Chapter 27
Tuberous Sclerosis (Bourneville Disease)

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Contents

Introduction

The first description and nomenclature are credited to Bourneville 1880 [1]; in 1890, Pringle reported adenoma sebaceum, but in 1862, Friedrich Daniel von Recklinghausen was the first person to recognize the condition [2, 3]. Between 1880 and 1900, Bourneville and Brissaud summarized the clinical findings in ten additional cases of TSC and correlated the cutaneous abnormalities with renal lesions [4, 5]. The relationship between Bourneville and Pringle syndromes was published

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for the first time in 1908 by Vogt [6], who was also the first to define and link adenoma sebaceum (now more appropriately termed "facial angiofibroma") to mental insufficiency and epilepsy. Later, Van der Hoeve detailed the histology of autopsy tissue derived from the optic nerve and retina in patients with TSC [7].

Tuberous sclerosis complex does not show a geographic, racial or sexual predilection. It carries a prevalence of approximately 1:6000. Approximately 20–30% of the cases show a familial autosomal dominant inheritance, and the remaining 70–80% are caused by de novo germline mutations. TSC is a multisystem genetic syndrome that can present at any age, affecting almost all organ systems of corpus (central nervous system, heart, kidneys, eyes, skeletal and lungs).

In 1998, the National Institutes of Health sponsored the first TSC Consensus Conference to develop recommendations for the diagnosis and clinical management of patients affected by TSC [8]. The International Tuberous Sclerosis Complex Consensus Conference updated the diagnostic criteria in 2012 to include pathogenic mutations of the TSC1 and TSC2 genes in establishing a diagnosis [9].

Genetics (Also See Chap. 1)

Although the hereditary nature of tuberous sclerosis was reported in 1910, causative gene mutations were not identified until the 1990s when multilinkage analysis of multigenerational families with TSC led to the identification of two genes, TSC1 and TSC2. Reviewing more than 4200 individuals with TSC and their families in whom disease-causing mutations have been identified, about 31% had a mutation in TSC1, and the majority of others possess a mutation in TSC2 [9]. Located on chromosome 9q34, TSC1 comprises 23 coding exons [10], while TSC2 is located on 16p13 and has 41 exons [10, 11]. Both genes are considered as tumour suppressors and follow Knudsons two-hit hypothesis for carcinogenesis: inactivation of both alleles is necessary for tumour development [12].

Most of the mutations in TSC1 yield premature protein termination. In TSC2, the mutational spectrum covers missense, nonsense, frameshift and large genomic deletions [10, 13]. Loss of heterozygosity in the tuberous sclerosis lesions has been demonstrated for both the 9q34 and 16p13 regions [14]. Some degree of mosaicism also has been reported, which has potential implications in molecular diagnosis and genetic counselling [15, 16]. Approximately 15% of patients with TSC do not have identifiable mutation in either gene. Disease severity can be variable, even within families, and may reflect differential expression of normal and mutant TSC alleles.

Signalling Pathways Affected in TSC

TSC1 and TSC2 encode for hamartin and tuberin, respectively. These proteins were noted early to interact [17] and contribute to cell cycle regulation. The current understanding supports both proteins form a TSC protein complex, mTORC1,

which functions as a tumour suppressor. Inactivation of either gene results in overactivation of the mTOR pathway. This signalling mediates cellular activity as a serine-threonine protein kinase that activates the GTPase activity of RHEB (Ras homolog enriched in brain) [18, 19].

Clinical Characteristics

Tuberous sclerosis complex features often are present in early infancy but may not be recognized as part of the syndrome. Over the life span, there can be varying and progressive involvement not only of the skin and CNS but also other organs and systems, such as the heart, kidneys, eyes, skeletal system and lungs. Skin lesions of TSC include hypomelanotic macules, also known as ash-leaf spots (85–97% of patients), shagreen patch (20–80%), facial angiofibromas (75%) and ungual fibromas (17–87%) [13, 20]. Hypomelanotic spots (Fig. 27.1) range from a few millimetres to centimetres in diameter and can be scattered across the body. In fair-skinned individuals, these are more visible under Wood's lamp of ultraviolet light.

