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ORIGINAL ARTICLE

The clinical and paraclinical manifestations of tuberous sclerosis complex in children

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Abstract

Tuberous sclerosis complex (TSC) is an autosomal-dominant, multi-system, neurocutaneous disorder characterized by hamartomas in multiple organs. This study aimed to evaluate the clinical and paraclinical manifestations of children with TSC. The clinical and paraclinical characteristics of 79 children with TSC were evaluated and the possible correlations between the factors were calculated. Among the studied children which composed of 41 females (51.9%) and 38 males (48.1%), skin manifestations as hypopigmented macules as well as the brain involvement as cortical tubers in all (100%) cases, seizure in 74 (93.7%), and sub-ependymal nodules in 73 (92.4%) patients were the most common findings. The renal angiomyolipoma was diagnosed in 36 (70.6%) out of 51 patients. Subependymal giant cell astrocytoma in 25 (3/54%) out of 46 patients, retinal hamartoma in 15 (42.9%) out of 35 patients, and cardiac rhabdomyoma in 17 (41.3%) out of 46 patients were diagnosed. Furthermore, 50 (63.3%) out of 79 patients had psychological disorders that had a significant correlation with the prevalence of seizures ($p=0.002$). Given the multi-systemic involvement of TSC, it is necessary that all organs of the patients even without any related clinical symptom or sign be examined regularly for proper therapeutic intervention and prevent disease progression. The growth of hamartomas in the brain and kidneys can be life-threatening; therefore, these organs have more importance to be regularly followed up and examined.

Keywords Children · Clinical manifestations · Paraclinical manifestations · Tuberous sclerosis complex

Introduction

Tuberous Sclerosis Complex (TSC) is a neurocutaneous disorder with autosomal-dominant inheritance. It is a multi-systemic disease with a variable clinical phenotype [1, 2]. All ethnic groups, both male and female genders, can be affected by TSC. Its estimated incidence is one in 6000–10,000 live births and a population prevalence of about one in 20,000 [3, 4]. The disease is characterized by the presence of multiple hamartia (non-growing lesions leading to abnormal tissue) and hamartomas (benign growth tumors) in various body organs, especially in the brain, eyes, kidneys, skin, lungs, and heart [5].

Nowadays, TSC is diagnosed based on its possible clinical features. Its major clinical features include sub-ependymal nodules (SEN), sub-ependymal giant cell astrocytoma (SEGA), shagreen patch, hypopigmented macules, angiofibromas (fibrous cephalic plaque), ungual fibromas, cardiac rhabdomyoma, retinal hamartomas, cortical dysplasia, lymphangioleiomyomatosis, and angiomyolipomas (AML). Nonrenal hamartomas, confetti lesion, intraoral fibroma, enamel pits, retinal hypopigmented macule, and renal cysts are considered as its possible minor features. The diagnosis can be confirmed when two major clinical features or one major plus two minor criteria are present. A probable diagnosis can also be made when one major feature or two (or more) minor features are present [2, 5]. Overall, TSC has variable clinical manifestations with different ages of onset from infancy to adulthood. The severity of organ involvement typically depends on age [6, 7]. Early diagnosis of this

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disease can be valuable in preventing or relieving the symptoms and complications of the disease. This study aimed to evaluate the characteristics and prevalence of clinical and paraclinical features in children with TSC.

Methods

The records of 79 children with TSC (diagnosed by the diagnostic criteria) who visited the neurology clinic of Tabriz Children Hospital during 2011–2019 were evaluated in the present descriptive–analytical study. The patients were recalled from October 2018 to March 2019 for more complete examinations. Based on the 2012 International Tuberous Sclerosis Complex Consensus Conference [1], they were advised to receive regular examinations of their eyes (by an ophthalmologist), heart (by a pediatric cardiologist), skin (by a dermatologist), psychologic impairment (by a psychiatrist), kidneys (including ultrasound) and brain magnetic resonance imaging (MRI), and electroencephalogram (EEG). Given that the pulmonary lymphangioleiomyoma often occurs in patients over 18 years of age, the lung high-resolution computed tomography (HRCT) was not taken from the patients (children) in this study. The data were recorded in questionnaires. A genetic pedigree was also drawn for each patient. A pamphlet containing follow-up recommendations was given to all patients. They were regularly followed up depending on their organ involvement. Eye examinations every 6 months, kidney ultrasound and skin examinations annually, and brain imaging every 1 or 3 years (SEGA-positives annually, SEGA-negatives every 3 years) were recommended.

