CLINICAL MANIFESTATIONS OF AND MAJOR COMPLICATIONS ASSOCIATED WITH TUBEROUS SCLEROSIS COMPLEX IN THAI CHILDREN

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Abstract. Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with variable clinical manifestations. The clinical features of and major complications associated with TSC in Thai children have never before been reported. The objective of this study was to investigate and report the clinical manifestations of and major complications associated with tuberous sclerosis complex (TSC) in Thai children. This cross sectional study was conducted in children aged 0-15 years who were diagnosed with TSC and treated at 1 of 10 tertiary care hospitals in Thailand during the January 2000 to December 2010 study period. Of 176 patients diagnosed with TSC during the study period, definite TSC was confirmed in 167 patients. Median age at presentation was 8 months, and only half of patients were diagnosed at initial presentation. The most common presenting symptoms were seizures (74.9%), skin lesions (10.2%), and cardiac manifestations (8.4%). Associated clinical features included at least one skin lesion (99.4%); epilepsy (89.2%); and neurobehavioral disorders, including pervasive developmental disorders, attention deficit hyperactivity disorder, developmental delay/mental retardation (58.1%), cardiac rhabdomyoma (54.5%), renal angiomyolipoma (AML) (42.2%), retinal astrocytoma (37.4%), and subependymal astrocytoma (18.7%). This is the first study to describe the clinical features of and major complications associated with TSC in Thai pediatric patients. The findings from this study are similar to those described in previous reports. Only half of patients were diagnosed at the initial visit. Delay in diagnosis may be due to the fact that multisystem involvement is slow to develop, and this can make TSC difficult to recognize when a patient presents with only one symptom. We recommend that any child presenting with seizure, developmental delay, and/or a finding of cardiac rhabdomyoma should be investigated for TSC. If TSC is diagnosed, regular clinical examination and surveillance should be performed in order to early detect evolving TSC complications.

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INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant genetic disorder with variable clinical manifestations. TSC is characterized by the presence of widely dispersed hamartomas in organs that include the brain, eyes, heart, lung, liver, and kidney (Curatolo *et al*, 2008). The estimated frequency of TSC is 1:6,000 to 1:10,000 live births (Northrup and Krueger, 2013). TSC1 and TSC2 encoding hamartin and tuberin, respectively, are two known genes that cause TSC, and they are found in up to 83% of patients (Dabora *et al*, 2001).

Since there is no specific sign or symptom in patients with TSC, diagnosis may be difficult. Clinical manifestations vary widely and they are different in each age group (Devlin *et al*, 2006). Complications, such as epilepsy (Chu-Shore *et al*, 2010), subependymal giant cell astrocytoma (SEGA) (Adriaensen *et al*, 2009), and renal angiomyolipoma (AML), are known causes of associated morbidity and mortality. Although the US National Institutes of Health proposed diagnostic criteria and guidelines for the management of TSC in 1999 (Roach *et al*, 1999), many patients were not early diagnosed (Staley *et al*, 2011). Early and accurate diagnosis of TSC leads to appropriate management, and diagnostic surveillance may limit morbid and mortality (Krueger and Northrup, 2013). In addition, some studies have reported the efficacy of mTOR (mammalian target of rapamycin) inhibitor in the treatment of major complications in this TSC patient population (Krueger *et al*, 2010 Bissler *et al*, 2013; Franz *et al*, 2013).

The clinical features of and major complications associated with TSC in Thai children have never before been reported. Accordingly, the aim of this study was to investigate and report the clinical manifestations of and major complications associated with tuberous sclerosis complex (TSC) in Thai children. We focused on neurologic, renal, cardiovascular, dermatologic, and ophthalmologic complications.

