk patients to minimize and prevent renal complications in the future.

Keywords Tuberous sclerosis complex · Renal cyst · Angiomyolipomas · Childhood · Adulthood

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Introduction

Tuberous sclerosis complex (TSC) is a multisystem genetic disease characterized by hamartomatous lesions mainly affecting the skin, central nervous system, kidneys, eye, heart, and lung [1]. The onset and complications of each affected organ depend on the age [2]. Renal manifestations occur with a high frequency and a wide range of severity. The frequency of renal lesions in TSC was estimated ranging from 60 to 80 % [3, 4]. Angiomyolipomas (AMLs) and cysts with subtle syndrome are the two most common renal pathologies in TSC. These lesions likely occur in infancy or early childhood and increase in size from adolescence to adulthood; they can

potentially be complicated by retroperitoneal hemorrhage [4, 5].

After neurologic complications in childhood, renal involvement in TSC is the second most common cause of morbidity and mortality in adulthood [6]. Lesions greater than 4 cm in diameter are more likely to become symptomatic and may warrant close monitoring to avoid complications [7]. Complications are generally treated with angiographic arterial embolization or surgical extirpation, with nephron-sparing procedure preferred over radical nephrectomy [8]. With advanced studies, a clinical trial has proven that the mammalian target of rapamycin (mTOR) inhibitor diminishes the growth or promotes regression of AMLs [9].

AMLs associated with TSC may present multifocal tumors with a potential for significant growth and subsequent hemorrhage. Recently, Hadley et al. [10] indicated that understood the long-term behavior of these lesions so that might prevent potential complications due to AMLs. However, very few reports have studied and clarified the growth rate of cyst/AML in the patients with TSC, and little is known about either the growth rate of the lesions or their stability over time [3, 11]. The aim of the retrospective study was to investigate the comorbidities, frequency, and size of cysts/AMLs of patients with TSC, and examine the association between the renal lesions and these patents in the different ages.

Methods

We performed a systematic evaluation of patients with TSC at integrated clinics for TSC at the Chung Shan Medical University Hospital (CSMUH) between 2009 and 2013. The institutional review board of CSMUH approved this study (CS12245).

All the patients had been diagnosed with TSC according to Roach's clinical diagnostic criteria, and patients with probable TSC were excluded. Most patients were referred from the Taiwan Tuberous Sclerosis Complex Association (http://www.ttsc.org.tw/) for integrated medical care, the remaining were previously followed up at CSMUH. The integrated clinics included dermatology, pediatric neurology, pediatric cardiology, pediatric nephrology, urology, pulmonology, diagnostic radiology, social workers, and a genetic consultant. The patients underwent a systematic evaluation with a medical history review, recording of cutaneous manifestations, magnetic resonance imaging (MRI) of the brain, chest computed tomography scan, and cardiac echography. Each patient was routinely evaluated with renal MRI. A renal cyst was defined as a sharply circumscribed, smooth-walled lesion. An AML was defined as an identifiable lesion within the parenchyma [11]. For the purpose of this study, the maximal diameters (in cm) of the largest renal cysts/AMLs of each individual were recorded during the first visit at the integrated clinics. Renal complications were defined as patients with TSC and subsequent medical conditions caused by larger AMLs, for which nephrectomy was performed for emergent renal conditions or transarterial embolization, for renal bleeding tendency.

Statistical analyses

The renal lesion and size in each TSC patient differed depending on the age of the study population. Correlations for the association between the lesion size and patients' age were conducted using the Wilcoxon signed-rank test and Spearman rank correlation coefficient. The variables between age groups were compared using the chi square and Fisher's exact tests. A $p < 0.05$ was considered statistically significant. All statistical analyses were conducted in SPSS for Windows (Version 14.0; SPSS Inc., Chicago, IL).

