Do cutaneous manifestations predict systemic manifestations of tuberous sclerosis complex? A study of 50 patients

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Abstract

Background: Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem neurocutaneous syndrome, characterized by the development of multiple hamartomas resulting in multisystem involvement. To date there is little evidence of biomarkers to indicate the different tissues being involved in TSC.

Objectives: To describe the cutaneous, neurological and other system manifestations of TSC in children and to determine the association between cutaneous manifestations and central nervous system, renal, cardiac and ocular involvement.

Method: All children with TSC attending the Lady Ridgeway Hospital for Children, Sri Lanka, over a period of two years were evaluated for clinical manifestations and imaging findings.

Results: There were 50 children with TSC during the study period. The median age was 42 months and first clinical presentation was with neurological manifestations in 58%, cutaneous manifestations in 36%, renal manifestations in 2% and cardiac manifestations in 2%. Seventy eight percent presented during infancy, 67% with neurological manifestations. All children had cutaneous features, 43 had neurological features whilst 16, 12 and 8 patients had renal, cardiac and ocular abnormalities respectively. The most common cutaneous manifestation was ash leaf macule (92%) which was present at birth in 87% cases. Most common neurological complication was epilepsy (91%). Statistically significant associations were found between a) fibrous plaque of forehead with ipsilateral structural cerebral lesions or contralateral seizures ($p<0.01$) and b) shagreen patches ($p<0.001$) and angiofibromas of the face ($p<0.001$) with renal manifestations. Shagreen patch was associated with ipsilateral renal involvement.

Conclusions: Fibrous plaque of forehead may be considered a cutaneous marker of ipsilateral central nervous system manifestations, Angiofibromas of the face and shagreen patches may be considered as markers of renal involvement.

(Key words: Tuberous sclerosis, cutaneous manifestations, systemic manifestations)

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Introduction

Tuberous sclerosis complex (TSC) is an autosomal dominant neurocutaneous syndrome, characterized by development of multiple hamartomas resulting in multisystem involvement. Diagnosis is based on the revised diagnostic criteria of Roach and Sparagana[1]. Birth incidence of TSC is around 1: 5800[2] and its presentation can be variable. For instance, renal angiomyolipomas do not occur until a certain age whereas cardiac rhabdomyomas appear in the fetus, and usually regress spontaneously in infancy[3]. There is variable involvement of different tissues i.e. skin (>90%), cerebral pathology (90%), renal abnormalities (70-90%) and retinal hamartomas (50%)[4]. Most prominent clinical issues in childhood are epilepsy, intellectual disability, specific learning disabilities, attention-deficit hyperactivity disorder, and autistic spectrum disorders[5]. Difficulty in achieving seizure control is a poor prognostic indicator of intellectual impairment[6] and cortical tuber count has been studied as a biomarker indicating the neurological severity of TSC[7,8].

The occurrence of each manifestation is explained by cellular hyperproliferation and appearance of numerous hamartomas anywhere in the body in which exact mechanism is not fully understood[3]. To date there is little evidence of any biomarkers to

indicate the different tissues being involved in TSC. Forehead plaque has been studied as a novel cutaneous marker to know the central nervous system (CNS) involvement in TSC at an early stage[9]. Lymphangioleiomyomatosis associated with renal angiomyolipomas in female patients are being studied[10]. There are no studies to see the correlation between cutaneous and other system manifestations.

Objectives

To describe cutaneous, neurological and other system manifestations of TSC in children presenting to the Lady Ridgeway Hospital for Children, Colombo and to investigate possible associations between cutaneous manifestations and other systems involved.

Method

The study was conducted at the Lady Ridgeway Hospital for Children. Patients from the paediatric dermatology and neurology services were invited to participate in this study. Children with "definite evidence of TSC" (according to the revised diagnostic criteria of Roach and Sparagana) were recruited from 2008-2010. Patients categorized under probable and possible TSC were not included for the analysis. Ethical approval was obtained from the ethical review committees of the Faculty of Medicine, University of Colombo and Lady Ridgeway Hospital.

