Actas Dermosifiliogr. 2009;100:596-601

ORIGINAL ARTICLE

Clinical Findings in 67 Patients With Tuberous Sclerosis

M. Fernández-Guarino,[a] P. Boixeda,[a] M.J. Anaya,[b] P. Beldar,[c] and P. Jaén[a]

[a]Servicio de Dermatología, Hospital Ramón y Cajal, Universidad de Alcalá de Henares, Madrid, Spain
[b]Servicio de Medicina Interna, Hospital Fernando Fonseca, Universidad de Lisboa, Lisboa, Portugal
[c]Servicio de Dermatología, Universidad de Alcalá de Henares, Hospital Universitario de Guadalajara, Guadalajara, Spain

Abstract. *Background.* Tuberous sclerosis is an uncommon neurocutaneous syndrome characterized by the appearance of hamartomas in multiple organs. Diagnosis is based on clinical criteria.
Objective. To report the clinical findings in a series of 67 patients with tuberous sclerosis.
Material and methods. This was a descriptive and observational retrospective study of patients with tuberous sclerosis referred to our dermatology clinics between January 1994 and March 2007.
Results. All patients presented neurological or dermatological disorders. Other disorders, in descending frequency, were psychiatric (55.5 %), renal (32.8 %), cardiac (22.4 %), skeletal and pulmonary (13.4 %), and ophthalmological (11.9 %).
Conclusions. We report the clinical findings in a series of patients with tuberous sclerosis. According to our literature search, this is the first such study in the Spanish population. Overall, our findings support those already published.

Key words: tuberous sclerosis, skin manifestations, neurological manifestations.

ESCLEROSIS TUBEROSA. HALLAZGOS CLÍNICOS EN 67 PACIENTES

Resumen. *Introducción.* La esclerosis tuberosa (ET) es un síndrome neurocutáneo infrecuente caracterizado por la aparición de hamartomas en múltiples órganos. Su diagnóstico se basa en criterios clínicos.
Objetivo. Describir los hallazgos clínicos en una serie de 67 pacientes afectos de ET.
Material y métodos. Llevamos a cabo un estudio retrospectivo, descriptivo y observacional de los pacientes con ET remitidos a nuestras consultas de Dermatología entre enero de 1994 y marzo de 2007.
Resultados. El 100 % de los pacientes presentaron alteraciones neurológicas o dermatológicas. El resto fueron, por orden: psiquiátricas (55,5 %), renales (32,8 %), cardíacas (22,4 %), esqueléticas y pulmonares (13,4 %) y oftalmológicas (11,9 %).
Conclusiones. Describimos los hallazgos clínicos en una serie de pacientes afectos de ET. Se trata, según la literatura revisada, del primer estudio de este tipo en la población española. Globalmente, nuestros datos apoyan lo hasta ahora publicado.

Palabras clave: esclerosis tuberosa, manifestaciones dermatológicas, manifestaciones neurológicas.

Introduction

Tuberous sclerosis (TS) is a neurocutaneous syndrome with an autosomal dominant inheritance pattern and is characterized by the appearance of hamartomas in multiple organs. The classic clinical triad consists of angiofibromas, mental retardation, and epilepsy; however, these only appear in 29% of the patients and 6% do not present any such characteristics.[1] The incidence of TS is estimated to range between 1:5800 and 1:10 000 and in two-thirds of the patients TS is due to sporadic mutations.[2] Two genes responsible for the disease have been identified: *TSC1* on chromosome 9 and *TCS2* on chromosome 16.[3] The enormous clinical variability of TS is explained by mutations on these genes and mosaicisms, as well as variable penetrance. The diagnosis of TS is principally clinical and is based on a series of criteria (Table 1), since there is no single diagnostic finding.[4] Morbidity

Correspondence:
Montse Fernández Guarino.
Servicio de Dermatología
Hospital Ramón y Cajal
Crta. Colmenar Viejo km 9,100
28034 Madrid, Spain
montsefdez@msn.com

Manuscript accepted for publication November 12, 2008.

and mortality in TS are usually related to neurological manifestations.[2]

In this study, we report the findings in a series of 67 patients and compare our results to those of the reviewed literature.

