Tuberous Esclerosis in different organs

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Learning objectives

- Identify the radiologic features of multiorganic involvement in patients with tuberous sclerosis.

- Identify which organ manifestations can be the clue to suspect the presence of tuberous sclerosis even if no clinical signs are found.
Tuberous sclerosis (TS) is an autosomal dominant genetic disease characterized by a variety of hamartomatous lesions that involves multiple organ systems. TS does not have racial or sexual predilection. The estimated prevalence is around 1 in 6,000 live births, and approximately two-thirds of the cases are sporadic.

Two different genes mutations have been identified in patients with TS: TSC1 and TSC2. Both genes are tumor suppressor genes that help to regulate cell growth and differentiation.

TSC1 is situated on the long arm of chromosome 9 and encodes the protein hamartin. The mutations on this gen are less common than on the other one and its clinical phenotype is slightly different: less risk of intellectual impairment, a lower frequency of seizures, fewer subependymal nodules...

The TSC2 is located on the short arm of chromosome 16 and encodes a protein called tuberin. The location of the TCS2 gene is contiguous with the polycystic kidney disease 1 (PKD1) gene, that is why multiple renal cysts are described in patients with TS. The phenotype of these patients is more expressive and they have increased risk of renal cysts than those with mutations on TSC1.

Classically, TS has been characterized by the clinical triad of: mental retardation, epilepsy and adenoma sebaceum. However, recent experience has shown that half of TS patients have normal intelligence and that a quarter do not have epilepsy.

As a result of the high clinical variability of TS, there have been established either mayor and minor criteria to make the diagnosis of esclerosis tuberosa (Table 1).

Infantile spasms or myoclonic seizures that begin in infancy or early childhood are the presenting symptom of approximately 80% of patients, and they are not common in neonates.

<table>
<thead>
<tr>
<th>Major Features</th>
<th>Minor Features</th>
</tr>
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<tbody>
<tr>
<td>Cutaneous manifestations:</td>
<td>Cutaneous manifestations:</td>
</tr>
</tbody>
</table>
- Facial angiofibromas
- Hipomelanotic macules (more than three).
- Shagreen patch (connective tissue nevus).
- Nontraumatic ungula or periungual fibromas.
- "Confetti" skin lesions.

<table>
<thead>
<tr>
<th>Intracranial manifestations:</th>
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</tr>
</thead>
<tbody>
<tr>
<td>- Cortical tubers</td>
<td>- Cerebral white matter radial migration lines.</td>
</tr>
<tr>
<td>- Subependymal nodules</td>
<td></td>
</tr>
<tr>
<td>- Subependymal giant cell astrocitoma.</td>
<td></td>
</tr>
</tbody>
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<thead>
<tr>
<th>Non-central nervous system manifestations:</th>
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</tr>
</thead>
<tbody>
<tr>
<td>- Retinal hamartomas</td>
<td>- Retinal achromatic patches.</td>
</tr>
<tr>
<td>- Cardiac rhabdomyomas.</td>
<td>- Multiple pits in dental enamel.</td>
</tr>
<tr>
<td>- Lymphangioleiomyomatosis.</td>
<td>- Gingival fibromas.</td>
</tr>
<tr>
<td>- Renal angiomyolipoma.</td>
<td>- Multiple renal cysts.</td>
</tr>
<tr>
<td></td>
<td>- Bone cysts.</td>
</tr>
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<td></td>
<td>- Hamartomatous rectal polyps.</td>
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- **Definite TSC:** Either two major features, or one major plus two minor features.
- **Probable TSC:** One major plus one minor feature.
- **Possible TSC:** Either one major feature or two or more minor features.

**Notes:**

a) Cortical tubers together with cerebral white matter radial migration lines are counted as one feature if they occur together.

b) When both Lymphangioleiomyomatosis and renal angiomyolipomas are present, other features should be present before a definite diagnosis.
Imaging findings OR Procedure details

Cutaneous Manifestations:

**Adenoma sebaceum** Fig. 1 on page is a characteristic component of tuberous sclerosis that appears between 1 and 5 years in 75% of the patients. It is a nodular rash of brownish red colour over the face. It typically originates on the nasolabial folds and spreads over the nose and the middle of the cheeks (butterfly pattern). Histologically are angiofibromas.

