Tuberous sclerosis complex

Tuberous sclerosis complex, composed of the Latin tuber (swelling) and the Greek skleros (hard), refers to the pathological finding of thick, firm and pale gyri, called “tubers,” in the brains of patients postmortem. These tubers were first described by Désiré-Magloire Bourneville in 1880; the cortical manifestations may sometimes still be known by the eponym Bourneville’s disease.

Key concepts

- most cases are due to spontaneous mutation. Inherited cases are autosomal dominant. Incidence: 1 in 6K–10K live births.
- classic clinical triad: seizures, mental retardation, and sebaceous adenomas; the full clinical triad is seen in < 1/3 of cases.
- typical CNS finding: subependymal nodules (“tuber”)—a hamartoma.
- commonly associated neoplasm: subependymal giant cell astrocytoma (SEGA)
- 2 tumor suppressor genes: TSC1 (on chromosome 9q34) codes for hamartin and TSC2 (on chromosome 16p13) encodes tuberin
- CT shows intracerebral calcifications (usually subependymal).

Tuberous sclerosis complex (TSC), AKA Bourneville’s disease, is a neurocutaneous disorder characterized by hamartomas of many organs including the skin, brain, eyes and kidneys. In the brain, the hamartomas may manifest as cortical tubers, glial nodules located subependymally or in deep white matter, or giant cell astrocytomas. Associated findings include pachygyria or microgyria.

Tuberous sclerosis complex (TSC) was initially described approximately 150 years ago by von Recklinghausen in 1862.¹

Tuberous sclerosis complex (TSC) is an autosomal dominant multisystem disease usually diagnosed in childhood.

Subependymal giant cell astrocytomas (SEGA) are benign brain lesions occurring in up to 20% of patients with TSC.
**Epidemiology**

Studies estimate a frequency of 1/6000 to 1/10,000 live births and a population prevalence of around 1 in 20,000 \(^2\)\(^3\).

**Etiology**

Autosomal dominant inheritance; however, spontaneous mutation accounts for the majority of cases.

Two distinct tumor suppressor genes have been identified: the TSC1 gene (located on chromosome 9q34) codes for TSC1 (AKA hamartin), and the TSC2 gene (on chromosome 16p13.3) codes for TSC2 (tuberin). Only 1 gene needs to be affected to develop TSC. These proteins work together to inhibit the activation of rapamycin (mTOR). Genetic counseling for unaffected parents with one affected child: 1-2% chance of recurrence \(^4\)\(^5\).

**Clinical features**

This rare multi-system genetic disease causes benign tumors to grow in the brain and on other vital organs such as the kidneys, heart, eyes, lungs, and skin. A combination of symptoms may include seizures, intellectual disability, developmental delay, behavioral problems, skin abnormalities, lung and kidney disease.

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At least 50% of patients with tuberous sclerosis complex present with intractable epilepsy; for these patients, resective surgery is a treatment option.

The diagnosis of TSC is based on clinical features, but the variability of phenotype and age at symptom onset makes this challenging.

In the infant, the earliest finding is of “ash leaf” macules (hypomelanotic, leaf-shaped) that are best seen with a Wood’s lamp. Infantile myoclonus may also occur.

In older children or adults, the myoclonus is often replaced by generalized tonic-clonic or partial complex seizures, which occur in 70–80%. Facial adenomas are not present at birth but appear in > 90% by age 4 yrs (these are not really adenomas of the sebaceous glands, but are small hamartomas of cutaneous nerve elements that are yellowish-brown and glistening and tend to arise in a butterfly malar distribution, usually sparing the upper lip).

Retinal hamartomas occur in ≈ 50% (central calcified hamartoma near the optic disc or a more subtle peripheral flat salmon-colored lesion). A distinctive depigmented iris lesion may also occur.
**Diagnosis**

*Tuberous sclerosis complex diagnosis.*

**Pathology**

Subependymal nodules ("tubers") are benign hamartomas that are almost always calcified, and protrude into the ventricles.

▶ **Subependymal giant cell astrocytoma** (SEGA). Almost always located at the foramen of Monro. Occurs in 5–15% of patients with TSC.

**Treatment**

*Tuberous sclerosis complex treatment.*

**Outcome**

In a nationwide multi-center study on resective epilepsy surgery, resulted in improved seizure outcomes and quality of life and intelligence quotient improvements in patients with tuberous sclerosis complex. Seizure freedom was often achieved in patients with an outstanding tuber on MRI, total removal of epileptogenic tubers, and tuberectomy plus. Quality of life and intelligence quotient improvements were frequently observed in patients with postoperative seizure freedom and preoperative low intelligence quotient.

