Tuberous Sclerosis Complex

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28.1 Overview

- Tuberous sclerosis complex (TSC) is an autosomal dominant dysgenetic disorder characterized by hamartomas and neoplasms involving the central nervous system (CNS) and various other tissues.
- The causative mutations are in the *TSC1* and *TSC2* genes located on 9q and 16p, respectively.
- Worldwide, 1–2 million individuals are affected by TSC. The estimated prevalence is 1 out of every 5000–6000 births.
- The definitive diagnosis of TSC is established if either the genetic or the clinical criteria are met [1]:
  - *Genetic diagnostic criteria*: The identification of either a *TSC1* or *TSC2* pathogenic mutation in DNA from normal tissue is sufficient to make a definite diagnosis of TSC. A pathogenic mutation is defined as a mutation that clearly inactivates the function of the TSC1 or TSC2 proteins.
  - *Clinical diagnostic criteria*: Definite diagnosis implies two major features or one major feature with two or more minor features:
    - Major features
      - Hypomelanotic macules (≥3, at least 5 mm diameter)
      - Angiofibromas (≥3) or fibrous cephalic plaque
      - Ungual fibromas (≥2)
      - Shagreen patch
      - Multiple retinal hamartomas
      - Cortical dysplasias
      - Subependymal nodules
      - Subependymal giant cell astrocytoma (SEGA)
      - Cardiac rhabdomyoma
      - Lymphangioleiomyomatosis (LAM)
      - Angiomyolipomas (≥2)
    - Minor features
      - "Confetti" skin lesions
      - Dental enamel pits (>3)
      - Intraoral fibromas (≥2)
      - Retinal achromic patch
      - Multiple renal cysts
      - Nonrenal hamartomas

28.2 Clinical Features

- About half of TSC patients have a positive family history.
- Children with TSC can present with seizures, and seizures are present in the majority of pediatric patients [2].
- Patients with SEGA may present with signs of hydrocephalus associated with blockage of cerebrospinal fluid (CSF) circulation, but early diagnosis of SEGA may be difficult because smaller tumors are often asymptomatic.
- Cognitive and mental dysfunction and developmental delay are commonly seen in children with TSC.

28.3 Neuroimaging

- Several characteristic lesions can be seen in patients with TSC. Neuroimaging may underestimate the extent of neuropathological changes in TSC patients [3]. More recently, 7-T imaging was able to identify lesions not recognized with lower-resolution magnets [4].
- Subependymal nodules often protrude into the ventricle; they are often isointense to white matter on T1-weighted images, and are hypointense on T2-weighted images.

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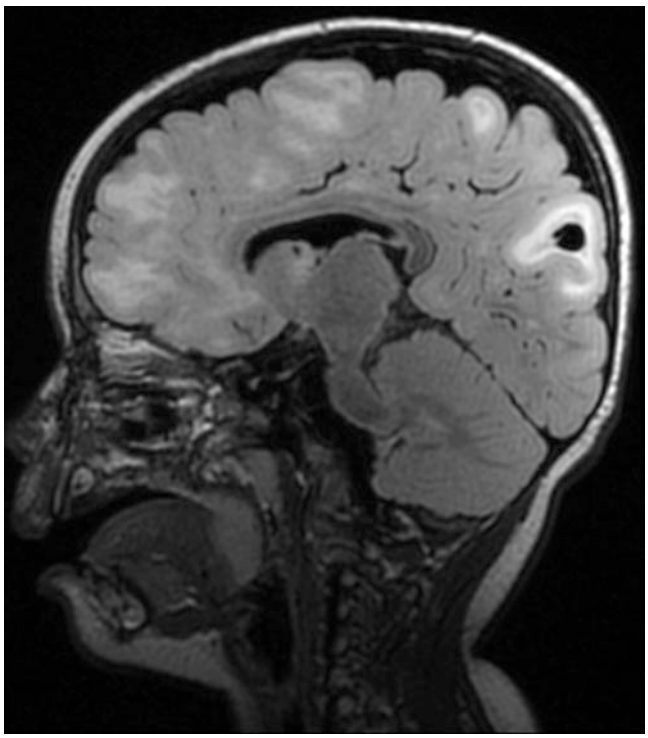