**Hypopigmented macules, Fig. 2 on page 10** called also "ash leaf spots" occur in more than 90% of patients with TS. They appear sooner than adenoma sebaceum; they are often present at birth.

Detection of at least three of these skin lesions can be a first step in diagnosis of TS, because they are the only major diagnostic criteria that can be evaluated under clinical examination.

Neurologic involvement:

Characteristic neurological abnormalities are present in more than 95% of affected patients; and they are present before the time of birth. Because of that, neuroimaging plays an important role in the diagnosis of TS.

**Cortical tubers:**

Cortical tubers are developmental abnormalities of the cerebral cortex in patients with TS that appear as enlarged, atypically shaped gyri. Histologically, they are indistinguishable from focal cortical dysplasia both histologically and on neuroimaging. The number of cortical tubers is supposed to be in relation with neurologic manifestations: If a patient has many tubers he will tend to have more cognitive impairment and more difficulty for seizure control.

Approximately 50% of cortical tubers are seen in the frontal lobe, although they can appear anywhere. They are more common supratentorial and tend to calcify.
On CT cortical hamartomas appear as lucencies within broadened cortical gyri in neonates and youth children. With age, they are difficult to recognize if they are not calcified.

Magnetic resonance (MR) imaging is better than CT for detection of cortical tubers. It is useful to know that their appearance change with age.

Tubers have a low intensity center on T1-weighted images and high signal intensity on T2-weighted and FLAIR images. Fig. 3 on page 11

In newborns, the brain white matter is unmyelinated. Because of this, tubers tend to show a higher signal than the surrounding white matter on T1 weighted and lower intensity on T2-weighted images. At some point of the myelination process, the signal becomes the same of the surrounding white matter, and the tubers may be very difficult to recognize both on T1 and T2-weighted images. On follow-up MR studies, tubers will end up showing their classic radiological appearance when the brain gets wholly myelinated.

In adults, when the brain is mature, cortical tubers become isointense with normal white matter on T1- weighted images, and hyperintense on T2-weighted images.

Calcification and central cystic degeneration may occur.

**Subependymal nodules and subependymal giant cell astrocytoma (SGCA):**

Subependymal nodules represent hamartomatous changes in subependymal tissue, so they tend to be located along the ventricular surface, typically along the caudate nucleus (sulcus thalamo-striatus), posterior to the foramen of Monro. 88% of them calcify over the years. CT is useful for detecting subependymal nodules when they are calcified, but they are rarely calcified within the first year of life. Fig. 4 on page 12

In neonates, subependymal hamartomas can be detected by transfontanelle sonography, on which they can appear as echogenic subependymal masses. Germinal matrix hemorrhages or gray matter heterotopias may look the same on ultrasound.

On MR, subependymal hamartomas appear as irregular subependymal nodules that protrude into the adjacent ventricle. Their appearance changes as the signal of the surrounding white matter changes. Fig. 5 on page 13
On unmyelinated white matter, the hamartomas are relatively hyperintense on T1-weighted images and hypointense on T2-weighted images. As the brain myelinates, they gradually become isointense with the white matter. Subependymal nodules tend to have lower signal intensity on T2-weighted images than do cortical tubers, probably because subependymal nodules have high water content.

T2* weighted images are optimal to show calcification. Fig. 6 on page 14

When we notice that a subependymal hamartoma is enlarging we must think about a Subependymal Giant Cell Astrocytoma (SGCA). They are usually situated near the foramen of Monro, tend to grow into the ventricle and rarely invade the brain parenchyma. Fig. 7 on page 15 y Fig. 8 on page 16. This characteristic location and their tendency to grow usually results in hydrocephalus if the foramen of Monro gets obstructed. Fig. 9 on page 17.