Material and Methods

This was a descriptive and retrospective, observational study of the patients with TS referred to our dermatology clinics between January 1994 and March 2007. All the patients who fulfilled a definitive diagnosis of TS according to the diagnostic criteria (Table 1) were included in the study. Patient data were extracted from an Excel spreadsheet, supplemented by their medical records and any ophthalmological, neurological, and psychiatric studies, etc, undergone by patients. Patient age, sex, and family history of TS were recorded. Any associated disorder was recorded and classified as follows: dermatological disorders, cardiac disease, central nervous system (CNS) disease, psychiatric disorders, renal, skeletal, and respiratory disorders, and ophthalmological disorders.

Skin manifestations were studied in greater detail, as follows:

1. Angiofibromas were classified according to their location on the face (cheeks, nose, nasogenian fold and forehead), their pattern of presentation (crazy paving or sebaceous), and distribution (unilateral or bilateral) (Figure). The sebaceous pattern is defined as the appearance of isolated lesions, separated from each other, and the crazy paving pattern when lesions form a patch with multiple lobulations on its surface.
2. Hypomelanotic macules were classified into 4 groups: lanceolate or ash-leaf shaped, confetti pattern, fingerprint-shaped, and other (none of the 3 previous groups). In addition, their location on the anterior thorax, posterior thorax, arm, leg, and abdomen was taken into account.
3. If Koenen tumors were present, it was noted whether they appeared on the hands or feet. Shagreen or sharkskin patches were also classified according to their location.

Results

A total of 67 patients (35 women and 32 men) were included, with a mean age of 27.61 years (range, 15 to 80 years). There was a family history of TS in 21%. The results are summarized in Table 2. All patients presented dermatological disorders; of these, the most frequent

Table 1. Diagnostic Criteria for Tuberous Sclerosis[4]

Major Criteria	*Developmental Age*
Angiofibromas or plaque on the forehead	Childhood-adult
Nontraumatic periungual fibromas	Adolescent-adult
Hypomelanotic macules (3 or more)	Childhood-adult
Shagreen patch (connective-tissue nevus)	Childhood
Multiple retinal hamartomas	Childhood
Cortical tubers	Fetal stage
Subependymal nodules	Childhood-adolescence
Subependymal astrocytoma	Childhood-adolescence
Single or multiple cardiac rhabdomyoma	Fetal stage
Lymphangioleiomyomatosis	Adolescent-adult
Renal angiomyolipoma	Childhood-adult
Minor Criteria	
Multiple pits in dental enamel	
Hamartomatous rectal polyps	
Bone cysts	
Cerebral white-matter radial migration lines	
Gingival fibromas	
Nonrenal hamartomas	
Retinal achromic patches	
Confetti skin lesions	
Multiple renal cysts	

Definitive diagnosis: 2 major criteria or 1 major and 2 minor; probable: 1 major and 1 minor; possible: 1 major and 2 or more minor

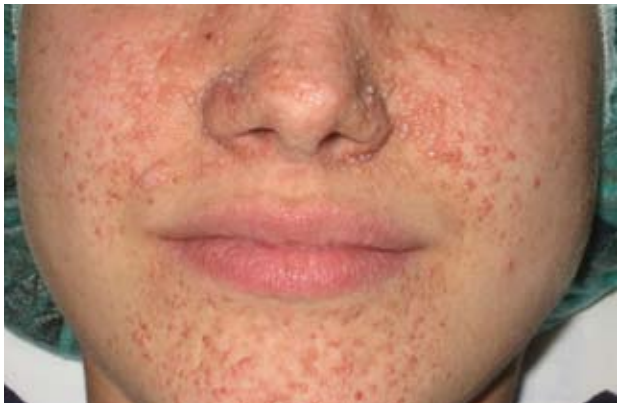

Figure. Angiofibromas on the cheeks, chin, and nose, with a predominant crazy paving pattern and bilateral distribution.