Results

There were 23 male and 34 female patients with age ranging from 1 month to 68 years old at enrollment. Fifty-five (96.5 %) patients presented with intracranial lesions, 53 (93.0 %) with cutaneous features, and 55 (96.5 %) manifested extra-neurocutaneous lesions (Table 1). Of the 57 patients, 56 patients underwent routine MRI for renal lesions and only one performed with renal CT because of emergent abdomen tenderness at the first visit. Forty-two (73.7 %) patients presented with renal cysts/AMLs and 40 (95.2 %) of the 42 patients were bilateral. The patients were classified into the following subgroups according to the different ages: group 1: preschool age (<6 years, $n = 13$), group 2: school age, (6–18 years, $n = 20$), group 3: young adulthood (18–30 years, $n = 14$), and group 4: middle-aged (>30 years, $n = 10$). The frequency of cysts/AMLs increased with age from 45.4 % in group 1, to 75.0 % in group 2, 85.7 % in group 3, and 100 % in group 4. Renal comorbidities increased from 0, 10, 21.4, and 70 % in each age group (Fig. 1). The sizes of cysts/AMLs in childhood were small in groups 1 (0.57 ± 0.18 cm) and 2 (2.05 ± 2.24 cm) and increased rapidly in groups 3 (5.54 ± 3.42 cm) and 4 (10.67 ± 3.62 cm) (Fig. 2). The trend of maximal sizes was significantly correlated with the age of the patients ($p < 0.001$, Fig. 2). Our results showed that the rate (45.4 %) of renal cysts/AMLs in young age group (preschool) was lower and the sizes (0.57 ± 0.18 cm) were smaller than those in other age groups. There was no larger than 5 cm in diameter of cysts/AMLs in the preschool group. We noted that only three patients had the cysts/AMLs ≥5 cm in diameter before the

age of 18 years old; all were in the school-age group (6–18 years). These diameters of cysts/AMLs were 8.3, 6.3, and 5.2 in the patient of 13, 14, and 16 years old, respectively, with necessitating transcatheter arterial embolization in two.

There were 11 patients in whom at least two abdominal MRIs were performed. There were five patients in childhood aged from 11 months to 11 years 5 months with follow-up MRI intervals ranging from 7 to 36 months, and the remaining 6 patients in young adulthood aged 24 years 10 months to 28 years with follow-up MRI intervals ranging from 12 to 52 months. In a longitudinal follow-up, the lesion size increased with age in 10 patients and the remaining one showed no significant change at an interval of 12 months (Fig. 3). The growth rates in maximal diameter were significant difference in either childhood or adulthood group (Table 2). In Table 3, we divided the patients into groups of childhood (<18 years, $n = 33$) and adulthood (≥18, $n = 24$), in which the presence of complications/interventions, the frequency of cysts/AMLs, and the size of maximal diameter were statistically significant ($p = 0.001$, $p = 0.009$, and $p < 0.001$, respectively). Comparisons of subgroups of cardiac rhabdomyoma, chest lymphangiomyomatosis (LAM), and retinal hamartoma of TSC with comorbidities between the childhood and adulthood groups, only the presence of chest LAM was significantly different ($p < 0.001$, Table 3). There was a significant difference in renal lesions between male patients (13/23, 56.5 %) and female patients (29/34, 85.3 %) ($p = 0.018$). Only 22 patients underwent genetic analysis for genotyping that identified genotype TSC1 in 6 and TSC2 in 16. Of them, 5 (83.3 %) of 6 patients and 11

Table 1 Demographic data and clinical characteristics of patients with TSC ($n = 57$)