Isolated small spots, "confetti" lesions, are a minor rather than a major criterion. Some patients with TSC have a tuft of white hair (poliosis). The characteristic facial angiofibromas are located on the nose and symmetrically on the cheeks and chin (Fig. 27.2). They consist of small, red and brown nodules that appear during early childhood (1–4 years). Initially, these can be flat and later raised; they are present in 40–90% of the patients with tuberous sclerosis. Fibrous cephalic plaque can be a finding specific to TSC. Shagreen patches appear as large and discoloured plaques to the lower back or flank. Fibromas under or around the nails are encountered in

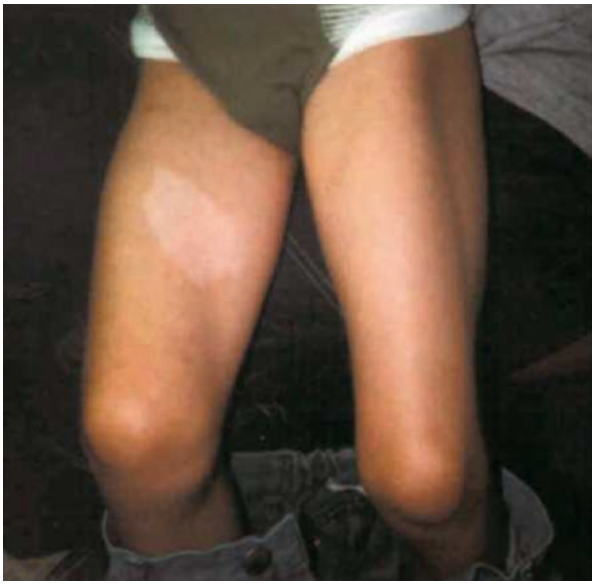

Fig. 27.1 Hypomelanotic spot on the right leg in tuberous sclerosis

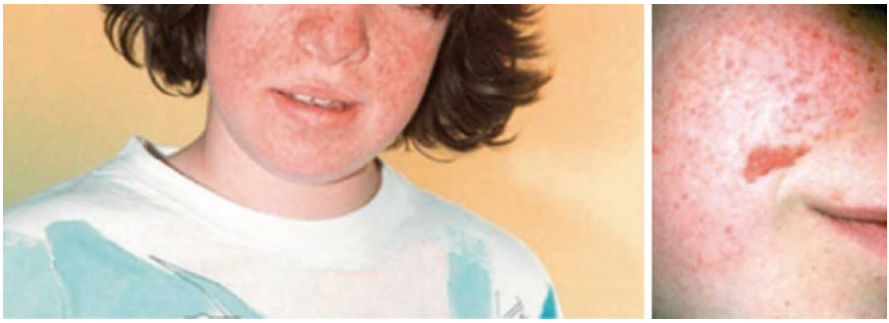

Fig. 27.2 Facial angiofibroma on the cheek

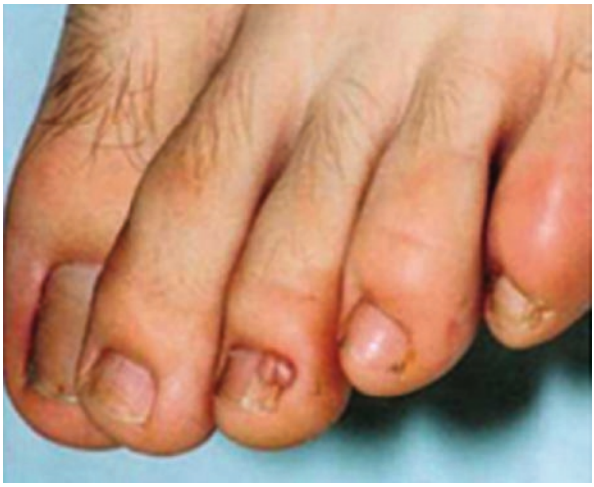

Fig. 27.3 Fibromas over the nail of the middle toe of the left foot in tuberous sclerosis

15–50% of the adult patients, more commonly found in the feet than in the hands (Fig. 27.3). Oral fibromas of the gums occur in 10% of the patients. Erosions of the enamel manifest as dental pits in 70–100% of the adult patients.