All patient reviews were performed by an advanced trainee in dermatology and a paediatric neurologist. Detailed clinical history and examination for the different manifestations were performed. The family members (parents and siblings) were screened by a detailed family history to cover a 3 generation pedigree chart and detailed clinical examination. Computerized tomography (CT) / magnetic resonance imaging (MRI) of the brain, echocardiography, ultrasound scans of kidneys and eye examination were performed in all. Electroencephalograms (EEG) were performed in those who presented with seizures. Epilepsy in these patients was categorized according to the International League against Epilepsy 1989 classification. Epilepsy control was described using a modified Engel's classification system. The Chi-squared test (or Fisher exact test when appropriate) was used to determine significant differences in proportions between categorical variables.

Results

Fifty children (27 females, 23 males) were studied. The median age was 42 months (3 days to 16 years). The first presentation to a health professional was due to a neurological manifestation in 58%. Cutaneous (36%), cardiac (4%) and renal (2%) manifestations were less frequent as first manifestations. Thirty nine (78%) had their first clinical presentation within the first twelve months of life. The two cardiac presentations were very early (three days and two weeks). In those with infantile presentation, 66.7% were with neurological manifestations. The only patient presenting with a renal manifestation (polycystic kidney disease) did so at fifteen months.

On examination, all 50 children had cutaneous features, 43 had neurological symptoms or signs, 16 had renal abnormalities, 12 had cardiac abnormalties and 8 had ocular abnormalities. Two deaths were observed during the study period. First was a child who presented at 3 days with a cardiac tumour and died at one month due to arrhythmia. The second was a 5 year old child with epilepsy and developmental delay who died due to pneumonia. A variety of cutaneous manifestations were observed in our series with a variable age of presentation of different features. The spectrum of cutaneous manifestations is shown in Table 1. Involvement of systems other than skin is shown in Table 2.

Table 1: ***Spectrum of cutaneous manifestations***

Cutaneous feature	Number of patients			Common age of presentation
	Total *n=50*	Male *n=23*	Female *n=27*	
Ash leaf macules	46 (92%)	20	26	86.9% at birth
Confetti macules	33 (66%)	17	16	63.6% in infancy
Café-au-lait spots	30 (60%)	14	16	90% at birth
Angiofibromas	22 (44%)	10	12	72.7% at 1- 5 years
Shagreen patch	24(48%)	14	10	66.7% at 1- 5 years
Fibrous plaque	21 (42%)	08	13	85.7% at birth
Periungual fibromas	02 (04%)	01	01	100% at 1- 5 years
Poliosis	02 (04%)	00	01	100% at birth
Molluscum fibrosum pendulum	01 (02%)	01	00	100% at birth

Table 2: ***Involvement of systems other than skin*** *(n=50)*

Neurological *(n=43)*	**Renal** *(n=16)*	**Cardiac** *(n=12)*	**Ocular** *(n=8)*
Epilepsy (39, 78%) Developmental delay (32, 64%) Intellectual disability (10, 20%) Learning disorders (10, 20%) Developmental regression (3, 6%) Behavioural problems (9, 18%) Focal neurological deficit (3, 6%)	Renal cysts (14, 28%) Angiomyolipomas (5, 10%) Polycystic kidneys (1, 2%) Renal failure (0, 0%)	Tumours (8, 16%) Septal defects (6, 12%) Conduction defects(1, 2%)	Retinal haemagiomas (8, 16%) Disc elevation with suspected astrocytoma (1, 2%)

The two main types of epilepsies on presentation were infantile spasms (30%) and partial seizures (28%). Several children experienced multiple types of seizures (6%). A definite evolution from one syndrome to another was seen in 10%. Isolated speech delay occurred in 18%. Although 88% of the patients had undergone neurological imaging characteristic features of TSC were seen in 80%. Only 20% had undergone MRI scanning. Of the 16 patients with renal manifestations of TSC, 87.5% had renal cysts and 31.3% had renal angiomyolipomas. Of the 12 patients with cardiac manifestations of TSC, 75% had tumours and 50% had septal defects. All 8 patients with ocular manifestations of TSC had retinal haemangiomas. Association of neurological manifestations with fibrous plaque of the forehead is shown in Figure 1.