Parameters	Item	*n* (%)
Gender	Male	23 (40.4)
	Female	34 (59.6)
Age (years)	<6	13 (22.8)
	6–18	20 (35.1)
	18–30	14 (24.6)
	>30	10 (17.5)
Organ involvement		
Skin lesions	55 (96.5)	
Facial angiofibroma		43 (75.4)
Periungual fibroma		20 (35.1)
Hypomelanotic macules		46 (80.7)
Shagreen patch		29 (50.9)
Intracranial lesions	53 (93.0)	
Cortical tuber		39 (68.4)
Subependymal nodule		46 (80.7)
SEGA		16 (28.0)
Extra-neurocutaneous	55 (96.5)	
Retinal hamartomas		16/30 (53.3)
Cardiac rhabdomyoma		32/57 (56.1)
Lymphangiomyomatosis		13/44 (29.5)
Renal cysts/angiomyolipoma		42/57 (73.7)

TSC tuberous sclerosis complex, *SEGA* subependymal giant cell astrocytoma

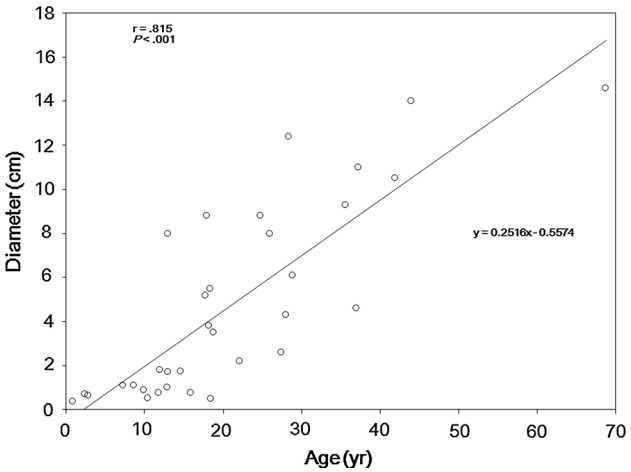

Fig. 2 Lesions sizes (cm) were correlated with increasing age in TSC patients with cysts/AMLs, which showed a significantly positive association ($n = 42$, $p < 0.001$)

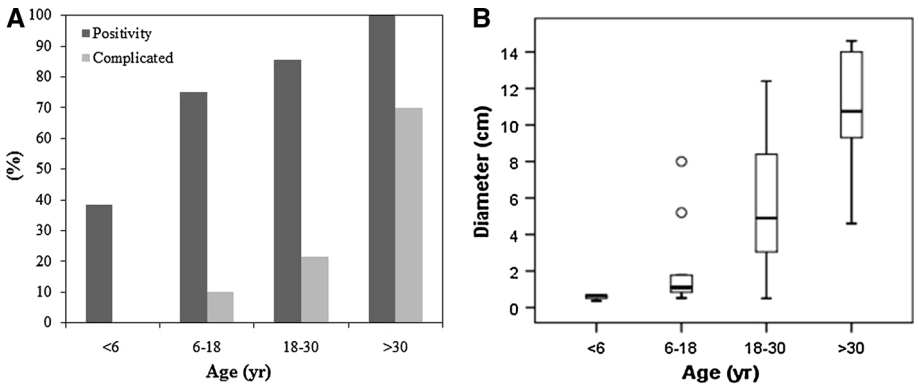

Fig. 1 The frequencies of renal complicated lesions (**a**) and maximal size (**b**) in the different age groups of TSC patients with cysts/AMLs. Renal complicated lesions included renal embolization and nephrectomy ($n = 57$)