Statistical analysis

Statistical analysis was performed using SPSS software version 16.0. Initially, the variables were statistically checked for normality by one-sample Kolmogorov–Smirnov test. Data were shown as the mean ± standard deviation (SD) or percentages as suitable. Independent-samples t-test was performed for comparisons involving continuous variables between male and female patients. Chi-square and Fisher's exact tests were performed to evaluate and compare categorical variables. The correlations between the factors were analyzed by Pearson's correlation coefficient method. A p value of less than 0.05 was considered statistically significant.

Results

Seventy-nine patients, including 41 (51.9%) girls with a mean age of 10.81 ± 5.33 years, and 38 (48.1%) boys with a mean age of 9.74 ± 5.26 years (at inclusion time of the study) ($p = 0.374$) were examined in this study. The mean age of disease onset was 1.67 ± 0.34 years. As shown in Table 1, all patients were suffering from at least one of the cutaneous manifestations including hypopigmented macules in all (100%) cases, facial angiofibroma in 55 (69.6%) [24 (43.6%) boys,31 (56.4%) girls; $p = 0.229$], shagreen patches in 33 (41.8%) [13 (39.4%) boys, 20 (60.6%) girls; $p = 0.190$], and ungual fibromas in 6 (7.6%) [3 (50%) boys, 3 (50%) girls; $p = 0.923$] patients. According to the CT scan findings, CNS involvements were diagnosed as cortical tubers in all (100%), and SEN in 73 (92.4%) [34 (46.6%) boys, 39 (53.4%) girls; $p = 0.344$] patients. The SEGAs were detected in 25 (54.3%) [11 (44.0%) boys, 14 (56.0%) girls; $p = 0.938$] out of 46 patients undergoing MRI. Everolimus was administered to 14 patients with SEGAs (≥ 1.0 cm in the longest diameter). Among 35 patients undergoing the complete ophthalmologic examination, 15 (42.9%) [6 (40.0%) boys, 9 (60.0%) girls; $p = 0.767$] patients had retinal hamartoma. Only one girl was suffering from vision loss.

Seventy-four out of 79 (93.7%) patients [35 (47.3%) boys, 39 (52.7%) girls; $p = 0.582$] were suffering from seizure. The mean age of seizure onset was 10.51 ± 5.1 months among the patients. Thirty-nine (52.7%) [22 (56.4%) boys, 17 (43.6%) girls; $p = 0.097$] out of 74 cases with seizure had refractory epilepsy. Initially (at the diagnosis time), the most common type of seizure was infantile spasm seen in 62 (83.8%) [30 (48.4% boys, 32 (51.6%) girls; $p = 0.670$] cases out of 74 patients. However, at the inclusion time, the focal tonic was the most prevalent type of seizure (habitual seizure) seen in 34 (45.9%) [18 (52.9%) boys, 16 (47.1%) girls; $p = 0.201$] cases out of 74 patients.

In terms of cardiac involvement, among 46 patients undergoing cardiac and echocardiographic examinations, 17 (37%) [8 (47.1%) boys, 9 (52.9%) girls; $p = 0.544$] cases had cardiac rhabdomyoma. Among 51 patients undergoing kidney ultrasound examination, AML was diagnosed in 28 (54.9%) [9 (32.1%) boys, 19 (67.9%) girls; $p = 0.080$], and kidney cysts in 10 (19.6%) [5 (50.0%) boys, 5 (50.0%) girls; $p = 0.625$] patients. Eight (15.7%) [4 (50.0%) boys, 4 (50.0%) girls; $p = 0.670$] patients had cysts and AML, simultaneously. Everolimus was administered to 13 patients with AML with a volume of more than 3 cm.