All 21 patients who had fibrous plaque of the forehead had associated ipsilateral cerebral abnormalities or contralateral seizures ($\chi^2 = 1.07$, $p< 0.05$). The positive predictive value of association of this fibrous plaque with CNS manifestations was 100%.

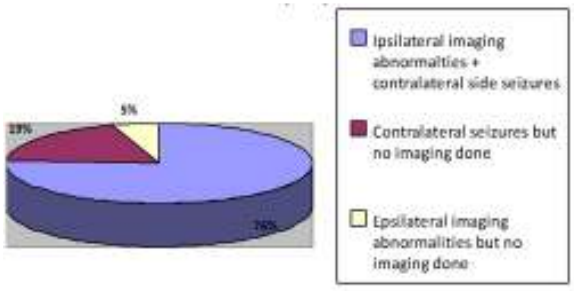

Figure 1: ***Neurological manifestations associated with fibrous plaque of forehead (n=21)***

There was a 48.8% sensitivity level to have forehead plaque in association with CNS changes of TSC. Other cutaneous manifestations did not show any statistically significant association with the presence of neurological manifestations. There was no statistically significant association with the gender difference in above findings.

The association of cutaneous manifestations with other system manifestations is shown in Table 3.

Table 3: ***Association of cutaneous manifestations with other system manifestations***

	With CNS	**Without CNS**	**With Renal**	**Without Renal**	**With Cardiac**	**Without Cardiac**	**With Ocular**	**Without Ocular**
With ash leaf macules	29	04	13	20	09	24	04	29
Without ash leaf macules	01	01	00	02	01	01	02	00
Association with ash leaf macules	P value = 0.269		P value = 0.519		P value = 0.496		P value = 0.025	
With angiofibromas	14	03	11	16	02	15	03	14
Without angiofibromas	16	02	02	06	02	16	03	15
Association with angiofibromas	P value = 0.658		P value = 0.003		P value = 0.06		P value = 1.00	
With shagreen patch	12	05	12	05	03	14	02	15
Without shagreen patch	18	00	01	17	07	11	04	14
Association with shagreen patch	P value = 0.019		P value = 0.003		P value = 0.264		P value = 0.065	
With café-au-lait macules (CALM)	19	05	12	12	06	18	04	20
Without café-au-lait macules	11	00	01	10	04	07	02	09
Association with CALM	P value = 0.157		P value = 0.027		P value = 0.689		P value = 1.00	
With fibrous plaque of forehead	16	00	08	08	04	12	03	13
Without fibrous plaque	14	05	05	14	06	13	03	16
Association with fibrous plaque	P value = 0.049		P value = 0.27		P value = 0.723		P value = 1.00	

There was a statistically significant association of angiofibromas, shagreen patch and café au lait macules (CALM) with manifestations of renal involvement. Out of the 16 patients with renal manifestatioins 15 (93.8%) had assocaited ipsilateral shagreen patch. Out of the 34 patients who did not have renal involvement, 25 (77.8%) did not show the shagreen patch. Shagreen patch being associated with ipsilateral renal manifestations was stasitically significant (χ^2=1.07, p<0.05). There was no statistically significant association with the gender difference in the above findings. The positive predictive value (PPV) of the association of shagreen patch with renal manifestations is 62.5%, the sensitivity of having shagreen patch in association with renal manifestations of TSC is 93.8% and the specificity to exclude any renal involvement when there is no shagreen patch is 73.5%.The PPV of association of angiofibromas of the face with renal manifestations is 59.1%, the sensitivity of having angiofibromas in association with renal manifestations of TSC is 81.2% and specificity to exclude any renal involvement when there is no angiofibromas is 73.5%. The PPV of association of CALM with renal manifestations is 50%, the sensitivity of having CALM in association with renal manifestations of TSC is 93.7% and specificity to exclude any renal involvement when there is no CALM is 55.9%. There was no statistically significant correlation between the cutaneous manifestations and cardiac or ocular manifestations in our series.

