Tuberous sclerosis - not just cortical tubers. Multimodality imaging review of multiorgan involvement

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Learning objectives

Describe the imaging findings on CT, MRI and plain film of the intracranial and extracranial involvement in patients with Tuberous Sclerosis.
Tuberous sclerosis is a rare autosomal dominant neurocutaneous syndrome (phacomatosis) found in between 1 in 6000 and 1 in 12000 of the population (1, 2). While mutation of two genes, TSC1 and TSC2, is involved in these inherited cases, at least two thirds are spontaneous. The classic triad of mental retardation occurs in less than 30% of tuberous sclerosis patients. Features are divided into major and minor manifestations. A definite diagnosis requires the presence of two major features or one major and two minor features.

Major features include:

- Facial angiofibroma
- Shagreen patch
- Hypomelanotic macules
- Cortical tubers
- Multiple retinal nodular hamartomas
- Cortical tubers
- Subependymal nodules
- Subependymal giant cell astrocytomas
- Cardiac rhabdomyoma (single or multiple)
- Lymphangiomyomatosis (LAM)
- Renal angiomyolipoma

Minor features include:

- Hamartomatous rectal polyps
- Dental enamel pits
- Bone cysts
- White matter migration lines
- Multiple renal cysts
Findings and procedure details

A. Neurological Manifestations

The neurological features of tuberous sclerosis often manifest as seizures, occurring in 90% of patients (3). 25-30% of these have intractable seizures. Mental retardation occurs in 50% and is usually in those with underlying seizures (4). There are four main neurological features of tuberous sclerosis:

- Cortical tubers
- Subependymal nodules
- Subependymal giant cell astrocytomas (SGCA)
- White matter abnormalities

(i) Cortical tubers

These are developmental abnormalities of the cortex that occur in between 95 and 100% of patients (1). They are related to symptoms such as epilepsy and cognitive issues, and symptoms are known to be worse in those with increased numbers of tubers (4). They are commonly found in the cerebrum, usually in the frontal lobes. They are less common in the cerebellum, and are only rarely found in the brainstem and spinal cord. 95% are multiple (5). On MRI they appear as low T1/high T2 signal lesions in a cortical/subcortical location (Fig. 1). Between 3 and 10% are shown to enhance post contrast. Calcification and cystic degeneration can occur.

(ii) Subependymal nodules

These are due to hamartomatous change in the subependymal region. They are usually also multiple in number and are located on the walls of the lateral ventricles, most commonly located at the caudothalamic groove (5). There is no correlation between the number of nodules and the disease severity. They appear as discrete areas of rounded hypertrophic tissue which are calcified in up to 88%, best seen on CT (Fig. 2). They exhibit high T1/variable T2 signal on MRI (Figs 3 & 4) and can enhance post contrast (Fig 5 & 6).

(iii) Subependymal giant cell astrocytomas (SGCA)

In 5-10% of cases, subependymal nodules enlarge and degenerate into SGCAs when greater than 1cm. They most commonly occur at the foramen of Munroe (1, 5). They are a benign lesion but grow slowly and can eventually cause on obstructive hydrocephalus. There is minimal surrounding oedema. Lesions often contain calcification. There tends to be marked contrast enhancement (Fig. 7).
(iv) White matter abnormalities

In addition to cortical tubers, further abnormalities of the white matter can occur in patients with TS. Radial migration bands appear as thin straight or curvilinear bands of high T2/low-to-intermediate T1 signal lesions in the subcortical white matter. They represent heterotopic glia and neurons that occur along the cortical migration path (Fig. 8)(5, 6). More superficial white matter lesions can occur, as can CSF signal cyst-like white matter lesions in the deep white matter.

B. Renal Manifestations

(i) Angiomyolipoma (AML)

AMLs are benign renal neoplasms that occur in between 55 and 75% of TS patients. 20% of all AMLs are found in TS patients (1, 7). They tend to occur at a younger age than in the general population and are larger and more often bilateral. Histologically, they are composed of abnormally thickened blood vessels, immature smooth muscle and adipose tissue. Often AMLs are asymptomatic but can cause pain and are at risk of rupture and bleeding. Severe haemorrhage can result. Tumours may be found in the renal cortex or medulla. On ultrasound, they appear as hyperechoic lesions with posterior acoustic shadowing (Fig. 9). CT shows a non-calcified tumour that contains fat (HU less than -20) (Fig 10). There are varying degrees of associated soft-tissue component with or without haemorrhage. On MRI, the fat component shows increased T1 signal that suppresses on fat-saturation sequences (Figs 11-13).

(ii) Renal cysts

These are benign lesions that then to occur in younger patients. They are usually asymptomatic if few in number. They can be multiple, giving an appearance that resembles autosomal dominant polycystic kidney disease (8). Cysts occur in the renal cortex and the medulla and are bilateral.