Neurological involvement includes epilepsy, and the identification of early-life seizures often is the presenting sign contributing to diagnosis. About 80% of TSC patients will present with seizure onset in the first 3 years of life and 2/3 of them in the first 12 months. Neonatal epilepsy seems to be quite rare, but it has been reported as well [21]. The age at seizure onset, the timing of appearance of epileptiform abnormalities on the EEG and the localization of abnormalities might relate to the location of cortical tubers detected on MRI in up to 90% of cases and may coincide with functional maturation of the cortex. An earlier expression has been demonstrated for temporo-occipital regions compared to frontal [22, 23]. In the same child, focal seizures may precede, coexist with or evolve into epileptic spasms [24]. Subtle focal seizures can occur, such as unilateral tonic or clonic phenomena mainly localized in the face or limbs, tonic eye deviation, head turning and unilateral grimacing. These may be missed by the parents until the third or fourth month of life when

epileptic spasms occur. Therefore, every effort should be made to diagnose TSC before the onset of epilepsy, thus having the opportunity to educate parents in recognizing subtle focal seizures.

EEG monitoring every 4 weeks in the first 6 months of life, and later every 6 weeks, has been studied for the appearance of epileptiform abnormalities or even ictal activity before the development of clinical seizures [25]. Trials of vigabatrin for the prevention of or delay in seizure onset have been under way in Europe [26] and in the United States with promising results. The vast majority of TSC children with early onset seizures will later develop refractory seizures, often associated with multifocal EEG abnormalities (see Chap. 50) [23, 27]. In particular, almost all children presenting with infantile spasms will have other seizure types, and precise electroclinical differential diagnosis between Lennox-Gastaut syndrome (LGS) and focal symptomatic epilepsy arising from the frontal lobe may be extremely difficult.

For some, long-term video-EEG monitoring can reveal subtle electroclinical abnormality suggestive of a focal seizure onset. In these patients, high time-resolution topographic EEG analysis and dipole localization methods may detect secondary bilateral synchrony (SBS), often originating in frontal regions and corresponding to prominent cortical tubers detected by MRI in the mesial surface of the frontal or the anterior temporal lobes.

Epilepsy surgery can provide short-term or long-term seizure remission, and even incomplete reprieve of seizure burden can improve quality of life and comorbidities (see Chaps. 48 and 49). Although epilepsy in TSC is usually a paediatric issue, about 12% of patients with TSC will experience their first seizure during adulthood, highlighting that the risk for seizure is high during the entire life span [21]. Although refractory epilepsy is a major concern in TSC patients, approximately a third of patients become seizure-free, in some cases even after experiencing early onset seizures and infantile spasms [28].

Even if prognostic factors have been proposed, predicting the course of epilepsy in TSC remains a major challenge. However, seizure onset in the first 3 years of life, the presence of frequent and multiple seizure types, an incomplete response to antiepileptic agents, the presence of multifocal EEG abnormalities with the occurrence of new EEG foci over time as well as a high tuber burden or the presence of cystic tubers should be considered as unfavourable prognostic factors, indicating a high risk of developing refractory epilepsy [24].

Neurocognitive and psychopathological manifestations are a common feature in TSC and may show striking variability [29] with possible combinations of psychomotor delay, cognitive delay, behavioural disturbances, autism spectrum disorders (ASD) and attention-deficit hyperactivity disorder (ADHD). In adults, additional psychiatric problems might present, such as anxious and/or depressed mood [30, 31]. Some individuals in the same family can be impaired and have severe autism and challenging behaviours, whereas others lead normal lives. A bimodal distribution of intelligent quotient (IQ) exists between a population with severe intellectual disability (30%, mean IQ = 30–40) and a population with less severe intellectual disability (>50%, mean IQ = 93) [32]. Patients with TSC who display average intelligence may, however, be prone to specific cognitive deficits of memory, attention or executive skills [33, 34].