Discussion

The identification of fibrous plaque with the ipsilateral CNS abnormalities and the presence of facial angiofibromas and the ipsilateral shagreen patch with renal abnormalities were the major findings in our study.

The age dependent appearance of characteristic features of TSC has historically presented challenges for diagnosis in early childhood, and requires a broad understanding of the wide range of its manifestations. Despite the availability of genetic testing for case confirmation in the developed world, in a developing country like ours thorough cutaneous, fundoscopic, and neurological evaluation will remain essential to its diagnosis. In our series of patients with 100% cutaneous involvement, a careful skin examination of patients at risk continues to be the easiest and most accessible method of diagnosis.

Occurrence of each cutaneous manifestation in our series, was compared with the findings of international data[6,11]. Ash leaf macule, shagreen patch and fibrous plaque of the forehead in our study were seen in equal proportions to that described elsewhere. However, in our series, angiofibromas were seen only in 44% compared to 80% in international studies. Periungual fibromas were seen only in 44% compared to 12% in other studies. The reduced prevalence of these features is explained by the younger age of the participants.

Determining the associations between cutaneous and renal, CNS, cardiac and ocular manifestations is useful in diagnosis and investigating for complications of the disease. Forehead plaque has been studied as a cutaneous marker of CNS involvement earlier[3]. Rama Rao GR, Krishna Rao PV, et al described an association between these plaques and occurrence of CNS manifestations[12]. They described that 7 out of 8 cases with seizures had a forehead plaque. In our study, the association of forehead plaque showed 100% PPV of an ipsilateral structural CNS abnormality in imaging or ipsilateral origin of seizures (n=21). We also observed that absence of a forehead plaque had a specificity of 100% to exclude any CNS involvement. Establishing this observation in a population would prevent unnecessary radiological screening. This PPV of a forehead plaque for CNS involvement has not been described in the literature previously. As fibrous plaque of the forehead is mostly evident at birth, it would be a good marker of ipsilateral brain involvement even in early life. This would render early diagnosis and help prevention of major complications.

Renal involvement in TSC has long been known, but it was only 40 years ago that TSC was reported to cause chronic kidney disease[10]. In 1991, investigators from the Mayo Clinic reported that kidney disease was a common cause of death in this population[10] and also a major cause of morbidity[13]. Of the 355 patients with TSC who were followed up, 40 died, 11 due to renal involvement[10]. Thus, early identification of renal involvement and proper follow up would be of major benefit in reducing morbidity and mortality of TSC. The proximity of the autosomal dominant polycystic kidney disease gene to the TSC gene, on chromosome 16, is one explanation for the occasional individual with TSC and polycystic kidneys and one patient (2%) in our series showed this phenomenon[14]. There are no previous studies describing any association between cutaneous features and renal manifestations. Thirty two percent of our patients showed renal abnormalities. There are statistically significant associations with angiofibromas, shagreen patch and café au lait macules (CALM) with

manifestations of renal involvement according to our study. When considering shagreen patch and its association with renal involvement, ninety percent of patients with renal problems in our series, had an ipsilateral shagreen patch. This would be an important diagnostic tool if it can be applied to the population of TSC. Furthermore, shagreen patch occurring on the same side as the renal involvement is also an important finding. The PPV of association of angiofibromas of the face with renal manifestations was 59.1%, the sensitivity of having angiofibromas in association with renal manifestations was 81.2% and specificity to exclude any renal involvement when there is no angiofibromas was 73.5%.

CALM is a nonspecific feature of TSC and is a more important finding in conditions such as neurofibromatosis, and the PPV of association of CALM with renal manifestations being 50%, and specificity to exclude any renal involvement when there is no CALM being 55.9% is not of such value as the above two markers.

Conclusions and recommendations

The association of fibrous plaque of the forehead with the ipsilateral central nervous system abnormalities and associated facial angiofibromas and the ipsilateral Shagreen patch with renal abnormalities, would be very important in predicting the later complications of Tuberous sclerosis. Larger clinical studies are warranted to establish these associations.

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