Table 2. Abnormalities Found in the Patients

Abnormality	*Type of Abnormality*	*Frequency in Our Series*	*Frequency in the Literature*
Dermatological (100%)	Angiofibromas	89.6% (n=60)	74.5%[5]-83%[1]
	Hypomelanotic macules	58.2% (n=39)	97.2%[5]
	Shagreen patch	34.3% (n=23)	48.1%[5]-54%[1]
	Koenen tumor	29.8% (n=20)	68%[1]-74.5%[5]
	Acrochordons	8.95% (n=6)	22.6%[5]
Cardiac (22.4%)	Cardiac rhabdomyomas	22.4% (n=15)	50-70%[6,7]
Psychiatric (55.5%)	Mental retardation	35.8% (n=24)	40-50%[8]
	Behavioral disorders	19.7% (n=12)	40-50%[8]
Neurological (100%)	Epilepsy	67.2% (n=43)	70-80%[5,9]
	CNS tubers	46.2% (n=31)	80%[5,9]
Renal (32.8%)	Angiomyolipoma	25.3% (n=17)	55-75%[5,10]
	Polycystosis	6% (n=4)	3%[5,10]
	Renal cell carcinoma	1.5% (n=1)	2-3%[5,10]
Skeletal (13.4%)	Scoliosis	10.4% (n=7)	NS
	Bone cysts	3% (n=2)	NS
Pulmonary (13.4%)	Pulmonary cysts	7% (n=7)	1-26%[11]
	Abscesses	1.5% (n=1)	NS
	Tuberculosis	1.5% (n=1)	NS
Ophthalmological (11.9%)	Astrocytoma of the optic nerve	1.5% (n=1)	NS
	Retinal hamartoma	10.4% (n=7)	40-50%[12]

Abbreviations: CNS, central nervous system; NS, not specified.

were angiofibromas in 89.6%, followed by hypomelanotic macules in 58.2%, shagreen patches in 34.3%, Koenen tumors in 29.8%, and acrochordons in 8.95%. Fifteen of the 67 patients presented cardiac disorders, all of which were classed as rhabdomyoma (22.4%). Psychiatric disorders were present in 55.5% of the patients, in the form of mental retardation in 35.8% and behavioral disorders in 19.7%. All patients presented neurological disorders: 67.2% were diagnosed with epilepsy and 46.2% presented tubers in imaging studies of the CNS. Renal disorders were present in 32.8%, angiomyolipomas in 25.3%, polycystic kidney disease in 6%, and renal cell carcinoma in 1 patient (1.5%). A total of 9 patients presented skeletal disorders: scoliosis in 7 (10.4%) and bone cysts in 2 (3%). Pulmonary disorders were observed in 9 patients: simple cysts in 7 (10.4%), an abscess in 1 (1.5%), and tuberculosis in 1 (1.5%). Ophthalmological disorders were diagnosed in 10 patients: retinal hamartomas in 7 (10.4%), and astrocytomas of the optic nerve in 3 (4.47%).

The dermatological disorders are summarized in Table 3. Angiofibroma was found in 60 patients and the most frequent location was on the cheeks (78.3%). To a lesser extent, they were located on the nose (48.3%), chin (33.3%), and on the nasogenian fold and forehead (13.3%). The most frequent presentation was crazy paving pattern in 80% and followed by a sebaceous pattern in 20%. The great majority were distributed bilaterally (98.33%), although 1 patient presented a unilateral distribution. Hypomelanotic macules appeared in 39 of the 67 patients. The most frequent shape was lanceolate or ash-leaf pattern (76.92%), followed by confetti pattern (51.28%), and fingerprint form (30.76%). A total of 40% of hypomelanotic macules could not be classified in any of the previous groups. The most typical location was on the anterior thorax (58.97%), legs (56.41%), arms (33.33%), posterior thorax (12.82%), and abdomen (10.25%). Koenen tumors were observed in 20 patients, with similar involvement of the hands (60%) and feet (55%). Sharkskin or shagreen patch was observed in 23 patients, mainly in the lumbar region (73.91%), although it also presented on the dorsal region (21.73%).

Table 3. Description of the Dermatological Disorders

Angiofibromas 89.6 % (n = 60)	Location	Cheeks: 78.3% (n=47)
		Nose: 48.3% (n=29)
		Chin: 33.3% (n=20)
		Nasogenian fold, forehead: 13.3% (n=8)
	Presentation pattern	Crazy paving: 80% (n=48)
		Sebaceous: 20% (n=12
	Distribution	Bilateral: 98.33% (n=59)
		Unilateral: 1.6% (n=1)
Hypomelanotic macules 58.2% (n= 39)	Shape	Lanceolate or ash-leaf: 76.92% (n=30)
		Confetti: 51.28% (n=20)
		Fingerprint: 30.76% (n=12)
		Other: 40% (n=24)
	Location	Anterior thorax: 58.97% (n=23)
		Legs: 56.41% (n=22)
		Arms: 33.33% (n=13)
		Posterior thorax: 12.82% (n=5)
		Abdomen: 10.25% (n=4)
Koenen tumors 29.8% (n=20)	Location	Hands: 60% (n=12)
		Feet: 55% (n=11)
Shagreen patch 34.3% (n= 23)	Location	Lumbar: 73.91% (n=17)
		Posterior trunk: 21.73% (n=5)