Fig. 28.1 Sagittal fluid-attenuated inversion recovery (FLAIR) image of a young boy with tuberous sclerosis complex (TSC), demonstrating numerous cortical tubers that are hyperintense to white matter. Note the dark, calcified nodule in the posterior parietal and superior occipital region

They show limited and variable enhancement after contrast administration.

- SEGA is an almost entirely intraventricular tumor, which rarely demonstrates a parenchymal component. Tumors are isointense to hypointense on T1-weighted images and isointense to hyperintense on T2-weighted images; they show strong, diffuse enhancement on gadolinium administration.
- Cortical tubers are often multiple cerebral lesions with variable calcifications, sometimes in a gyriform fashion. The MR appearance of cortical tubers varies with the age of the patient. The signal changes over time that slowly become isointense to white matter should be interpreted with caution. Tubers are often hyperintense on T2 and fluid-attenuated inversion recovery (FLAIR) modalities and typically do not enhance [5]. Calcifications often accompany cortical tubers as T2 dark foci (Fig. 28.1).

28.4 Histopathological Features

- Subependymal nodules are often calcified and partially covered by a layer of ependymal cells. They are mostly composed of large cells with glial phenotype and multinucleated cells with extensive glial processes. There is little or no cytological difference between the predominant cell in subependymal nodule and the cells of SEGA. Most cells in subependymal nodules have ambiguous expression of glial and neuronal markers, as in SEGA.

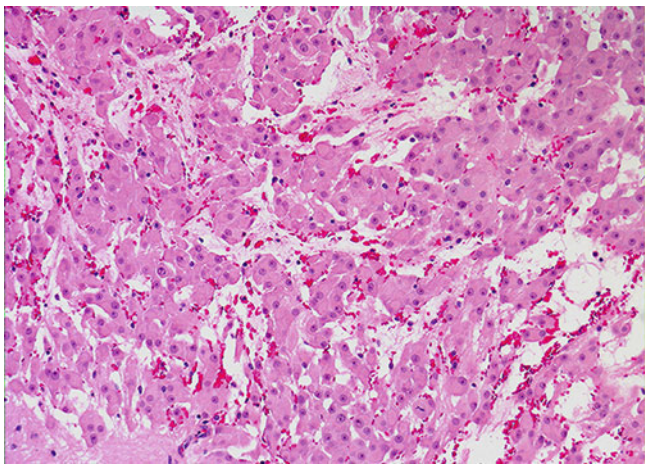

Fig. 28.2 Medium magnification of subependymal giant cell astrocytoma (SEGA) composed of gemistocyte-like cells arranged in a sweeping fashion and in fascicles. This tumor appears somewhat discohesive, but most examples demonstrate a solid architecture with no intervening parenchyma

- SEGA is a well-circumscribed neoplasm and is considered World Health Organization (WHO) grade I. The tumor is characterized by gemistocyte-like cells with ample glassy, eosinophilic cytoplasm and eccentric nuclei with prominent nucleoli in a "streaming" pattern (Fig. 28.2). This pattern portends a more spindled morphology for some of the tumor cells, and some tumors may display a striking pleomorphism. There is a striking glial background with rich fibrillarity. Binucleated or occasionally multinucleated cells may be seen within the neoplasm, as well as rare mast cells. Some tumors demonstrate perivascular lymphocytic infiltrates. Typically, the tumor cells are positive for glial fibrillary acidic protein (GFAP), but similar to subependymal nodules, many cells in SEGA demonstrate an ambiguous glial/neuronal immunohistochemical pattern. The proliferation indices are often very low. Rare mitotic figures can be encountered in SEGA. Exceptional cases demonstrate necrosis, but this is often in the form of geographic, and not palisaded necrosis.
- Cortical tubers are firm, wartlike protrusions that are composed of jumbled-up elements of neuropil with bizarre ganglionlike cells with short processes (Fig. 28.3). These bizarre cells are often found in clusters with a gliotic background and large collections of glial processes. Microcalcifications are often present.