An early age at seizure onset is one of the most important risk factors for a subsequent cognitive impairment [23, 33], and early seizures may also increase the risk for autism spectrum disorders. Children with tuberous sclerosis may manifest epilepsy prior to the onset of autism, raising the issue of a causal relationship with seizures disrupting the developing brain and specifically cognitive and social skills. Early-onset epileptiform EEG activity within the temporal lobes, and perhaps in other locations, might have a deleterious effect on the development and establishment of key cognitive representations concerned with the processing of social information [35]. Therefore, prompt treatment of epilepsy is mandatory in order to reduce the severity of cognitive and behavioural impairment, although this does not guarantee a normal mental outcome [36]. There is also study regarding the impact of vigabatrin on long-term intellectual ability if implemented on the basis of epileptiform abnormalities present before the onset of epilepsy [37]. However, further randomized studies are needed to clarify this point.

Frequency of autism in infants with tuberous sclerosis might be significantly higher than frequency of cardiac or renal abnormalities, for which screening is routinely done. Children with cognitive impairment are significantly more likely to have autistic spectrum disorder and attention-deficit hyperactivity disorder [29]. Since an early diagnosis of TSC is increasingly possible, children should be monitored not only for the appearance of seizures but also for early signs of autism spectrum disorder, thus making an early intervention during the period of brain plasticity possible [35]. Children with TSC and epilepsy are at higher risk for other behavioural disturbances such as attention-deficit hyperactivity disorder (ADHD) [38]. In particular, those with frontal epileptiform EEG foci show deficits on tasks assessing impulse control and planning, as well as impaired inhibition and set shifting. Side of the seizure focus may contribute to executive dysfunction in patients with epilepsy; particularly, a left frontal focus can interfere with inhibitory processes [39]. Moreover, 90% of patients with TSC exhibit supratentorial brain lesions, including cortical tubers, subependymal nodules (as calcified tumours), subependymal giant cell astrocytoma (SEGA), white matter linear migration lines, corpus callosum agenesis or dysplasia and transmantle cortical dysplasia (see also chapter on neuropathology). Infratentorial brain lesions are less common (<2% of patients) and can include linear and gyriform cerebellar folia calcification, cerebral nodular white matter calcifications, agenesis and hypoplasia of the cerebellar hemispheres and vermis, enlargement of the cerebellar hemispheres and subependymal nodules and tubers in the brainstem and fourth ventricle [40].

Cortical tubers are characterized by proliferation of glial and neuronal cells and loss of the six-layered structure of the cortex. The most prominent abnormal cell types in tubers are large dysplastic neurons, giant cells and bizarrely shaped astrocytes. Dysplastic neurons have disrupted radial orientation in the cortex and abnormal dendritic arborization, showing γ-aminobutyric acid (GABA) transporter defect and low GABAergic inhibition [41]. Subependymal nodules are hamartomas, typically seen in the subependymal wall of the lateral ventricles. Some nodules protrude into the ventricular cavity. Subependymal nodules develop during foetal life, are present in most patients with tuberous sclerosis and are usually asymptomatic. Nodules bigger than 5 mm, which are located near the foramen of Monro, not calcified and enhanced by gadolinium, have a high probability of evolving into SEGA,

particularly in familial cases of tuberous sclerosis [42]. Transformation of a subependymal nodule into SEGA is usually a gradual process, of which the highest rate is in the first two decades of life. Rapid growth over 12 months has been reported rarely [42]. Occurring in about 10% of cases, these slow-growing tumours demonstrate mixed glioneuronal lineage, and they are the most common brain tumours in patients with tuberous sclerosis [42, 43]. Growth of these lesions at the foramen of Monro can block the flow of the cerebrospinal fluid, leading to progressive lateral ventricular dilatation and increased intracranial pressure.