Discussion

The term tuberous sclerosis was coined in 1880 by Bourneville.[13] In 1908, Vogt described the classic triad of mental retardation, epilepsy, and facial angiofibroma,[14] which is only present in 29% of the patients.[1] Since then, several studies have been published which have assessed the frequency of the clinical manifestations of the disease. Based on what has been published up until present, a wide clinical spectrum of presentation has been identified. In the last decade, the discovery of the genes implicated in TS (*TSC1* and *TSC2*), observations of *Drosophila melanogaster* models, the improved description of mosaicism, and the variable penetrance of the disease have helped answer the question of why some patients present minimal signs whereas others have serious disorders.

Diagnosis of TS is based on a series of major and minor criteria, since no single clinical criterion is of diagnostic value. The clinical manifestations of TS appear during different developmental periods (Table 1)[4]; thus, the validity of these criteria for early diagnosis is limited because some occur in late childhood or adolescence, and are further confounded by the numerous cases of atypical presentation. Thus, cardiac rhabdomyomas and cortical tubers appear during fetal development. Skin lesions are observed in 90% of patients of any age. The first to be detected are hypomelanotic macules in early childhood, whereas shagreen patch usually appears after the child is 5 years old. Facial angiofibromas can occur at any age, but mainly appear in late childhood. Periungual fibromas usually occur after puberty. Subependymal astrocytomas can develop in childhood and adolescence, renal angiomyolipomas in early childhood or adolescence, and lymphangioleiomyomatosis in late adolescent girls or adult women. The mean age of our sample was 27.6 years, suggesting that the great majority of skin manifestations had already appeared in these patients.

In our series, all patients presented dermatological disorders. Thus, conducting a detailed dermatological examination in patients with suspected TS is very cost-effective, as well as being widely available and easy to perform. The most frequent finding in our patients was facial angiofibroma (89.6%), whereas in the reviewed literature hypomelanotic macules were the most frequent finding. In a series of 106 children with TS, Jòzwiak[5] observed hypomelanotic macules in 97.2%. In our group

of patients, these appeared in 58.2%. We observed shagreen patch in 34.3%, with frequencies similar to those reported in the literature (48%-54%).[1,5] However, the frequency of Koenen tumors and acrochordons was less than that described in the literature (29.8% and 8.95%, respectively).

No detailed study of the dermatological lesions appears in the reviewed literature. In our sample, the most frequent form of presentation of angiofibroma was on the cheeks (78.3%), with a crazy paving pattern (80%) and bilateral location (98.33%). Other less frequent locations were the nose (48.3%) and chin (33.3%). One patient presented lesions with a unilateral distribution, probably as a segmental type I manifestation of mosaicism,[15] since all the patients were formally diagnosed with TS. These skin lesions cause patients severe esthetic, psychological, and medical problems. The current treatment of choice for angiofibroma is laser therapy, since it provides the most selective form of lesion destruction, minimizing residual thermal damage and, thus, adverse effects. The treatment of choice for angiofibroma with a high fibrous component or for protruding angiofibroma is carbon dioxide laser therapy administered in different modes. In a recently published retrospective study conducted in our center, the long-term results of carbon dioxide laser treatment (continuous and superpulsed modes) for angiofibromas were assessed.[16] That study demonstrated a high percentage of recurrences (60.9%), despite the good and even excellent initial outcomes. Recurrences occurred earlier when the patients were treated before reaching 20 years of age.