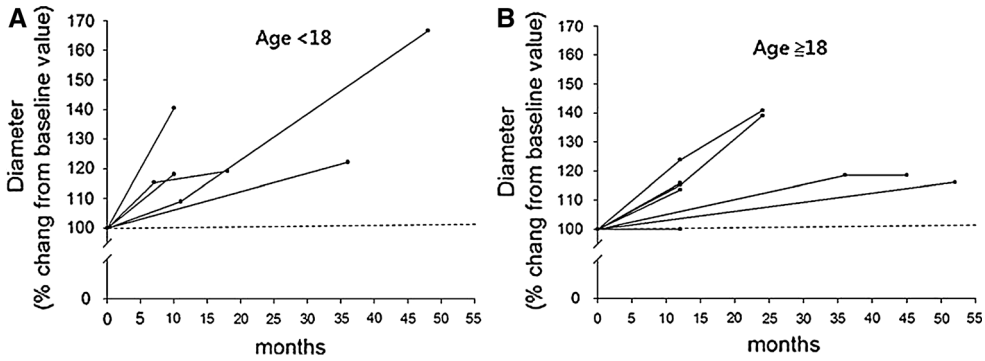

Fig. 3 Trends of growth rates of 5 patients in childhood (**a**) and 6 patients in adulthood with cysts/AMLs (**b**) during follow-up

Table 2 Growth rate of cyst/AML in childhood and adulthood in TSC patients

	n	Duration (month mean ± SD)	Cyst/AML diameter (cm)		*p* value†
			First imaging	Second imaging	
All	11	19.09 ± 14.94	3.42 ± 3.74	4.03 ± 4.44	0.005
Childhood (<18 years)	5	14.80 ± 11.95	0.73 ± 0.29	0.87 ± 0.33	0.042
Adulthood (≥18 years)	6	22.67 ± 17.28	5.65 ± 3.83	6.67 ± 4.59	0.043

TSC tuberous sclerosis complex, *SD* standard deviation

† Wilcoxon signed-rank test

Table 3 Relationship between comorbidities in childhood and adulthood in patients with TSC ($n = 57$)

Parameters	Childhood (<18 years)	Adulthood (≥18 years)	*p* value
Number	33	24	
Renal cysts/AMLs			
Frequency			0.009
Negative	13	2	
Positive	20	22	
Maximal diameter (cm)			<0.001
<1	9	1	
1–5	6	3	
>5	5	18	
Complication/ interventions			0.001
Negative	31	14	
Positive	2	10	
Comorbidity			
Cardiac rhabdomyoma			
Negative	10	8	0.291
Positive	21	10	
Chest LAM			
Negative	25	8	<0.001
Positive	1	11	
Retinal hamartoma			
Negative	8	15	0.305
Positive	8	6	

TSC tuberous sclerosis complex, *AML* angiomyolipoma, *LAM* lymphangiomyomatosis

(68.5 %) of 15 were positive for renal lesions; however, there was no difference in the renal lesions between TSC1 and TSC2 ($p = 0.459$).

Discussion

Although the frequency of renal lesions in TSC is well-known, little is known about the predictors and growth rate in the different age groups. The results highlight the importance of follow-up for patients with renal lesions, especially from school age through adulthood. The current results correlate with a significant association between increasing age and the size of cysts/AMLs in TSC patients. Of all the medical problems in TSC, neurologic comorbidities are most likely to occur in patients with intractable seizures in childhood and in those with cardiac hamartoma in infancy [12, 13]. After neurologic manifestations in childhood, renal lesions are the most common cause of morbidity in TSC with increasing age [6], indicating that awareness of these diverse TSC manifestations with progressive growing renal lesions may minimize and avoid such renal complications [1].

Very few reports correlate the growing rate of cysts/AMLs in TSC patients with age. Although the average onset of renal lesions was estimated to be between 9 and 11 years, the onset of lesions was proposed since infancy with them progressively developing in adolescence [3, 11]. Little is known about either the growth rate of the lesions or their stability over time. Our results show that renal