Neonatal SEGA are extremely rare; however, large SEGA have been identified in utero as early as 19 weeks of gestation [44]. The clinical diagnosis of a SEGA can be extremely difficult. They often present insidiously with subtle changes in behaviour, cognitive function or seizures long before clearcut symptoms of increased intracranial pressure, including headache and vomiting [45]. Obstructive hydrocephalus (in some cases) with clinical signs of intracranial hypertension or progressive hydrocephalus without obvious signs of increased intracranial pressure and new neurological deficits, such as blindness or worsening of a preexisting deficit, are considered indications in favour of prompt surgical resection [46]. Enlarging SEGAs alternatively can be treated with mTOR inhibitors such as everolimus, especially in cases when surgical intervention threatens eloquent cortex [47, 48].

SEGA are responsible for an estimated 25% of mortality attributable to TSC [42]. The potential for poor outcome from these lesions has led to recommendations to use cranial imaging to help identify SEGA at a presymptomatic stage [49]. According to guidelines of the NIH Consensus Conference, children with a diagnosis of TSC should have a brain MRI performed every 1–3 years, generally up to the age of 21 years [50, 51]. This recommendation is based on evidence that neuroradiological surveillance, early detection and early intervention for SEGA in TSC are associated with better neurological, cognitive and behavioural outcomes than in children with TSC who did not have surveillance for SEGA.

The kidneys can harbour angiomyolipomas (AMLs), single or multiple cysts, renal cell carcinoma and oncocytomas in 75–80% of the patients over the age of 10 years [52, 53]. Angiomyolipomas are histologically benign tumours made of blood vessels, connective and lipoid tissues and smooth muscle fibres (Fig. 27.4). They can replace renal parenchyma. Cysts may be present at any age, and renal tumours tend to grow mainly in older children and adults (Fig. 27.5). Symptoms usually occur during adulthood when the tumours grow beyond 4 cm in size. They can cause major bleeding and renal failure, especially when both kidneys are affected [54]. The symptoms include haematuria, hypertension, lumbar pain and renal insufficiency. Occasionally, some adults are diagnosed with tuberous sclerosis complex as a result of renal or pulmonary presentation. Tumours rarely become malignant. The combination of renal cysts (20–30% epithelial cysts) and angiomyolipomas is another characteristic of TSC [55]. A particularly aggressive phenotype occurs with contiguous gene deletion of the adjacent TSC2 and PKD1 genes, resulting in multiple renal cysts from infancy. Renal failure is a leading cause of early death [56]. Extrarenal angiomyolipomas (AMLs) are rare. In a retrospective study of sonographic and CT images, Fricke et al. [57] found 8 hepatic AMLs in 62 patients with TSC and bilateral diffuse renal angiomyolipomas.

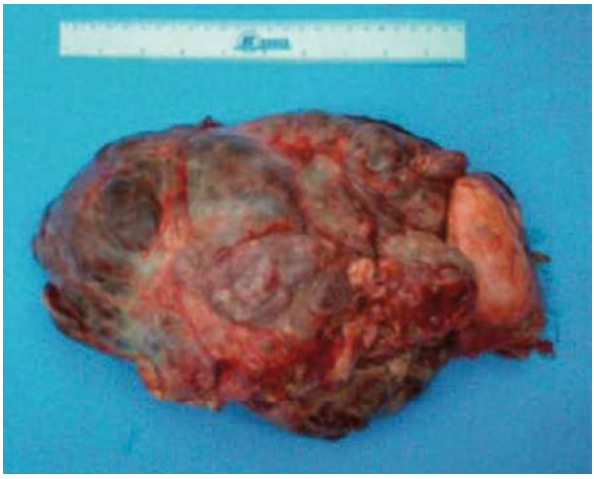

Fig. 27.4 Angiomyolipoma of the kidney in tuberous sclerosis

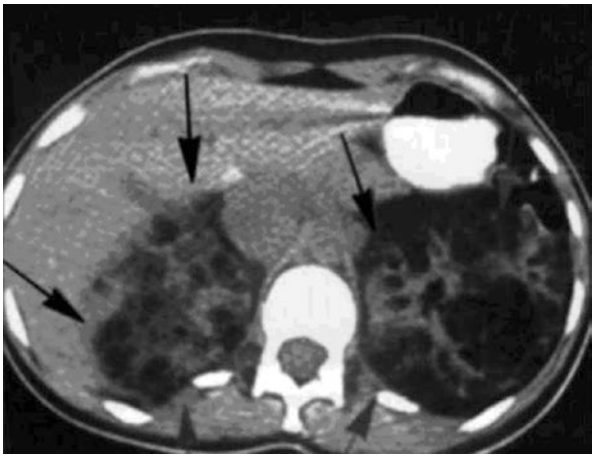

Fig. 27.5 Bilateral renal angiomyolipomas in a patient with tuberous sclerosis and large renal masses in CT scan (arrows)