A three-generation pedigree was drawn for all patients. Eleven (9.13%) [4 (36.4%) boys, 7 (63.6%) girls; $p = 0.401$] cases had a positive family history of TSC among whom 4 (36.3%) [2 (50.0%) boys, 2 (50.0%) girls; $p = 0.938$] cases had the maternal history (36.3%), 4 (36.3%) [1 (25.0%) boy, 3 (75.0%) girls; $p = 0.343$] patients had the paternal history, and 3 (27.3%) [1 (33.3%) boy, 2 (66.7%) girls; $p = 0.602$] cases had a history of the disease in other family members. The psychiatric status of the patients was also examined that among them, 49 (62%) [27 (55.1%) boys, 22 (44.9%) girls; $p = 0.111$] cases

Table 1 Multi-body systems manifestations in patients with TSC

Body systems	Manifestations	n/N (%)	M	F	*p* value[a]
Skin	Hypopigmentation	79/79 (100%)	38 (48.1%)	41 (51.9%)	1
	Angiofibroma	55/79 (69.6%)	24 (43.6%)	31 (56.4%)	0.229
	Shagreen patch	33/79 (41.8%)	13 (39.4%)	20 (60.6%)	0.190
	Ungual fibroma	6/79 (7.6%)	3 (50%)	3 (50%)	0.923
CNS	Cortical tubers	79/79 (100%)	38 (48.1%)	41 (51.9%)	1
	SEN	73/79 (92.4%)	34 (46.6%)	39 (53.4%)	0.344
	SEGA	25/46 (54.3%)	11 (44.0%)	14 (56.0%)	0.938
	Seizure	74/79 (93.7%)	35 (47.3%)	39 (52.7)	0.582
Eyes	Retinal hamartoma	15/35 (42.9%)	6 (40.0%)	9 (60.0%)	0.767
	Vision loss	1/35 (2.8%)	0 (0.0%)	1 (100.0%)	0.380
Heart	Rhabdomyoma	17/46 (37%)	8 (47.1%)	9 (52.9%)	0.544
Kidneys	AML	28/51 (54.9%)	9 (32.1%)	19 (67.9%)	0.080
	Cyst	10/51 (19.6%)	5 (50.0%)	5 (50.0%)	0.625
	Cyst + AML	8/51 (15.7%)	4 (50.0%)	4 (50.0%)	0.670
Psychologic	ID	13/49 (26.5%)	5 (38.5%)	8 (61.5%)	0.447
	ASD	4/49 (8.1%)	1 (25.0%)	3 (75%)	0.343
	ADHD	8/49 (16.3%)	5 (62.5%)	3 (37.5%)	0.390
	More than one psychological disorders	24/49 (49%)	16 (66.7%)	8 (33.3%)	0.029

ADHD attention-deficit/hyperactivity disorder; *AML* angiomyolipomas; *ASD* autistic spectrum disorder; *CNS* central nervous system; *F* females; *ID* intellectual disability; *M* males; *SEGA* sub-ependymal giant cell astrocytoma; *SEN* sub-ependymal nodules

[a]Comparison between males and females

had psychological disorders including intellectual disability (ID) in 13 (26.5%) [5 (38.5%) boys, 8 (61.5%) girls; $p = 0.447$], autistic spectrum disorder (ASD) in 4 (8.1%) [1 (25.0%) boy, 3 (75%) girls; $p = 0.343$], and attention-deficit/hyperactivity disorder (ADHD) in 8 (16.3%) [5 (62.5%) boys, 3 (37.5%) girls; $p = 0.390$] patients. A total of 24 (49%) [16 (66.7%) boys, 8 (33.3%) girls; $p = 0.029$] patients simultaneously had more than one of these psychological disorders that were more prevalent among male patients. It was also found that 49 (66.2%) out of 74 patients with seizures had psychological disorders; while among five patients without seizures, no one had any mental disease. The results indicated that there was a significant relationship between seizures and psychological disorders ($p = 0.002$).