On imaging, SGCAs are identified by the demonstration of tumor growth on serial studies. Neither signal intensity nor the presence or absence of enhancement is useful to differentiate between benign hamartomas and giant cell tumors.

White matter abnormalities:

White matter abnormalities in TS include:

- Superficial white matter abnormalities associated with cortical tubers that reflect areas of hipomyelination. They are seen as high-intensity areas on T2-weighted images and decreased-intensity on T1-weighted images. On the unmyelinated brain these areas show a misleading appearance, with high signal on T1-weighted images and low signal on T2-weighted images. Fig. 10 on page 18, Fig. 11 on page 19, Fig. 12 on page 20, Fig. 13 on page 21, Fig. 14 on page 22 y Fig. 15 on page 23.

- Radial white matter bands reflect altered development along the migratory pathways of neurons and glial cells.

At MR imaging, we can see curvilinear bands of hyperintensity on T2-weighted images and iso- to hypointense to normal white matter on T1-weighted images. Once the white matter becomes well myelinated, they may be difficult to see on T1-weighted images sequences. Fig. 16 on page 24
Cysticlike white matter lesions are less common. They are located in deep white matter, typically near the lateral ventricles.

Cardiac involvement:

Benign rhabdomyomas of the heart are less common than renal hamartomas but are important because they can present as a congenital cardiomyopathy. 50 to 60% of the patients with TS have rhabdomyomas; and conversely, 40-80% of patients with cardiac rhabdomyoma have TS. Thus, if a cardiac rhabdomyoma is found at echocardiography, TS should be highly suspected, even if there are no symptoms or familiar history. Rhabdomyomas show high echogenicity on ultrasound exams, and are often calcified. Fig. 17 on page 25.

They usually occur before the age of 1 year, even intrauterus. Most of them regress before birth, but sometimes they can persist until the age of 4 years.

Pulmonary involvement:

Pulmonary lymphangioleiomyomatosis (LAM) is a rare entity that can be found radiologically in 26-39% of female patients with TS.

It is characterized by diffuse interstitial proliferation of bundles of smooth cells and cystic changes in the pulmonary parenquima.

On CT the typical finding is round, thin-walled cysts of variable size and contour. The distribution is symmetric and uniform throughout the lungs.

Pneumotorax and chylous effusion are the two major complications of LAM. Fig. 18 on page 26.

Lymphangioleiomyomatosis can also affect the retroperitoneum. Histologically is identical to its pulmonary presentation. Radiologically, cystic lesions can be found in the retroperitoneum, which may reflect dilatation of lymph vessels due to obstruction. Fig. 19 on page 27. So that, when retroperitoneal cystic masses are found in patients with TS, we should suspect retroperitoneal LAM, instead of other cystic tumors such as necrotic adenopathy, lymphangioma or abscess.

Renal involvement:
- Renal angiomyolipoma (AML) Fig. 20 on page 28 is a common manifestation of TS with a frequency of 55-75%.

AMLs are the most common benign tumors of the kidney. Although they are sometimes asymptomatic, they may cause variable symptoms. The most alarming complication is their rupture because of their vasculature, associated with the presence of aneurysms. The AMLs seen in patients with TS tend to manifest earlier, are multiple, larger and bilateral in contrast with general population.

With CT we can make the diagnosis of AMLs demonstrating intratumoral fat in a non calcified cortical tumor. But in the cases that it can not be demonstrated, a renal cell carcinoma must be included in our differential diagnosis. Fig. 21 on page 29 y Fig. 19 on page 27.

- Renal cysts or polycystic kidney disease are a minor criteria in patients with TS. They appear in younger children than AMLs do, and are more frequently associated with hypertension or renal failure. Fig. 19 on page 27 y Fig. 21 on page 29.

- In the past, it was said that renal cell carcinoma had a significant association with TS, but recent studies showed that the incidence was the same in general population. The difference is that in patients with TS, tumors appear in younger people and its growth is slower.

Gastrointestinal involvement:

Polyps are the most common gastrointestinal manifestation. They can appear anywhere along the digestive tract and are usually multiple.