The most frequent type of hypomelanotic macules were ash-leaf shaped (76.92%), as described in the classic form of the disease. Confetti pattern (51.28%) and fingerprint forms (30.76%) were less common. A total of 40% of macules could not be classified into any of the previous forms, once again indicating the clinical variability of this disease. The most common location was on the anterior thorax and arms and legs. Koenen tumors were almost equally distributed between the hands and feet (60% and 55%, respectively). Shagreen patch was most frequently located in the lumbar region (73.91%) as described in the classic texts; however, some were located in upper areas of the body, such as the posterior trunk (21.3%).

As was the case for dermatological disorders, all patients in our series presented neurological disorders. These are the leading cause of morbidity and mortality in patients with TS and include epilepsy and findings of cortical tubers detected by neuroimaging techniques (computerized tomography [CT] or magnetic resonance imaging [MRI]). These 2 findings are closely linked as tubers are the cause of the seizures. Tubers are developmental disorders of the cerebral cortex. Histological study shows that its normal organization into 6 layers is lost and abnormally-shaped neurons, large astrocytes, and a special type of cell known as a giant cell can be observed.[17] These persist throughout life and are benign, except for any direct symptoms that may arise. According to the literature, up to 70%-80% of patients with TS present epilepsy[5,9] and 80% present cortical tubers.[5,9] The percentages are again lower in our series of patients, with epilepsy diagnosed in 67.2% and findings of tubers in the CNS in 46.2%.

The third most prevalent disorder was psychiatric and affected 55.5% of the patients. Mental retardation was diagnosed in 35.8% and almost 20% had behavioral disorders. In the literature, these percentages are as high as 40%-50%[8]; however, these figures pool patients with psychological disorders and those with mental retardation in general, rather than treating them separately as we did. These types of disorder are also closely associated with the presence of cortical tubers, especially those located in the forebrain. The behavioral disorder most frequently associated with TS was autism.[5]

Specific renal disorders are found in close association with TS. Angiomyolipoma is the most frequent manifestation, since it appears in 55%-75% of the patients. Angiomyolipomas are benign tumors made up of abnormal vessels, immature smooth muscle cells, and fat cells. In some patients with TS, these are bilateral and multiple.[10] They are detected by echography, CT, or MRI. Their main complication, especially in those larger than 3 cm, is bleeding.[5,10] This was detected in 25.3% of our patients. Other findings were polycystic kidney disease in 6% (3% in the literature) and renal cell carcinoma in 1.5% (2%-3% in the literature). The incidence of renal cell carcinoma in the general population is similar to that of patients with TS, although this is usually diagnosed in the latter group at earlier ages.[10]

Cardiac rhabdomyoma is an intracavitary or intramural tumor that has been detected in 50%-70% of patients, but leads to a far lower percentage of problems among them. It usually presents as heart failure during childhood and as tachyarrhythmias. It is one of the first manifestations of TS and can be detected in utero, and is one of the main prenatal diagnostic markers of TS. In addition, it is the most frequently detected cardiac tumor during the neonatal period.[7] This was found in a lower percentage (22.4%) of our patients.

The most commonly associated pulmonary lesion is lymphangioleiomyomatosis, and appears in women affected by TS in the second or third decade of life. It is characterized by smooth muscle cell proliferation leading to pulmonary cyst formation and pneumothorax. It worsens during pregnancy and with the administration of estrogens.[5,18] In the literature, it appears in 57% of the patients affected with TS,[11] whereas in our series it was

diagnosed in only 7%. It was only studied in clinical cases in our group, and thus patients presenting subclinical changes were not identified. This fact may explain the lower percentages found in our study.

Retinal hamartomas are the ocular disorders most frequently associated with TS and appear in 40%-50% of patients. They remain stable and asymptomatic during the patient's lifetime.[12] In our series, a lower percentage of 10.4% was observed, perhaps due to the low mean age of our patients (27 years), given that the incidence of retinal hamartomas increases with age.

In general, in our series of patients, there were fewer clinical findings than those reported in the reviewed literature. This could be due to the limitations of the study itself (retrospective study, the inclusion method, and the low number of patients). On the other hand, in clinical terms, TS is a highly polymorphic disease that includes a broad spectrum of disorders, ranging from very mild cases to severe ones, and with variable expression over time—observations which could explain the different percentages found. Nevertheless, our series constitutes research conducted in clinical practice, and the patients, with specific disorders, were not studied in the same manner, since the complementary tests were determined by the symptoms present. However, if the associated disorders in our series of patients and those in the reviewed literature (Table 4) are ordered by frequency, the observed differences are minimal, confirming that at least the relative orders tally.

