CASE REPORTS

Tuberous sclerosis complex: report of two intrafamilial cases, both in mother and daughter

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Abstract

Tuberous sclerosis complex (TSC) is a multisystem syndrome characterized by neurological symptoms and tumors in multiple organs including kidney, brain, skin, eyes, heart and lung. Kidney and brain are the two most frequently affected organs in TSC. TSC is an autosomal disorder with extensive clinical variability. We described TSC in a family at a mother and her daughter. We emphasized the importance of Computed Tomography in the discovery of some asymptomatic organic involvement as bilateral renal angiolipoma in the mother.

Keywords: tuberous sclerosis, hamartoma, angiofibroma.

Introduction

Tuberous sclerosis complex (TSC) is an inherited neurocutaneous disorder characterized by the potential for the presence of hamartomas in almost every organ, most notably in the skin, brain, kidney, heart and eyes [1]. The condition was described by von Recklinghausen in 1862 [2].

In 1880, Bourneville described the pathologic features of the sclerotic tubers found post mortem in patients with epilepsy and mental retardation and coined the term “sclerose tuberuse” [1].

The term “tuberous sclerosis” refers specifically to the presence of multiple sclerotic masses scattered throughout the cerebrum. The diagnosis of TSC is based on the identification of hamartomas in more than one organ system. A hamartoma is a benign tumor composed of an overgrowth of mature cells and tissues that normally occur in the affected tissue, but often with one predominating element. The hamartoma formation is most notable in the skin, brain, kidneys, heart and eyes [1].

The kidney and brain are two of the most frequently affected organs in TSC [3].

The disease is an autosomal disorder with extensive clinical variability. The presence of hamartomas in two different organ systems is considered by some clinicians to be sufficient for the diagnosis [4].

Patients and Methods

We will describe two cases of patients belonging to the same family, a mother (case no. 1), aged 34-year-old and her daughter (case no. 2), aged 4, both displaying cutaneous TSC – suggesting lesions on their faces. Moreover, the woman told us that her daughter has been suffering from infantile spasms since she was 3-year-old. She consulted many specialists and was recommended a CT examination. Apart from this, the girl is well-developed physically and intellectually, according to her age. The woman is apparently in complete health condition, without any subjective signs of neurological, renal, pulmonary or digestive affections. The family history shows that all the other family members are apparently healthy, with normal intellect. Both cases were highly examined clinically and paraclinically. There were drawn fragments from the cutaneous lesions and histopathologically examined. Cutaneous fragments were fixed in 10% formalin paraffin-embedded and routinely stained with Hematoxylin–Eosin. Imagistic tests were used to discover organic affections without any clinical expression, and in this case CT was preferred. CT scanning was performed with a 5 mm slice thickness and interval native, after intravenous administration by bolus injection of nonionic contrast material at rate of 1 mL/s, on a CT Philips Aura. A CT-scan indicated clear pointed nodular calcifications.
Results

General clinical examination was performed within normal limits for both the mother (case no. 1) and her daughter (case no. 2). During dermatologic examination, both mother and daughter presented pink to red small nodules of 1–5 mm diameter symmetrically distributed in the nasolabial folds, cheeks and nose. Most of the nodules were yellowish and firm, others were telangiectatic and soft, with a glossy smooth surface (Figures 1 and 2). The lesions were conspicuous in case no. 1 (the mother) (Figure 2). Besides, the woman had some small pulpous bud-like proliferations emerging from peri-nail folds (Figure 3) at fingers and toes and numerous confetti, hypopigmented macules on the trunk and lower extremities. At the ophthalmologic examination, the woman’s diagnosis was “optic primitive atrophy, whitish juxta-papillar placard of the left eye and thin arteries with whitish striations in the right eye”. Histopathologically, in both cases the images are typical for angiofibroma (misnamed adenoma sebaceum).

In the second case, the epithelium presents minimum acanthosis with hyperkeratosis and parakeratosis, associated with fibroblastic proliferation of capillary elements in superficial derma, with marked atrophy of sebaceous glands, typical changes of an angiofibroma (Figure 4, a and b).

Figure 1 – Pink to red small nodules symmetrically distributed in the nasolabial folds, cheeks and nose.

Figure 2 – Pink to red, yellowish and telangiectatic small nodules of 1–5 mm diameter, with glossy smooth surface symmetrically distributed in the nasolabial folds, cheeks and nose.

Figure 3 – Periungual fibromas (Könen tumors); smooth buds flesh-colored at the base of nail and periungual with partial disrupt of the nail.