MATERIALS AND METHODS

This cross sectional study was conducted in children aged 0-15 years who were diagnosed with TSC and treated at 1 of 10 tertiary care hospitals in Thailand during the January 2000 to December 2010 study period. The protocol for this study was approved by the Institutional Review Board of each participating hospital. Only patients who met the clinical criteria for definitive diagnosis of TSC (Roach *et al*, 1999) were included. Clinical manifestations and major associated complications were retrospectively reviewed and analyzed. The presenting symptom or sign was the first clinical manifestation of TSC presented to a healthcare provider. Clinical evaluations and investigations, such as dermatologic and ophthalmologic evaluations, echocardiography, abdominal ultrasound, and neuroimaging studies, were recorded. Clinical data were reviewed, retrieved, and entered into a standard case record form.

Statistical analysis

Data analysis was performed using PASW Statistics version 18.0 (IBM, Armonk, NY). Patient characteristics were summarized using descriptive statistics. Data are presented as number, number (percentage), or median (mean and range).

RESULTS

Of 176 patients diagnosed with TSC during the study period, definite TSC was confirmed in 167 patients. There were 80 boys and 87 girls. Demographic and clinical characteristics of patients are shown in Table 1. The median age at presentation was 8 months. Seventy-

six percent of patients had their first clinical manifestation before 6 months of age, and 50% were diagnosed during the first two years of life. Distribution of age at initial manifestation and at diagnosis is presented in Fig 1.

The most common presentations were seizure (125, 74.9%), skin lesion (17, 10.2%), and prenatal finding of cardiac manifestation (14, 8.4%). Associated clinical features are given in Table 2. Skin lesions were found in (166, 99.4%) patients, and hypopigmented macules were the most common feature. One hundred forty-nine (89.2%) patients had epilepsy. Of those, 95 (63.7%) had focal seizure, 48 (32.2%) had infantile spasm (IS), 29 (19.7%) had generalized tonic-clonic (GTC) seizure, and 1 patient each had myoclonic and atonic seizure. Fifty-seven (60%) patients with focal seizure were refractory to multiple antiepileptic drugs (AED). Twenty (41.7%) patients with IS also had other types of seizure. Neurobehavioral problems, including pervasive developmental disorders, attention deficit hyperactivity disorder (ADHD), and mental retardation, were found in 97 (58.1%) patients. Developmental delay or intellectual disability was found in 83 (49.7%) children.

Of 123 patients who had neuroimaging studies, 23 (18.7%) were found to have SEGA at a median age of 124 months (range: 5-204). Of those 23 patients, 14 were symptomatic and treated with surgical removal. Four of 23 SEGA patients had increased intracranial pressure as

Table 1
Demographic and clinical characteristic of included TSC patients.

Patients	167
Gender (M:F)	80:87
Age at first presentation	
Prenatal (case)	7
Post natal (case)	160
Age at presentation (mo.), median (mean, range)	8 (24.4, 0-150)
Age at diagnosis (mo.), median (mean, range)	24 (43.79, 1-168)
Age at last follow-up (mo.), median, (mean, range)	108 (116.4, 6-336)
Duration of follow-up (mo.), median, (mean, range)	81 (91.8, 1-334)
Duration between first manifestation and diagnosis (mo.), median, (mean, range)	3 (20.3, 0-157)
Presenting symptoms	
Seizure, *n* (%)	125 (74.9)
Skin lesions, *n* (%)	17 (10.2)
Cardiac manifestation, *n* (%)	14 (8.4)
Prenatal finding of cardiac rhabdomyoma, *n* (%)	7 (50.0)
Cardiac symptoms (cardiac arrhythmia, CHF), *n* (%)	7 (50.0)
Neurodevelopmental problems, *n* (%)	5 (2.9)
Increased intracranial pressure (due to SEGA), *n* (%)	4 (2.4)
Others*, *n* (%)	2 (1.2)

CHF, congestive heart failure; SEGA, subependymal giant cell astrocytoma.
*Myopia and following diagnosis in sibling in one of each.