Rhabdomyoma of the heart (Fig. 27.6) represents (along with hypopigmented skin spots) the earliest signs of TSC, preceding the onset of seizures [58]. Rhabdomyomas are observed in 43% of TSC patients and may sometimes be seen on prenatal ultrasound studies. Foetal rhabdomyoma (giant cardiac rhabdomyomas) is the most common foetal cardiac tumour and is often associated with tuberous sclerosis. Usually the tumours are relatively small and show no mediastinal shift. Foetal hydrops and pericardial effusion are rarely seen. The tumours may remain clinically insignificant and they tend to shrink as time passes. Cardiac dysfunction, when it does arise, can present as heart failure soon after birth. The tumours are responsible for interruption of the electrical conduction or cardiac arrest, depending on their size. Even after involution of the visible rhabdomyoma on imaging, electrocardiogram can demonstrate arrhythmia [59]. Diagnosis usually is made by ultrasound. The echocardiogram of the heart provides longitudinal follow-up of the tumour, and surveillance electrocardiogram also is recommended.

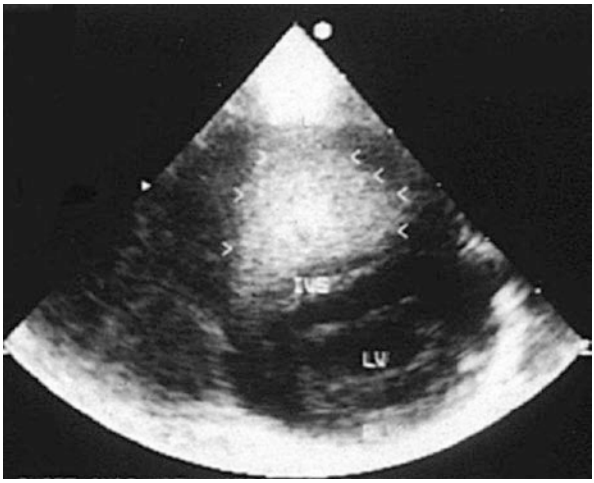

Fig. 27.6 Demonstration of a rhabdomyoma of the heart in an infant with tuberous sclerosis by sonography

Another cardiovascular complication of TSC is aortic aneurysm. Arterial aneurysms, mostly aortic and intracranial, probably through dysfunction of smooth muscle cells, have been reported sporadically in TSC. Kimura et al. [60] reported a case of a 2-year-old boy with a descending aortic aneurysm, and Boronat et al. [61] found three cases of intracranial aneurysm in a cohort of 404 patients.

Pulmonary involvement carries high morbidity and mortality when present and symptomatic. The diagnosis of lymphangioleiomyomatosis (LAM), which consists of reticular infiltration, multicystic formation and micronodular pneumocyte hyperplasia, is age-dependent. It is estimated that LAM occurs in 30–80% of women with TSC in 10–12% of men; the involvement increases with age and men rarely are symptomatic [47]. The mean age of diagnosis for TSC-associated LAM is 28 years compared to 35 years for sporadic LAM. The tumour suppressor genes TSC1 and TSC2 have been implicated in the aetiology of LAM, as mutations and loss of heterozygosity in TSC2 have been detected in LAM cells [62]. LAM manifests as dyspnoea, haemoptysis and spontaneous pneumothorax [63]. Multifocal micronodular pneumonocyte hyperplasia may be detected by CT of the chest, revealing numerous thin-walled cysts. Tissue biopsy with special stains (HMB-45) should be reserved for cases with atypical presentations. Preventive strategies include avoidance of cigarette smoking and estrogen-containing medications; for moderate to severe disease, mTOR inhibitor sirolimus has been indicated to stabilize lung function [64].