Figure 4 – (a) Squamous epithelium fragment with minimum acanthosis and parakeratosis (HE stain, ob. 10×); (b) Fibrovascular proliferation with atrophy of sebaceous gland (HE stain, ob. 20×); (c) Squamous epithelium fragment with marked acanthosis, parakeratosis and papillomatosis (HE stain, ob. 10×); (d) Derma–perivascular fibromatous proliferation (HE stain, ob. 20×); (e) Diffuse and perivascular sclerofibrous proliferation with dilatation of sebaceous glands (HE stain, ob. 10×); (f) Periglandular sclerofibrous proliferation (HE stain, ob. 20×).
In the first case, covering epithelium shows marked papillomatosis, acanthosis, hyperkeratosis and parakeratosis. In subjacent derma, histopathological examination shows dense fibrous connective tissue and perivascular proliferation with marked atrophy of sebaceous glands (Figure 4, c and d), which alternates with diffuse fibrous sclerosis and also periglandular fibrous proliferation, with circumferential arrangement. Intraglandular eosinophilic content (Figure 4, e and f) it is an argument for sebaceous adenoma. Both described forms – angiofibroma and sebaceous adenoma – are characterized by a marked fibroblastic proliferation with pericapillar and periglandular sclerohyaline dystrophy.

Histopathological examination of the other cutaneous lesions at mother shows:
- only vascular fibrous tissue in periungual tumor;
- excessive collagen in lumbar lesion;
- white macules localized on the trunk containing abnormal melanocytes.

Computed tomography shows:
- at the daughter: calcified subependymal nodule periventricular – IVth ventricle (Figure 5a), and along the lateral border of temporal horn of right lateral ventricle; cyst-like lesions in the white matter and punctate calcifications conglomerated in left cerebellar hemisphere with serpiginous enhancement (Figure 5b), and smaller calcified nodules in the subependymal region of both lateral ventricles and in the cortex of the parietal region (Figure 5c);
- at the mother: subependymal calcified nodules in the typical sites, along the lateral walls of the body of the lateral ventricles (Figure 6a); multiple angiofibrolipoma at left kidney (Figure 6b), and right kidney (Figure 6, c and d).
Discussion

Tuberous Sclerosis Complex (TSC) is an autosomal dominant disorder characterized by hamartomas in many organs [5]. It is an inherited disease with almost complete penetrance but variable expressivity [6, 7]. Two-thirds (65%) of cases are sporadic and are thought to represent new mutation [5, 8, 9]. Two genes associated with TSC have been cloned: TSC1 located on the long arm of chromosome 9 (9q34) and TSC2 located on the short arm of chromosome 16 (16p13.3). TSC1 encodes hamartin and TSC2 encodes the protein tuberin. TSC is caused by mutations affecting either of the presumed tumor suppressor genes, TSC1 and TSC 2. Both appear to function as tumor suppressor genes, because different manifestations can develop in affected members of the same family [10]. This disorder affects about 1 per 100 000 individuals in the USA and Western Europe. It has a worldwide distribution and involves both sexes.

Clinical presentation

The disease has protein manifestations and affects every organ, even though the classic features are mental deficiency, epilepsy and adenoma sebaceum.

Four types of skin lesions are pathognomonic:

1. Adenoma sebaceum (Pringle) or facial angiofibroma is rarely present at birth but usually appears around the age of 5 to 6-year-old. The lesions increase in size and number until puberty and remain stationary thereafter. They are pink to red nodules with a smooth, glistening surface [11], symmetrically distributed in the nasolabial folds, cheeks, and nose in a butterfly pattern. The upper lip is notably spared [11]. The chin, ears, forehead, and eyelids may be involved. The lesions are usually discrete, but occasionally they may coalesce. Facial angiofibromas are comprised of vascular and connective tissue elements and are found in approximately 75% of patients with TSC [6]. Forehead plaque, a variant of angiofibromas, is seen in up to 20% of patients with TSC [6, 12]. These lesions appear in early childhood, grow very slowly, and present as firm, elevated plaques that are yellow-brown to flesh-colored [6].

2. Hypomelanotic macules or “ash leaf spots” named after the European mountain ash tree [12] are usually present at birth and almost all lesions are evident within the first two years of life [6]. Typically, the macules are rounded at one end and tapered on the other. These macules are found in more than 90% of patients with TSC [6]. In fair-skinned individuals, Wood’s light helps in their detection [11]. They may be the only cutaneous sign of tuberous sclerosis and that is why they are of great diagnostic importance.