During the patients' follow-up in this study, SEGA enlargement (more than 1 cm) was found in 14 patients; however, due to the medication (Everolimus), the SEGA volume and severity of seizures decreased. Only one patient developed hydrocephalus due to the SEGA enlargement resulted in ventriculoperitoneal shunt placement. Also, one patient underwent a right total nephrectomy due to increased angiomyolipoma size (12 cm). Moreover, among 17 patients with rhabdomyoma, a significant regression was found in 14 patients.

Discussion

TSC is an autosomal-dominant inherited syndrome caused by defects in the genes *TSC1* and *TSC2*. *TSC1* located on chromosome 9 (9q34), and *TSC2* on chromosome 16 (16p13.3), are responsible for the expression of Hamartin and Tuberin proteins, respectively. The Hamartin–Tuberin complex has tumor suppressor activity. Therefore, any defect in *TSC1* and/or *TSC2* leading to loss of the Hamartin–Tuberin complex causes an uncontrolled cell cycle that can eventually lead to forming hamartomas in multiple body organs [5, 8]. Using publicly available datasets, "The Human Protein Atlas" (https://www.proteinatlas.org/), *TSC1*, and *TSC2* are expressed throughout the body tissues. *TSC1* can be found with high expression in the cerebellum, placenta, heart muscle, skeletal muscle, and bone marrow. It has low expression in soft and adipose tissues, and moderate expression in other tissues. *TSC2* is moderately expressed by several tissues such as the cerebral cortex, cerebellum, hippocampus, lung, stomach, duodenum, small intestine, liver, gallbladder, kidney, and heart muscle. It is lowly expressed by other tissues. Therefore, it may be initially expected that organs that significantly express both *TSC1* and *TSC2* such as the brain, will be

more affected by the disease. However, tumor formation is multifactorial, and it has been revealed that the most affected organs in TSC are the skin, brain, kidney, and heart [9]. In this study, the main clinical and paraclinical findings in children with TSC were evaluated. There were 11 (13.9%) cases with a positive family history based on pedigree, among whom 4 (36.3%) patients had a maternal history, 4 (36.3%) patients had a paternal history, and 3 (27.3%) cases had a disease in other family members. In a study by Napolioni et al.[10], family history was positive in 33% of patients. Also, it was 30% in a study by Larissa et al. [2]. In this study, the low incidence of positive family history might be due to the refusal of some families to get further examinations such as the kidney ultrasound, brain MRI, wood's lamp and/or ultraviolet light examinations. Skin findings are common manifestations of the disease in patients with TSC that its prevalence is more than 90% in most studies [2, 11, 12]. In this study, the overall prevalence of skin manifestations was 100% in patients among whom 79 (100%) patients had hypopigmented macules, 55 (69.6%) had facial angiofibromas, 33 (41.8%) had shagreen patches, and 6 (7.6%) had ungual fibromas. In other studies [2, 11–14], the prevalence of hypopigmented macules was about 90–100%, 70–90% with facial angiofibromas, 25–40% with shagreen patches, and 10–20% with ungual fibromas. There is considerable heterogeneity in neurological manifestations. In this study, the CNS involvements were diagnosed as cortical tubers or calcification in all 79 (100%) cases and SEN in 73 (92.4%) cases. Based on the previous studies [15–17], the prevalence of cortical tubers and SEN among TSC patients were 84–94% and 90–93%, respectively. Although SEGA as a type of brain tumor develops in 10–15% of children with TSC, it can lead to high intracranial pressure, hydrocephalus, and even death [2, 18, 19]. In this study, SEGAs were detected in 25 (54.3%) cases out of 46 patients.

Seizures are the most common neurological manifestations seen in 70%–90% of individuals with TSC [21, 22]. In this study, 74 (93.7%) out of 79 patients had seizures, of which the predominant semiology of the primary seizure type was infantile spasm seen in 62 (83.8%) cases. In terms of seizure type at inclusion time, the focal tonic was the most common seizure semiology. Thirty-nine (52.7%) patients had refractory epilepsy. In a study by Nabbout et al. [20], epilepsy was seen in 83.6% of patients with TSC, among which 38.9% had the infantile spasm, and 67.5% of seizures were focal. In this study, 28 (37.8%) patients had focal seizures. The low percentage of focal seizures in this study was probably because of that the parents sometimes did not notice the onset of focal seizures and reported the secondarily generalized seizures as the generalized seizures [21, 22].