lesions in patients with TSC are infrequently symptomatic in preschool-age patients, but increase in number in school-age patients and grow rapidly into adulthood. We emphasize that close follow-up is crucial for these patients, especially in adulthood. The pathophysiology of TSC involves mutations in *TSC1* or *TSC2* genes subsequent to the mTOR signaling cascade dysfunction that consequently dysregulate cell growth and proliferation, causing hamartoma formation in multiple organ systems [14]. Compared with *TSC1* mutations, those in *TSC2* exhibit a higher incidence and severity of pulmonary and renal lesions, which implies that genetic testing may predict of renal outcome [3, 15]. However, the current study did not find the association of renal lesion with genotyping, suggesting that these sample sizes for genotyping may have been too small to reveal a statistically significant difference. Pulmonary LAM is an interesting gender-based TSC complication. The overwhelming majority of affected individuals with TSC are adult women, possibly reflecting the effect of hormones [16, 17]. AMLs are also known to exhibit predominance in female patients that may be attributed to the presence of hormone receptors [3, 18]. Pulmonary LAMs are highly associated with renal AMLs in TSC; however, the co-occurrence and the relationships between these pathologies are not yet fully clarified [19, 20].

AMLs can occur at any location within the kidney and produce variable symptoms and are noted as multiple discrete lesions, poorly defined and diffusely infiltrating the renal parenchyma [11]. As lesions get progressively larger, particularly those larger than 4 cm in diameter, patients can potentially develop subsequent retroperitoneal hemorrhage [21, 22]. It may occur when dysplastic aneurysm blood vessels associated with an AML rupture. To date, the growth rate of cysts/AMLs is not well established by renal lesion measurements in a large population study [3]. The current results demonstrate the critical importance of obtaining follow-up renal size through adulthood and display the age-dependent size of renal cysts/AMLs, which increased rapidly in adulthood. These findings imply a potential risk factor for bleeding tendency and alert the patient to preventive medical interventions.

For initially identifying renal lesions in patients with TSC, routine ultrasound was recommended as the first step if single or multiple small lesions (<4 cm) exist and a follow-up with MRI/MR angiography is recommended for lesions greater than 4–6 cm with abnormal vasculature on Doppler ultrasonography. Optimal surveillance protocols for renal imaging recommend that all pediatric TSC patients undergo a baseline renal ultrasound and are followed up every 2–3 years if initially negative or annually if positive initially [11, 21]. The current results, which follow-up renal lesions revealed on routine MRI from preschool age, school age, and adulthood patients with serial high-resolution MRI, enable clinical physicians to predict the growth rate of such progressive renal lesions with increasing age.

Although renal embolization is effective in controlling hemorrhage in the acute setting, it has limited value in long-term management [21]. Most cysts/AMLs are asymptomatic or subtle until a huge mass effect causes symptomatic retroperitoneal hemorrhage [19]. In the current study, the frequency of renal cysts/AMLs was 45.4 % in the preschool-age group; it increased rapidly after school age to 75.0 % and further increased after middle adulthood to 85.7 %. The presence of renal lesions larger than 5 cm was 60 %, and the occurrence of renal complications/intervention was 72.7 % in patients >30 years. These findings are also important for education of the index patients and their families. Understanding the age-dependent complications associated with TSC and the increased tendency of bleeding during the disease progression may facilitate the patients for further close follow-up.

The main strength of this study is the routine MRI for renal lesions that was performed for young children to elderly with TSC, and serial follow-up MRI enables physicians to draw a correlation of the growth chart of renal lesions with different age groups. The study also has a limitation. The limited number of Taiwanese with TSC might be a limitation in this study. A previous epidemiologic study with nationwide health insurance investigation included a total of 208 subjects with TSC registered in Taiwan [13]. The current study enrolled 57 patients (a rate of 27.4 % of the 208 patients) with TSC that may regard as an adequate representative population in the epidemiologic condition of renal manifestations in Taiwan.

In conclusion, renal cysts/AMLs are noninvasive, nonimmigrating neoplasms that slowly progress to cause medical emergency. The study demonstrates that the growth rate of cyst/AMLs progresses markedly with increasing age, especially after the adulthood. The results highlight that awareness of the diverse manifestations of TSC and the positive correlation of growing renal lesions with increasing age. Clinicians may design a managing strategy for the high-risk patients to minimize and prevent future renal complications.

Conflict of interest The authors declare that they have no conflict of interest.

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