3. The shagreen or “leather” patch is an irregularly shaped plaque of thickened skin, slightly elevated, with a “peau d’orange” surface. Characteristically, the patch is in the lumbosacral region and is the result of an accumulation of collagen. Occasionally, a central patch may have smaller satellite lesions around [11]. The shagreen patch is found in 20% to 30% of patients with TSC [13].

4. Periungual and ungual fibromas (Köenen tumors) are found in approximately 20% of unselected patients with TSC and are more common in adolescents and adults than in young children [13]. These tumors appear as smooth buds at the base of the nail or subungually and may reach a size sufficient to disrupt the nail bed [11]. They are flesh-colored, usually multiple, and may affect fingers and toes. The nails of toes are more commonly involved than those of the fingers [12, 14]. These lesions occasionally develop subsequent to trauma [13].

Other less pathognomonic lesions are multiple skin tags of the neck and axillae, “café au lait” spots in up to 30% of patients with TSC [6], confetti lesions (stippled hypopigmentation), polyoma (a white patch or forelock) and thumbprint macules [13, 15]. Neurological manifestations are often the presenting feature and major cause of morbidity/mortality. Symptoms of cortical tubers may include seizures, mental retardation, learning disabilities, and abnormal behavior. Seizures have a focal or multifocal origin, this clinical feature depending on the localization of the cortical tubers [16]. The most common types of seizures are infantile spasm, partial motor seizures, and generalized tonic clonic seizures [15, 16]. Infantile spasms are most common during infancy. Epilepsy associated with TSC is often intractable, but seizure control has benefited from the introduction of the new antiepileptic drugs. Mental retardation occurs in approximately 50% of patients with TSC. Almost all mentally retarded children will have seizures. Conversely, many patients with TSC have seizures, but not mental retardation [15].

In general, the earlier the onset of the seizures is particularly infantile spasms, the greater the risk of mental retardation, cognitive impairment, and behavioral disorders [18, 20]. The intracranial abnormalities include tubers, subependymal nodules and subependymal giant cell astrocytomas [21]. No correlation was found between the number of subependymal lesions and the clinical severity of TSC. Computed tomography (CT) and magnetic resonance (MR) features of the brain lesions in patients TSC were an important support for diagnostic. CT clearly demonstrates calcified subependymal nodules. MR imaging more clearly demonstrates cortical and white matter lesions than CT, since MR imaging provides an excellent image. Contrast between various normal structures and high sensitivity in detecting pathological states due to intrinsic differences in proton density and in particular, in proton relaxation times of tissues [22]. Renal manifestations of TSC are a very significant cause of morbidity and mortality [23].

Three types of tumors occur in TSC kidneys: (1) angiomyolipomas, which are benign tumors composed of smooth muscle, fat and vessels; (2) epithelial cysts; and (3) malignant tumors [3]. Angiomyolipomas are the most common renal lesions. They are found in as many as 75–80% of the affected children older than 10 years [13] and must be distinguished from multiple renal cysts that occur less commonly. Females are more often affe-
lesions have been described including classic “mulberry”
most lesions are asymptomatic. Three types of retinal
with TSC and are bilateral in a third of cases [30, 31].
Retinal hamartomas occur in 40% to 50% of patients
maximal size, and cause the most clinical symptomato-
thirds of newborn infants with TSC and are usually
angiomyolipomas in this disease. Other organs are also
uishing multiple renal cysts from the more common
ography, CT and arteriography are important in disting-
mal tubule [26]. The combination of cystic kidneys and
is lined by a distinct, perhaps unique epithelium of marked hypothro-
and renal impairment, although relatively uncommon,
may occur before other evidence of the syndrome [27–
Renal cysts are identified in children younger than
to present angiomyolipomas [30]. Cysts greater
4 cm in diameter are more likely to be symptomatic
adrenal gland, and number with age [7, 13]. Typical angiomyolipomas
usually do not cause symptoms, but lesions larger than
4 cm in diameter are associated to an increased risk of
serious hemorrhage [7, 13]. Epithelioid angiomyolipoma-
oma is a recognized variant with malignant potential.

