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 TSC2 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...
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

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**Table 1. Diagnostic Criteria for Tuberous Sclerosis⁴**

<table>
<thead>
<tr>
<th>Major Criteria</th>
<th>Developmental Age</th>
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<tbody>
<tr>
<td>Angiofibromas or plaque on the forehead</td>
<td>Childhood-adult</td>
</tr>
<tr>
<td>Nontraumatic periungual fibromas</td>
<td>Adolescent-adult</td>
</tr>
<tr>
<td>Hypomelanotic macules (3 or more)</td>
<td>Childhood-adult</td>
</tr>
<tr>
<td>Shagreen patch (connective-tissue nevus)</td>
<td>Childhood</td>
</tr>
<tr>
<td>Multiple retinal hamartomas</td>
<td>Childhood</td>
</tr>
<tr>
<td>Cortical tubers</td>
<td>Fetal stage</td>
</tr>
<tr>
<td>Subependymal nodules</td>
<td>Childhood-adolescence</td>
</tr>
<tr>
<td>Subependymal astrocytoma</td>
<td>Childhood-adolescence</td>
</tr>
<tr>
<td>Single or multiple cardiac rhabdomyoma</td>
<td>Fetal stage</td>
</tr>
<tr>
<td>Lymphangioleiomyomatosis</td>
<td>Adolescent-adult</td>
</tr>
<tr>
<td>Renal angiomyolipoma</td>
<td>Childhood-adult</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Minor Criteria</th>
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<tbody>
<tr>
<td>Multiple pits in dental enamel</td>
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<tr>
<td>Hamartomatous rectal polyps</td>
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<tr>
<td>Bone cysts</td>
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<tr>
<td>Cerebral white-matter radial migration lines</td>
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<tr>
<td>Gingival fibromas</td>
</tr>
<tr>
<td>Nonrenal hamartomas</td>
</tr>
<tr>
<td>Retinal achromic patches</td>
</tr>
<tr>
<td>Confetti skin lesions</td>
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<tr>
<td>Multiple renal cysts</td>
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</tbody>
</table>

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

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**Figure.** Angiofibromas on the cheeks, chin, and nose, with a predominant crazy paving pattern and bilateral distribution.
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 7 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 hamartoma 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%).
Discussion

The term tuberous sclerosis was coined in 1880 by Bourneville. In 1908, Vogt described the classic triad of mental retardation, epilepsy, and facial angiofibroma, which is only present in 29% of the patients. 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); 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 angiomylipomas 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, Józwiak observed hypomelanotic macules in 97.2%. In our group

### Table 3. Description of the Dermatological Disorders

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

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. They are detected by echography, CT, or MRI.
Their main complication, especially in those larger than
3 cm, is bleeding. 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.

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. 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. In the literature, it appears in 57% of the
patients affected with TS, whereas in our series it was

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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. 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, with TS and compare them to previously published findings. 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.

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

<table>
<thead>
<tr>
<th>Reviewed Literature</th>
<th>Current Series</th>
</tr>
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<tbody>
<tr>
<td>Dermatological</td>
<td>Dermatological</td>
</tr>
<tr>
<td>Neurological</td>
<td>Neurological</td>
</tr>
<tr>
<td>Renal</td>
<td>Psychiatric</td>
</tr>
<tr>
<td>Cardiac</td>
<td>Renal</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>Cardiac</td>
</tr>
<tr>
<td>Ophthalmological</td>
<td>Pulmonary</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Ophthalmological</td>
</tr>
</tbody>
</table>

Conflicts of Interest
The authors declare no conflicts of interest.

References