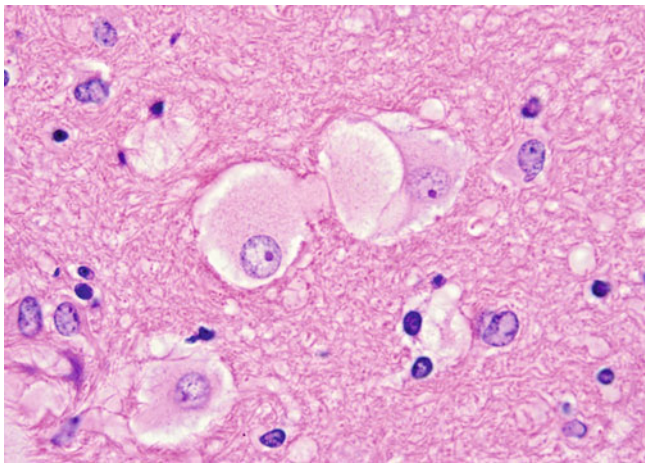

Fig. 28.3 High-magnification image of balloon cells in a cortical tuber from the patient in Fig. 28.1. The typical cortical tuber shows a markedly disorganized cortex, with abnormal glial proliferations, bizarre neurons, and balloon cells

28.5 Immunohistochemistry

- SEGAs are often positive with the neuronal antibodies such as neurofilament proteins, class III beta-tubulin, synaptophysin, and NeuN. The latter is only focally positive in a small percentage of cells, but the staining is variable among tumors.
- SEGA is variably positive for staining with GFAP and S-100 protein antibodies.
- Recent studies suggest thyroid transcription factor 1 (TTF-1) positivity in SEGAs [6].
- Olig-2, which is positive with most glial neoplasms, is almost entirely negative in SEGAs [7]. CD34 (positive in most glioneuronal tumors) is also negative.

28.6 Electron Microscopy

- Electron microscopy shows evidence of glial as well as neuronal differentiation.
- Microtubules, occasional dense-core granules, and, rarely, synapses can be observed.

28.7 Molecular Pathology

- Linkage studies have provided evidence for two distinct *TSC* loci on chromosome 9q34 (*TSC1*) and on chromosome 16p13.3 (*TSC2*).
- *TSC1* and *TSC2* gene products are components of a heterodimer that is critical in regulation of a number of cellular functions including proliferation; they are considered to be tumor suppressor genes. Gene products tuberin and hamartin form a complex that integrates and transmits cellular growth factor and stress signals to the PI3K/PKB signaling pathway, and negatively regulates mTOR activity.
- Loss of either *TSC1* or *TSC2* seems to result in a similar clinical picture, supporting the suggestion that both genes are involved in the same regulatory pathway [8].
- Mutations of the *TSC2* gene are more common than *TSC1* gene mutations.
- Virtually all mutations of *TSC1* seem to result in a truncated gene product.
- Mutations in the *TSC2* gene are more varied and include deletions, missense and nonsense mutations, frameshift deletions or insertions, and splice junction mutations.

28.8 Prognosis

- SEGA is essentially a benign neoplasm and often can be cured by resection.
- In recent years, rapamycin therapy has been suggested for cases where a gross total resection cannot be achieved [9].
- A last-resort treatment is gamma knife surgery for incompletely resected or chemotherapy-resistant tumors.
- Even though the prognosis of SEGA is quite favorable, the overall prognosis of TSC patients is dependent on the type and extent of CNS and extra-CNS lesions.

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