The second most frequent renal manifestation is a
renal cyst. The tubule cysts in this disease are lined by a
distinct, perhaps unique epithelium of marked hypertro-
 Entwicklung of the growth of angiomyolipomas [25]. Angiomyolipomas are benign tumors
composed of blood vessels with thickened walls, imma-
ture smooth muscle cells, and adipose tissue [7]. The
lesions are often multiple and bilateral and grow in size
and number with age [7, 13]. Typical angiomyolipomas
are benign but may have alarming properties: nuclear
pleomorphism and mitotic activity, extension in the
vena cava, and spread to regional lymph nodes, without
malignant progression [25]. Smaller angiomyolipomas
are often multiple and bilateral and grow in size
usually do not cause symptoms, but lesions larger than
4 cm in diameter are associated to an increased risk of
serious hemorrhage [7, 13]. Epithelioid angiomyolipoma-
oma is a recognized variant with malignant potential.

In the two cases of patients, belonging to the same
family whom we presented above, we can find out two
major criteria necessary for TSC diagnosis. However,
we must underline the importance of their imagistic
investigations, respectively CT, to discover any organic
alteration, which most of the time evolves asymptomati-
cally during long periods, but undergoes major complica-
tions. In case no. 1 (the woman’s case), following
imagistic investigations, there was discovered a signific-
ant renal affection – the presence of angiomyolipoma.

### Table 1 – Diagnostic criteria of TSC

<table>
<thead>
<tr>
<th>Major features</th>
<th>Minor features</th>
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<tr>
<td>Facial angiofibromas or forehead plaque;</td>
<td>• Multiple randomly distributed pits in dental enamel;</td>
</tr>
<tr>
<td>Nontraumatic ungual or periungual fibroma;</td>
<td>• Hamartomatic rectal polyps;</td>
</tr>
<tr>
<td>Hypomelanotic macules – more than three;</td>
<td>• Bone cysts;</td>
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<tr>
<td>Shagreen patch (connective tissue nevus);</td>
<td>• Cerebral white-matter “migration tracts”;</td>
</tr>
<tr>
<td>Cortical tuber;</td>
<td>• Gingival fibromas;</td>
</tr>
<tr>
<td>Subependymal nodule;</td>
<td>• Nonrenal hamartoma;</td>
</tr>
<tr>
<td>Subependymal giant cell astrocytoma;</td>
<td>• Retinal achromic patch;</td>
</tr>
<tr>
<td>Multiple retinal nodular hamartomas;</td>
<td>• “Confeti” skin lesions;</td>
</tr>
<tr>
<td>Cardiac rhabdomyoma, single or multiple;</td>
<td>• Multiple renal cysts.</td>
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<tr>
<td>Lymphangiomatomatosis;</td>
<td></td>
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<tr>
<td>Renal angiomyolipomas.</td>
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</tbody>
</table>

*Definite TSC – either two major features or one major feature plus two minor features; **Probable TSC – one major and one minor features; ***Possible TSC – either one major feature or two or more minor characteristics are present [34].

In the two cases of patients, belonging to the same family whom we presented above, we can find out two major criteria necessary for TSC diagnosis. However, we must underline the importance of their imagistic investigations, respectively CT, to discover any organic alteration, which most of the time evolves asymptomatically during long periods, but undergoes major complications. In case no. 1 (the woman’s case), following imagistic investigations, there was discovered a significant renal affection – the presence of angiomyolipoma. They are generally benign, but may lead to serious complications. On the other hand, a cranial affection was discovered at the woman’s daughter. Children seem to develop subependymal giant cell astrocytomas, possibly more frequently than adults do. These tumors are histologically benign but are locally invasive and may cause hydrocephalus because of their typical occurrence in the anterior lateral ventricle. Early identification of an enlarging giant cell tumor enables it to be removed before symptoms development and before it becomes locally invasive, probably reducing the likelihood of tumor
residual or recurrence. It is recommended for the children to undergo periodic cranial imaging with either CT or MRI scans every one to three years, depending on the level of clinical suspicion in a given child. It is also necessary an examination of the other family members who do not have any clinical obvious TSC manifestation, CT being the most preferred test. MRI may be more sensitive than CT, but it often detects lesions that are not so specific to TSC.

Conclusions

Clinical and histopathological examinations are essential because many of the major features of TSC are cutaneous, and these lesions often herald the diagnosis. Imaging evaluation plays an important role in the assessment of patients with tuberous sclerosis complex. In newly diagnosed patients, they help both to confirm the diagnosis of TSC and to identify clinically significant complications. For patients with a well-established TSC diagnosis, sometimes we can identify treatable complications in early stage. These investigations sometimes also provide evidence of TSC in asymptomatic patients with TSC.

References


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