We report the clinical findings in a series of patients with TS and compare them to previously published findings. Few studies of this type have been conducted, and the present study is the first one conducted in a Spanish population. Overall, our findings support those already published, although some small differences were observed.

Table 4. Manifestations of Tuberous Sclerosis in Descending Frequency as Reported in the Literature and in our Series of Patients

Reviewed Literature	*Current Series*
Dermatological	Dermatological
Neurological	Neurological
Renal	Psychiatric
Cardiac	Renal
Psychiatric	Cardiac
Ophthalmological	Pulmonary
Pulmonary	Ophthalmological

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. Webb DW, Clarke A, Fryer A, Osborne JP. The cutaneous features of tuberous sclerosis: a population study. Br J Dermatol. 1996;135:1-5.
2. Jòzwiak S, Schwartz RA, Janninger CK, Bielicka-Cymerman J. Usefulness of diagnosis criteria of tuberous sclerosis complex in paediatric patients. J Child Neurol. 2000;15:652-9.
3. Cheadle JP, Reeve MP, Sampson JR, Kwiatkowski DJ. Molecular genetics advances in tuberous sclerosis. Hum Genet. 2000;107:97-114.
4. Crino PB, Nathanson KL, Henske EP. The tuberous sclerosis complex. N Engl J Med. 2006;355:1645-56.
5. Jòzwiak S, Schwartz RA, Janniger CK, Michalowicz JC. Skin lesions in children with tuberous sclerosis complex: their prevalence, natural course and diagnostic significance. Int J Dermatol. 1998;37:911-7.
6. Jozwiak S, Kotulsa K, Kasprzyk- Obara J, Domanska-Pakiela D, Tomyn-Drabik M, Roberts P, et al. Clinical and genotype studies of cardiac tumours in 154 patients with tuberous sclerosis complex. Pediatrics. 2006;118:e1146-51.
7. Bader RS, Chitayat D, Helly E, Ryan G, Smallhorn JF, Toi A, et al. Fetal rhabdomyoma: prenatal diagnosis, clinical outcome, and incidence of associated tuberous sclerosis complex. J Pediatr. 2003;143:620-4.
8. Prather P, de Vries P. Behavioural and cognitive aspects of tuberous sclerosis complex. J Child Neurol. 2004;19:666-74.
9. Weiner HL. Tuberous sclerosis and multiple tubers: localizing the epileptogenic zone. Epilepsia. 2004;45:41-2.
10. O'Callaghan FJ, Noakes MJ, Martyn CN, Osborne JP. An epidemiological study of renal pathology in patients with tuberous sclerosis complex. BJU Int. 2004;94:451-6.
11. Vicente MP, Pons M, Medina M. Pulmonary involvement in tuberous sclerosis. Pediatr Pulmonol. 2004;37:178-80.
12. Rowley SA, O' Callaghan FJ, Osborne JP. Ophthalmic manifestations of tuberous sclerosis: a population-based study. Br J Ophtalmol. 2001;85:420-3.
13. Bourneville DM. Sclèrose tubéreuse des circonvolution cérébrales: idiotie et épilepsie hemiplégique. Arch Neurol. 1880;1:81-91.
14. Vogt H. Zur Daignostik der tuberosen sklerose. Z Erfrosch Behandl Judeudl Schwachsinns. 1908;2:1-6.
15. Happle R. Segmental type 2 manifestation of autosome dominant skin diseases. Development of a new formal genetic concept. Hautarzt. 2001;52:283-7.
16. Belmar P, Boixeda P, Baniandrés O, Fernández-Lorente M, Arázola JM. Seguimiento a largo plazo de angiofibromas tratados con láser de CO2 en 23 pacientes con esclerosis tuberosa. Actas Dermosifiliogr. 2005;96:498-503.
17. Goodman M, Lamm SII, Engel A, Shepher CW, Houser OW, Gómez MR. Cortical tuber count: a biomarker indicating neurologic severity of tuberous sclerosis complex. J Chile Neurol. 1997;12:85-90.
18. Schwartz RA, Fernández G, Kotulska K, Józwiak S. Tuberous sclerosis complex: advances in diagnosis, genetics and management. J Am Acad Dermatol. 2007;57:189-202.