C. Cardiac Manifestations

(i) Rhabdomyoma

These are benign myocardial tumours that can occur anywhere in the heart, but are most commonly found in the ventricular and septal walls (1, 9). They appear as smooth, well-defined lesions. Over 50% of all rhabdomyomas are found in patients with TS. They can be signal or multiple. They often present in the neonatal or postnatal period. They can cause severe obstruction of intracardiac inflow/outflow necessitating urgent surgical resection. Arrhythmias such as AV node dysfunction, atrial tachycardia and ventricular pre-
excitation can occur. Echocardiography is used to detection and follow-up. Lesions are hyperechoic (Fig 14). On MRI, they are isointense to myocardium on T1 and hyperintense on T2.

(ii) Focal myocardial fat

Multiple foci of fat can be often found in myocardium of patients with TS (10). These typically occur in the interventricular septum and left ventricular septum and vary in size. Up to 65% of TS patients have been shown to have them. There is no difference in prevalence between males and females, or with different TS mutation type. These lesions follow fat signal on MRI, show absent enhancement and a lack of invasive behaviour (Fig 15). Spontaneous regression of rhabdomyomas can occur.

D. Pulmonary manifestations

(i) Lymphangiomyomatosis (LAM)

This is a rare manifestation of TS. It is thought to be present in between 26 and 39% of female TS patients (11). LAM is characterized by interstitial proliferation of bundles of smooth muscle and manifested by cystic change in the lung parenchyma. Symptoms include shortness of breath on exertion, recurrent pneumothoraces or haemoptysis. The multiple cysts are uniformly distributed throughout the lungs and are thin walled, best seen on CT (Fig 16). Chylous pleural effusions can occur.

E. Hepatic manifestations

(i) Hepatic AMLs

Most hepatic AMLs are solitary and most are not associated with TS. They are rare, occurring on only about 6% of TS patients, but occur usually in conjunction with renal AMLs (12). They are usually asymptomatic but can cause pain. On imaging, they have a similar appearance to renal AMLs (Fig 17).

F. Bony manifestations

Sclerotic lesions are the most common bony manifestation of TS, occurring in up to two thirds of patients. They are most common in the pelvis, lumar spine and cranium (Fig 18). The lesions are usually round or oval. Other lesions include:

- Bone cysts (round/oval cysts with or without peripheral sclerosis), most common in the phalanges
• Hyperostosis of the inner skull table
• Periosteal new bone formation
Fig. 1: Axial T2 image of the brain in a 9-month-old boy showing subcortical areas of high signal in the left temporal and right occipital lobes.

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Fig. 2: Non-contrast axial CT image of the head in a 7-year-old girl showing calcified subependymal nodules along the lateral walls of the lateral ventricles.

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Fig. 3: Axial T2 image in a 17-month-old boy showing predominantly low signal subependymal nodules bilaterally along the lateral walls of the lateral ventricles. The low signal correlates with calcification

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**Fig. 4:** Coronal T2 images in a 17-month-old boy showing predominantly low signal subependymal nodules bilaterally along the lateral walls of the lateral ventricles. The low signal correlates with calcification

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**Fig. 5:** Axial T1 post gadolinium image in a 17-month-old boy showing enhancement of the subependymal nodules.

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Fig. 6: Coronal T1 post gadolinium image in a 17-month-old boy showing enhancement of the subependymal nodules.

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Fig. 7: Coronal T1 post gadolinium image in 6-month-old boy showing an enhancing nodule greater than 1cm in the region of the foramen of Munroe, a probable giant cell astrocytoma.

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**Fig. 8:** Axial T2 image in a 9-month-old boy showing linear high signal migration lines in the white matter (arrow).

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**Fig. 9:** Ultrasound image in 17-month-old girl showing a small hyperechoic lesion in the mid-pole of the right kidney

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Fig. 10: Axial CT image in a 43-year-old lady with TS showing multiple small fat-density lesions in the left kidney in keeping with multiple AMLs.

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**Fig. 11:** Axial T1 image in a 35-year-old female showing multiple high T1 signal masses in both kidneys in keeping with AMLs.

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**Fig. 12:** Fat suppression sequence in the same patient in Fig 11 showing loss of signal within these renal lesions, confirming the presence of lipid component.

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Fig. 13: India ink artefact on out-of-phase imaging confirms the presence of fat within these multiple lesions.

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Fig. 14: Apical 4-chamber view of the heart in a 17-month-old boy showing a large hyperechoic mass in related to the interventricular septum (arrow).

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Fig. 15: T1 black blood MRI sequence of a 3-year-old male with known Tuberous Sclerosis. High T1 signal is noted within the moderator band of the right ventricle in keeping with a fatty focus.

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Fig. 16: Multiple lung cystic lesions in a 43 year old female tuberous sclerosis patient in keeping with LAM (lymphangioleiomatosis)

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**Fig. 17:** Hyperechoic lesion (arrow) in the right lobe of liver in a 17-month-old girl corresponding with a hepatic AML.

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Fig. 18: Multiple sclerotic bony lesions in the sacrum of a 43-year-old lady with TS.

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Conclusion

Tuberous sclerosis is a neurocutaneous syndrome that affects not only the brain, but multiple systems throughout the body including cardiac, renal, hepatic, skeletal and pulmonary. It doesn't always present with the classical triad and as a result, the radiologist plays a key role in determining the presence of a wide range of intra and extra-cranial manifestations. This poster aims to help the radiologist with the identification of common and less common findings.
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