Early onset of seizures in the first years of life is associated with a high risk of developing cognitive and behavioral impairment. A broad clinical spectrum from a normal intelligence without any seizure to a severe intellectual disability with debilitating seizures can be seen in TSC patients [23]. In the case of psychiatric status, among all patients, 49 (62%) cases had psychological disorders including ID in 13 (26.5%) patients, ASD in 4 (8.1%), and ADHD in 8 (16.3%) patients. Furthermore, 24 (49%) patients simultaneously had more than one of these psychological disorders that was more prevalent among male patients. The prevalence of ASD and ADHD varied greatly in TSC in other studies [24, 25], but it was between 30 and 50% on average. The results also showed that there was no psychological manifestation in patients without seizures. Therefore, there might be a significant relationship between epilepsy and the incidence of psychological disorders. In a study by Jozwiak et al. [26], more than half of the patients with TSC had refractory epilepsy, and 40–70% of them had ID. Similar results were achieved in a study by Curatolo et al. [27].

Retinal hamartoma is the most common ocular manifestation of the disease with almost asymptomatic lesions. It can occur even from infancy. In some cases, large lesions in the macula could cause vision loss [2]. In this study, 15 cases (42.9%) were suffering from retinal hamartoma. The prevalence of this manifestation was about 30–50% in the other studies [2, 14, 28, 29].

In the case of cardiac manifestations, rhabdomyoma is the most common heart tumor occurring more in younger ages and infants. It may be even seen in the fetus. These lesions may regress after a few years [30]. In this study, 17 (37%) out of 46 TSC patients suffering from cardiac problems had rhabdomyoma. In other studies, its prevalence was 50–80%. The regression may occur in less than 50% of the patients [17, 31–33]. The low prevalence of cardiac rhabdomyoma in this study might be due to the older age of patients at inclusion time. On the other hand, unfortunately, some families skip the cardiac examination. In this study, 33 cases skipped the cardiac examinations.

Renal manifestations are considered the second cause of death in these patients. Among them, AML is the most common that affects approximately 75%–80% of TSC children older than 10 years. These lesions are often multiple and bilateral which are more common in females. Their size increases with age [34]. It is important to note that AML bigger than 4 cm is prone to rupture which may lead to death. In this study, AML was detected in 36 (70.6%) cases. In other studies, the prevalence of AML was 55–80%. The prevalence of renal cysts is 20–28% among TSC patients [17, 24, 35, 36]. In this study, only ten (19.6%) studied children suffered from kidney cysts.

Boys are more likely than girls to have multiple mental illnesses at the same time. It might be due to the possible differences in sex hormones and brain structure between boys and girls [37, 38]. No other significant difference was

found in the prevalence of TSC manifestations between male and female children. However, further studies are necessary to confirm the results.

In conclusion, TSC is an autosomal-dominant inherited multi-system disorder. In children with TSC, multiple hamartomas may be formed in nearly all organs, prominently in the skin, brain, kidneys, heart, eyes, and lungs. It is imperative that families be convinced to accept periodic follow-up based on existing guidelines. Appropriate diagnosis and intervention are more crucial for organs in which the involvement severity increases with age such as AML and SEGA. High intracranial pressure and hydrocephalus caused by SEGAs, and rupture of large AMLs, both can be life-threatening. Therefore, kidneys and brain have more importance to be regularly followed up and examined. Establishing a TSC registry system can also be useful for more comprehensive care of TSC patients. The lack of molecular genetic testing which can detect any possible defects in *TSC1* and/or *TSC2* genes of the patients and their families can be considered as a limitation of this study. Further studies with a larger sample size may be necessary to evaluate the association of gender with TSC manifestations and confirming the results.

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Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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Informed consent Informed consent was obtained from all parents of children included in the study.

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