Skeletal system involvement includes cysts in the long bones and metacarpal and metatarsal joints. The association between tuberous sclerosis and macrodactyly is very uncommon [65].

The visual system is affected in the majority of TSC patients (see Chap. 47). On fundoscopy, retinal lesions (Fig. 27.7) are seen in 87% of the patients, which may be missed without proper pupillary dilation, especially in small children. The retinal lesions of TSC are astrocytic hamartomas and achromic patches, similar to the hypopigmented skin lesions [58]. The lesions consist of whitish or yellowish elevated areas resembling mulberries, often near the optic discs (retinal astrocytomas). The frequency of retinal hamartomas in TSC varies (about 50% of cases). The

ophthalmic findings seldom include hypopigmentation of the iris. Retinal astrocytic lesions of TSC generally are nonprogressive but may also grow relentlessly and cause severe ocular complications [66].

Diagnosis

The diagnosis of TSC is based on clinical findings. Diagnostic criteria of the disease have been established by the Subcommittee of the Professional Advisory Board of the National TS Association revised by Roach and Sparagana [50, 52] and in 2012 by the International Tuberous Sclerosis Complex Consensus Group [9, 59]. Definite TSC is diagnosed when at least two major (or one major plus two minor) features are present. Probable tuberous sclerosis complex includes one major and one minor feature. Possible tuberous sclerosis complex includes one major or two or more minor features.

- Major features include skin manifestations (i.e. facial angiofibromas, ungual fibroma, more than three hypomelanotic macules and shagreen patches).
- Brain and eye lesions (i.e. cortical tubers, subependymal nodules, subependymal giant cell astrocytoma, multiple retinal nodular hamartomas).
- Tumours in other organs (i.e. cardiac rhabdomyoma, lymphangioleiomyomatosis, renal angiomyolipoma).

An early prenatal diagnosis, such as based on foetal rhabdomyoma, may help for an adequate planning of perinatal monitoring and treatment with involvement of a multidisciplinary team.

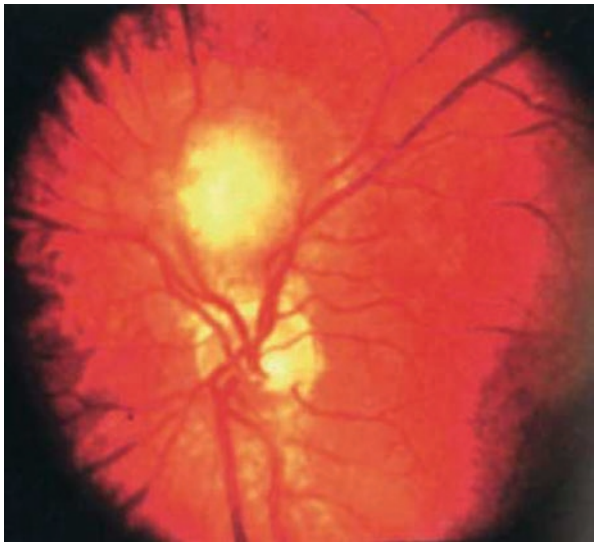

Fig. 27.7 Fundoscopy demonstrating retinal lesions

- Minor features include multiple randomly distributed pits in dental enamel
- Rectal polyps
- Bone cysts
- Cerebral white matter migration abnormalities on brain imaging
- Gingival fibromas
- Nonrenal hamartomas
- Retinal achromatic patches
- Confetti skin lesions and multiple renal cysts

Though not part of the diagnostic criteria, associated neurological features at the time of diagnosis and during disease surveillance also include seizures, autism or pervasive developmental disorders, mental retardation and various learning and behavioural disorders [40].

