Cross-sectional Imaging Review of Tuberous Sclerosis

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KEYWORDS

• Tuberous sclerosis • MR imaging • Tuber • Subependymal giant cell astrocytoma (SEGA) • mTOR • Angiomyolipoma • Lymphangioleiomyomatosis

KEY POINTS

- Tuberous sclerosis results from uninhibited activation of the mammalian target of rapamycin pathway secondary to inactivating mutations of tuberous sclerosis complex (TSC) 1 or *TSC2* genes (prototype tumor suppressor genes).
- Neurologic manifestations are the primary cause of morbidity and mortality in TSC. Pathologic findings include cortical and cerebellar tubers, radial migration lines, subependymal nodules, and subependymal giant cell astrocytomas (SEGAs).
- Imaging of neuropathological abnormalities depends on the age of the patient; most lesions under 6 months of age appear hyperintense on T1-weighted imaging. Serial growth of an enhancing nodule near the foramen of Monro suggests a SEGA.
- Renal angiomyolipomas (AMLs) are the second most common cause of morbidly and mortality in TSC. The risk of hemorrhage is higher in AMLs larger than 4 cm or AMLs with aneurysms larger than 5 mm.

INTRODUCTION

Tuberous sclerosis complex (TSC) is an autosomal dominant, neurocutaneous disorder that is characterized by development of hamartomatous tumors in multiple organs and neuronal migration abnormalities.[1] Although TSC was first described by von Recklinghausen in 1862,[2] it was recognized as a distinct disease by Bourneville in 1880 (thus also referred to as Bourneville disease). TSC affects 1 million people worldwide, and occurs in 1 in 6000 to 1 in 10,000 live births, with a population prevalence of around 1 in 20,000.[2] TSC is marked by high penetrance, albeit with variable phenotypic manifestations.

This article begins with a brief discussion on the advances in the genetics and etiopathogenesis of the condition as well as the recently updated criteria for the diagnosis of TSC. Cross-sectional imaging spectrum of the neurologic, abdominal, and thoracic manifestations of this protean disorder are discussed subsequently.

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CAUSE AND GENETICS

Tuberous sclerosis results from a mutation in one of 2 tumor suppressor genes: *TSC1* (located on 9q34 and encoding hamartin) or *TSC2* (located on 16p13 and encoding tuberin),[1] with *TSC2* mutations 3 times more common and associated with more severe disease manifestations.[3] The protein products of *TSC1* (hamartin) and *TSC2* (tuberin) form a heterodimer that functions as a master switch to primarily inhibit the mammalian target of rapamycin (mTOR) complex 1 (mTORC1).[4] mTOR is a key protein kinase that senses a variety of environmental signals, such as growth factors and metabolic milieu, while regulating many critical cellular processes, including protein/lipid synthesis, cell cycle progression, proliferation, cytoskeleton organization, and cell survival. In TSC, the inactivating mutations of the *TSC1* or *TSC2* genes result in uninhibited activation of the mTOR pathway.[5]

Although approximately one-third of patients have inherited mutations from their parents, most seem to be mutations that arose sporadically in very early somatic cells and may not equally affect all organ systems.[5] Some studies also suggest that a second hit (based on Knudson's two-hit hypothesis) may account for brain lesions.[6] Such genetic complexity may explain the considerable phenotypic diversity observed in patients with TSC. In addition, improved knowledge of the genetics of TSC and mTOR complex has led to the development of targeted therapeutics for management of patients with TSC.[5]

REVISED DIAGNOSTIC CRITERIA

In 2012, the second International Tuberous Sclerosis Complex Consensus Conference was held in Washington, DC, with the major goal to revisit the diagnostic criteria[2] (**Box 1**). One of the major changes was the inclusion of genetic testing for the identification of a pathogenic mutation in *TSC1* and *TSC2*. Because approximately 10% to 25% of patients with TSC do not have a genetic mutation by conventional genetic testing, a normal result does not exclude the diagnosis.

Pertinent changes include:

- Combination of radial migration lines (RMLs; previously minor criteria) and cortical tubers into one major criteria called cortical dysplasia
- The word renal removed from "renal angiomyolipoma" to accommodate liver angiomyolipoma (AML)
- To separate sporadic lymphangioleiomyomatosis (LAM) from tuberous sclerosis-related LAM; when both are present, together constitute only one major criterion

Because 2 major criteria constitute a definite diagnosis of TSC, it follows that the detection of these findings on an imaging study of the brain is conclusive in making a diagnosis of TSC even in the absence of other typical clinical signs and symptoms.

NEUROLOGIC MANIFESTATIONS OF TUBEROUS SCLEROSIS COMPLEX

Neurologic manifestations are present in approximately 85% of patients with TSC and are the primary cause of morbidity and mortality.[7,8] Seizures are present in most of these patients and often begin in the first year of life as intractable infantile spasms.[5] Certain neuroradiological features, such as greater than 7 tubers,[9] large tuber size,[10] and increased tuber/brain ratio, favor a more severe epilepsy or early onset of epilepsy as well as intellectual impairment. Other manifestations include cognitive impairment (>50% of patients), challenging behavioral problems, and autism.[5,11] There is a higher risk of severe cognitive and behavioral difficulties in patients with involvement of the temporal or occipital lobes, particularly the left temporal lobe in right-handed patients.[12] A recently coined term, TSC-associated neuropsychiatric disorders, refers to the constellation of behavioral, psychiatric, intellectual, and psychosocial difficulties than can affect more than 90% of patients with TSC.[13]

These clinical manifestations arise from underlying neuropathological abnormalities, including cerebral and cerebellar tubers, white matter RMLs, subependymal nodules (SENs), subependymal giant cell astrocytomas (SEGAs), and rarely vascular abnormalities such as intracranial aneurysms.

IMAGING TECHNIQUES

MR imaging is the primary imaging modality in the diagnosis, characterization, and monitoring of the intracranial lesions of TSC.[7,8] Although the classic subependymal calcifications are best seen by computed tomography (CT) (**Fig. 1**), MR imaging techniques such as gradient T2* and three-dimensional susceptibility-weighted imaging[14] may be an alternative to avoid ionizing radiation. Ultrasonography is most valuable in the prenatal period, although its main contribution is in the detection of cardiac rhabdomyomas.[7] Prenatal ultrasonography can detect subependymal nodules and tubers, although fetal MR imaging is more sensitive[15] (**Fig. 2**). Similarly, in the neonatal period, although transfontanelle ultrasonography can be used, MR imaging is still the preferred test.