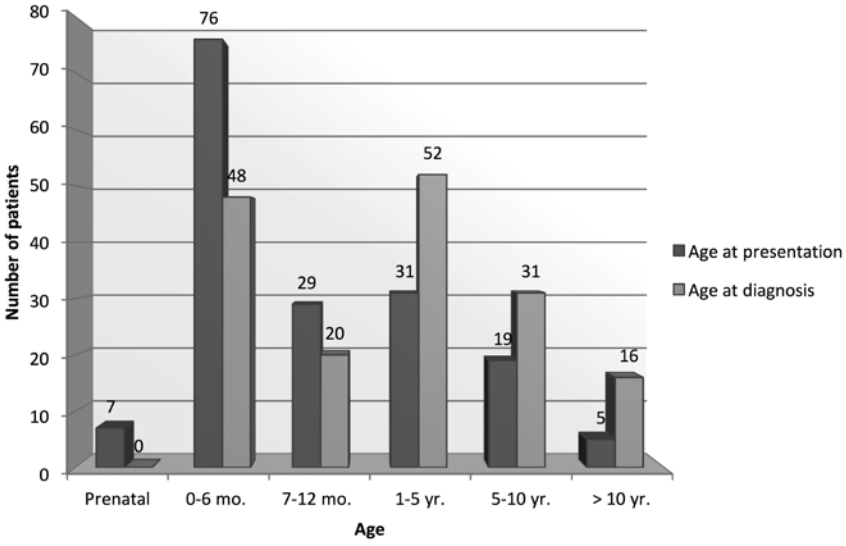

Fig 1– Distribution of age at initial manifestation and at diagnosis in patients with TSC.

Table 2
Associated clinical features in patients with TSC.

Associated features	No. of findings/No. of patients tested (%)
Dermatologic	
Hypopigmented macules	160/167 (95.8)
Facial angiofibroma	94/167 (56.3)
Shagreen patch	69/167 (41.3)
Facial plaque	18/167 (10.8)
Periungual fibroma	6/167 (3.6)
At least 1 skin lesion	166/167 (99.4)
Neurologic	
Epilepsy	149/167 (89.2)
Neurobehavioral	97/167 (58.1)
SEGA	23/123 (18.7)
Subependymal nodules	86/123 (69.9)
Cortical tubers	70/123 (56.9)
Cardiovascular	
Cardiac rhabdomyoma	67/123 (54.5)
EKG	10/63 (15.9)
Renal AML	49/116 (42.2)
Retinal astrocytoma	40/107 (37.4)

SEGA, subependymal giant cell astrocytoma; EKG, electrocardiogram; AML, angiomyolipoma.

their initial presenting symptom. Cardiac rhabdomyoma was found in 67/123 (54.5%) patients. Seven of those cases were found during the prenatal period and none were symptomatic. Of 60 patients whose cardiac rhabdomyoma was found during the postnatal period, the median age at finding was 19 months (range: 1-136). Seven of those 60 patients had cardiac symptoms, with cardiac arrhythmia observed in 6 patients and congestive heart failure observed in 1.

Renal AML was found in 49/116 (42.2%) patients at a median age of 115 months (range: 8-240) One patient that had AML diameter greater than 3 cm was treated with surgical removal.

Retinal astrocytoma was found in 40/107 (37.4%) patients and none had symptoms. The median age at finding was 37 months (range: 2-196).

DISCUSSION

Here, we report the clinical manifestations of and major complications associated with confirmed TSC in 167 Thai pediatric patients. These patients were recruited from pediatric neurology clinics located at tertiary referral centers in Thailand. While it could be argued that some bias may exist with regard to clinical presentation, the data presented in this report should be considered an accurate reflection of the overall clinical picture of pediatric TSC patients in Thailand.

Diagnosis of TSC was made according to the 1999 revised diagnostic criteria (Roach *et al*, 1999). In the present study, the most common age at presentation was <6 months of age, and 76% of patients had their first clinical presentation before 2 years of age, which is comparable to previous study (Yates *et al*, 2011). Diagnosis of TSC in our study was made after the first presentation in 47.9% of cases, which is lower than the rates from previous reports (Devlin *et al*, 2006; Staley *et al*, 2011). Sixty-two percent of our patients were diagnosed within 1 year, and this may, in part, reflect unawareness of TSC among treating physicians.