**Case series**

Liu et al. reported a nationwide multicentre retrospective study and analyzed the long-term seizure and neuropsychological outcomes of epilepsy surgery in patients with tuberous sclerosis complex. There were 364 patients who underwent epilepsy surgery in the study. Patients' clinical data, postoperative seizure outcomes at 1-, 4-, and 10-year follow-ups, preoperative and postoperative intelligence quotients, and quality of life at 1-year follow-up were collected. The patients' ages at surgery were 10.35 ± 7.70 years (range: 0.5-47). The percentage of postoperative seizure freedom was 71% (258/364) at 1-year, 60% (118/196) at 4-year, and 51% (36/71) at 10-year follow-up. Influence factors of postoperative seizure freedom were the total removal of epileptogenic tubers and the presence of outstanding tuber on MRI at 1- and 4-year follow-ups. Furthermore, monthly seizure (versus daily seizure) was also a positive influence factor for postoperative seizure freedom at 1-year follow-up. The presence of an outstanding tuber on MRI was the only factor influencing seizure freedom at 10-year follow-up. Postoperative quality of life and intelligence quotient improvements were found in 43% (112/262) and 28% (67/242) of patients, respectively. Influence factors of postoperative quality of life and intelligence quotient improvement were postoperative seizure freedom and preoperative low intelligence quotient. The percentage of seizure freedom in the
tuberectomy group was significantly lower compared to the tuberectomy plus and lobectomy groups at 1- and 4-year follow-ups. In conclusion, this study, the largest nationwide multi-centre study on resective epilepsy surgery, resulted in improved seizure outcomes and quality of life and intelligence quotient improvements in patients with tuberous sclerosis complex. Seizure freedom was often achieved in patients with an outstanding tuber on MRI, total removal of epileptogenic tubers, and tuberectomy plus. Quality of life and intelligence quotient improvements were frequently observed in patients with postoperative seizure freedom and preoperative low intelligence quotient.

Brain MRIs of 110 TSC patients (mean age 11.5 years; age range 0.5-38 years; 52 female; 26 TSC1, 68 TSC2, 8 without mutation identified in TSC1 or TSC2, 8 not tested) were retrospectively evaluated. Signal and morphological abnormalities consistent with olfactory bulb hypo/aplasia or with olfactory bulb hamartomas were recorded. Cortical tuber number was visually assessed and a neurological severity score was obtained. Patients with and without rhinencephalon abnormalities were compared using appropriate parametric and non-parametric tests.

Eight of 110 (7.2%) TSC patients presented rhinencephalon MRI changes encompassing olfactory bulb bilateral aplasia (2/110), bilateral hypoplasia (2/110), unilateral hypoplasia (1/110), unilateral hamartoma (2/110), and bilateral hamartomas (1/110); olfactory bulb hypo/aplasia always displayed ipsilateral olfactory sulcus hypoplasia, while no TSC patient harboring rhinencephalon hamartomas had concomitant forebrain sulcation abnormalities. None of the patients showed overt olfactory deficits or hypogonadism, though young age and poor compliance hampered a proper evaluation in most cases. TSC patients with rhinencephalon changes had more cortical tubers (47 ± 29.1 vs 26.2 ± 19.6; p = 0.006) but did not differ for clinical severity (p = 0.45) compared to the other patients of the sample.

Olfactory bulb and/or forebrain changes are not rare among TSC subjects. Future studies investigating clinical consequences in older subjects (anosmia, gonadic development etc.) will define whether rhinencephalon changes are simply an imaging feature among the constellation of TSC-related brain changes or a feature to be searched for possible implications in the management of TSC subjects.

Case reports

A novel technique is presented for the application of MRgLITT in a 6-month-old infant for the treatment of epilepsy associated with tuberous sclerosis complex (TSC).

To Hooten et al. from the Tuberous Sclerosis Complex Clinic, Duke University, Durham, North Carolina; and University of Florida, Gainesville, knowledge this is the youngest patient treated with laser ablation. They used a frameless navigation technique with a miniframe tripod system and intraoperative reference points. This technique expands the application of MRgLITT to younger patients, which may lead to safer surgical interventions and improved outcomes for these children.

References