Skeletal involvement:

On skeletal radiographs or CT, cortical or medullary cysticlike areas or sclerotic deposits can be found focally or diffusely. Fig. 22 on page 30.

Hyperostosis of the inner calvaria, periosteal new bone formation and scoliosis are other osseous manifestations.
Images for this section:

Fig. 1: Adenoma sebaceum

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Fig. 2: Hypopigmented macules

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Fig. 3: Cortical tubers. Coronal FLAIR image shows frontal cortical tubers as hyperintense. Subependymal giant cell astrocytoma with hydrocephalus is also showed on this image.

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Fig. 4: Noncontrast TC shows calcified hamartomas.

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**Fig. 5:** Axial T2-weighted image with subependymal nodules.

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Fig. 6: Axial DP shows calcified subependymal hamartomas

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Fig. 7: Axial T2-weighted image with a subependymal giant cell astrocytoma on the foramen the Monro.

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**Fig. 8:** Axial DP- image of the same patient of figure 5, which demonstrate the calcification of the SGCA.

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**Fig. 9:** Axial T2-weighted image shows a huge heterogeneous mass consistent with a SGCA which obstructs the foramen of Monro leading to hydrocephalus. There are also subependymal nodules.

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Fig. 10: Sagital T1-weighted image of a 7 day neonate shows white matter anomalies as frontal subcortical hyperintensities without any other finding of TS.

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Fig. 11: Axial T1-weighted image of the same neonate (7 days) of figure 8 shows bilateral frontal hyperintensities in relation with white matter anomalies on an unmyelinated brain.

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Fig. 12: Axial T2-weighted image of the same patient of figures 8 and 9 (7 days) shows curvilinear hypointensities on both frontal lobes which correspond with white matter abnormalities.

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Fig. 13: Sagital T1-weighted image of a follow-up RM of the same neonate in the three previous figures in which the only finding is a mild atrophy. No abnormalities of white matter are found because at this point of myelination the signal of the white matter abnormalities is the same as the signal of the surrounding white matter. In this moment of myelination and without any other feature of TS the diagnosis may be missed.

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Fig. 14: Axial T1-weighted image of the follow-up MR of the previous patient. Because of the progressive myelination no abnormalities are seen on the white matter.

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**Fig. 15:** Axial T2-weighted image of the same patient of the five previous figures in which subtle hypointense curvilinear lines on both frontal lobes can be seen abnormalities of white matter.

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**Fig. 16:** Axial DP image shows linear radial white matter bands extending from the lateral ventricles to the cortex.

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**Fig. 17:** Rhabdomyomas.

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**Fig. 18:** Thin section axial CT demonstrates multiple thin walled well-defined cysts distributed throughout the lung associated with a reticular pattern. Left pneumotorax is also seen.

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**Fig. 19:** Axial enhanced CT image demonstrate a retroperitoneal cystic mass consistent with LAM. Renal AML and multiple renal cyst are also shown.

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**Fig. 20:** Renal AML. Longitudinal US scan of the right kidney shows a round, well-defined lesion of increased echogenicity, which is consistent with angiomyolipoma.

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**Fig. 21:** Axial enhanced CT image demonstrates multiple fat-containing tumors in the kidneys. There is a retroperitoneal hemorrhage due to the rupture of the left AML.

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**Fig. 22:** Sagital CT image shows multiple esclerotic round bone lesions.

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Conclusion

The presence of common manifestations, including cortical or subependymal tubers, white matter abnormalities, cardiac rhabdomyoma and renal angiomyolipoma, allow us to confirm the diagnosis in cases with characteristic symptoms or skin lesions, and to suspect TS in undiagnosed patients. The lungs, digestive system, retroperitoneum and bone, which are less frequently involved, should also be evaluated.

TS has a wide variety of clinical and radiological manifestations. Familiarity with the clinical course, affected sites and frequency of involvement, can allow a correct diagnosis and treatment and therefore improve the quality of life of affected patients.
References