The most common presenting symptom in all age groups was seizure. Focal seizure was the most common seizure type, followed by infantile spasm and generalized tonic-clonic seizure. Although seizure was the most common presenting symptom, it was also the most commonly missed symptom in diagnosis of TSC (Staley *et al*, 2011). Even in patients with infantile spasm, which is well known to be related to TSC, diagnosis of TSC was still missed in some cases (Staley *et al*, 2011).

Overall, the most common clinical features of TSC were skin lesions, epilepsy, and neuropsychiatric disorders. In this study, one or more skin features were found in 99.4% of cases. Of these, hypopigmented macules were the most common lesion, followed by facial angiofibroma and shagreen patch. These findings are consistent with those reported from other studies (Jozwiak *et al*, 2000; Devlin *et al*, 2006; Yates *et al*, 2011). As possible diagnostic clues for TSC, hypopigmented macules are normally found early in life and facial angiofibroma, shagreen patch, and ungual fibroma are normally found later in life (Jozwiak *et al*, 2000).

The prevalence of epilepsy in TSC patients was reported to be 85-96% (Jozwiak *et al*, 2000; Devlin *et al*, 2006; Chu-Shore *et al*, 2010). In this study, seizure was found in 89.2% of patients. Focal seizure was the most common seizure type. GTC seizure was found in 19.7% of patients, but this may be an overestimate, because the diagnosis of seizure was based on clinical rather than electroencephalographic (EEG) characteristics. Infantile spasm was found in 32.2% of children, which is comparable to previous study (Chu-Shore *et al*, 2010). Previous studies reported that vigabatrin was effective in treatment of infantile spasm – especially in TSC patients (Parisi *et al*,

2007), and some patients may have normal intelligence and development (Goh *et al*, 2005). Given that prolonged duration of IS, prolonged time from treatment until seizure control, and poor control of IS all increase the risk of mental retardation in these patients (Goh *et al*, 2005), early diagnosis of TSC and early use of vigabatrin are essential. Developmental delay/intellectual disability was found in nearly 50% of patients in this study, which is lower than the rates reported from other studies (de Vries *et al*, 2007; Chopra *et al*, 2011). This may reflect the lack of formal neuropsychological evaluation among these patients.

SEGA was found in 23/123 patients (18.2%) in this study, and this is comparable to a previously reported rate (Adriaensen *et al*, 2009). Fourteen patients had increased intracranial pressure as their presenting symptom. As SEGA is associated with significant risk of morbidity and death, early detection and intervention results in a better outcome and a serial neuroimaging study is also recommended (de Ribaupierre *et al*, 2007; Krueger and Northrup, 2013). None of our SEGA patients was treated with mTOR inhibitor due to the severity of their symptoms and the unavailability of the drug.

Cardiac rhabdomyoma was found in 67/123 patients (54.5%) in this study, and this is similar to a previously reported rate (Jozwiak *et al*, 2000). Of these 67 patients, 7 had cardiac manifestation (congestive heart failure or cardiac arrhythmia), which occurred during the first month of life. Cardiac rhabdomyoma was found in 7 (10.5%) patients during the prenatal period, but none had any clinical symptoms. Up to 96% of infants with cardiac rhabdomyoma will be diagnosed with TSC (Bader *et al*, 2003). Thus, a finding of cardiac rhabdomyoma should heighten clinical suspicion for TSC.

Renal AML was found in 75-80% of TSC adult cases (Curatolo *et al*, 2008). In this study, AML was found in 49/116 (42.2%) patients, which is lower than adult cases. However, one study reported an increase in the incidence of AML from 16.7% during the first 2 years of life to 92.3% in patients 14-18 years of age (Jozwiak *et al*, 2000). As such, the lower incidence of AML found in this study may be attributed to the younger age when renal ultrasounds were performed. Only 1 patient had renal AML diameter greater than 3 cm. This patient had no clinical symptoms and the tumor was surgically removed.

Although TSC management and surveillance are well established (Roach *et al*, 1999), the surveillance rate among our patients was not consistent and it differed among our participating hospitals. A similar result was observed in the Asia-Pacific region (Lawson *et al*, 2014). Neuroimaging studies were performed in 123/167 (73.7%) patients, and most of those were cranial CT. Since cranial MRI can detect CNS lesions better than cranial CT (Krueger and Northrup, 2013), this may explain the lower incidence of cortical tubers and subependymal nodules in this study.

TSC is an autosomal dominant genetic disease. However, approximately two-thirds of cases result from new mutation (Caban *et al*, 2017). Of 138 patients with known family data, 101 (73.2%) had history of familial TSC. The 2 following genes are responsible for TSC: TSC1, which is localized at chromosome 9q34.3 coding hamartin protein; and, TSC2, which is localized at chromosome 16p13.3 coding tuberin protein (Curatolo *et al*, 2008). Hamartin and tuberin protein form a single complex that functions as a tumor suppressor by inhibiting mTOR kinase cascade. Mutation in either TSC1 or TSC2 results in increased activation of mTOR activity, which causes disorganized cellular overgrowth and abnormal differentiation (Curatolo *et al*, 2008).

Mutation in TSC1 and TSC2 are found in 83% of patients with TSC (Dabora *et al*, 2001). In the 2012 TSC diagnostic criteria update, genetic

testing was included (Northrup and Krueger, 2013). Genetic analysis of the TSC1 and TSC2 genes is not required for diagnosis of TSC. However, genetic analysis is helpful when patients do not meet clinical diagnostic criteria (especially in young children), and when screening apparently unaffected family members (Devlin *et al*, 2006; Caban *et al*, 2017). Since 10-25% of TSC patients have no identifiable genetic mutation, a normal genetic testing result does not exclude diagnosis of TSC (Northrup and Krueger, 2013). Given that TSC1 and TSC2 gene mutation analysis is not yet available in Thailand, the prevalence of genetic mutations is not known.

The major breakthrough in the management of TSC is the use of mTOR inhibitor (Jeong and Wong, 2016). This agent was found to be effective in managing SEGA (Krueger *et al*, 2010; Franz *et al*, 2013), renal AML (Bissler *et al*, 2008; Bissler *et al*, 2013), and epilepsy (French *et al*, 2016). This agent may also play a role in the improvement of lung function (McCormack *et al*, 2011) and skin features (angiofibroma) (Franz, 2011). There is also evidence that early use of mTOR inhibitor may alter the natural history of the disease (Kotulska *et al*, 2013).

This study has some mentionable limitations. First, given the retrospective design of this study, some data may have been missing or incomplete. However, the data from this study revealed that clinical presentations and associated features in Thai children are not different from those reported in other studies. Second, all of the patients included in this study were recruited from tertiary referral centers in Thailand. Given that patient referrals generally occur in complicated cases, it is possible that our results are not generalizable to all pediatric populations and locales in Thailand. Lastly, the absence of TSC1/TSC2 gene mutation analysis limited the ability to diagnose TSC, especially in cases with no other evident and telling clinical features.

In conclusion, this is the first study to describe the clinical features of and major complications associated with TSC in Thai pediatric patients. The findings from this study are similar to those described in previous reports. Only half of patients were diagnosed at the initial visit. Delay in diagnosis may be due to the fact that multisystem involvement is slow to develop, and this can make TSC difficult to recognize when a patient presents with only one symptom. We recommend that any child presenting with seizure, developmental delay, and/or a finding of cardiac rhabdomyoma should be investigated for TSC. If TSC is diagnosed, regular clinical examination and surveillance should be performed in order to early detect evolving TSC complications.

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CONFLICTS OF INTEREST

The authors hereby declare no personal or professional conflicts of interest regarding any aspect of this study.

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