Early recognition of the disease demands genetic counselling of the parents, dermatologic and ophthalmologic examination, echocardiogram and electrocardiogram, brain and kidney imaging studies and developmental assessment. EEG is warranted depending on whether the patient has manifest seizures or is at a developmental age vulnerable to seizures. CT or MRI scans of the brain show hypodense/hypointense subependymal nodules (Fig. 27.8) (see Chaps. 3 and 4). Calcified nodules are readily demonstrated with CT scanning; MRI better delineates the

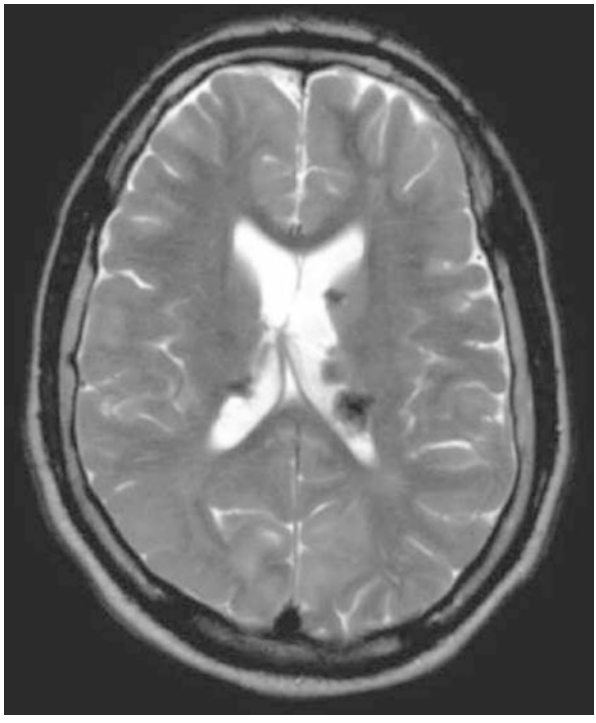

Fig. 27.8 MRI demonstrating SEGA and subventricular nodules in tuberous sclerosis

parenchymal lesions. White matter changes are hyperintense on T2-weighted sequences with a radial distribution from the ventricular ependyma to the normal cortex.

Extensive studies show variable EEG findings with epileptiform abnormalities and, rarely, with no abnormalities at all. The EEG may show multifocal hypersynchronous activity, while the primary characteristic of the infantile-type spasms is hypsarrhythmia and spike-and-wave discharges. Later, focal and generalized spikes and spike-and-slow-wave complexes may be shown. Visual recording techniques have led to significant progress in the classification of seizures associated with TSC, demonstrating that they have a focal or multifocal origin in the vast majority of the cases. In most cases, an awake interictal EEG shows focal or independent multifocal spike-and-slow-wave activity at onset and later a pseudo-hypsarrhythmic pattern. Although the pathophysiological mechanisms responsible for the co-existence of focal seizures and infantile spasms (IS) are still unclear, the latter may be the result of a rapid secondary generalization. Focal discharges are often associated with tumours within the cerebral parenchyma. It seems that the type of the initial seizures may be a significant prognostic factor.

As clinical features vary across the lifetime, surveillance testing at the time of diagnosis and at regular intervals is an important feature of comprehensive TSC care.

Management

A multidisciplinary team is necessary for achieving optimal patient therapy and outcomes.

Surgery management: As SEGAs are benign lesions, the surgical goal in the management of SEGAs is to perform a gross total resection whenever possible, which means an almost complete cure for many [67]. Therefore, previous attitudes towards operating on only symptomatic patients evolved towards a more aggressive approach to avoid the sequelae of raised intracranial pressure and hydrocephalus [68].

The surgical approach depends on tumour extension and the presence of hydrocephalus (see Chaps. 48 and 49). Transcortical, transventricular and transcallosal interhemispheric routes remain the most used approaches to the foramen of Monro [67]. However, new surgical strategies have evolved with time, and tools such as endoscopic procedures allow a less aggressive approach and lower morbidity [68, 69].

In the majority of children operated on early, the surgical outcome fluctuates between good and excellent. Some studies confirm the benefits of early surgical removal of SEGAs, especially when the tumour's diameter is less than 3 cm [43, 70]. Complications after surgical removal of SEGAs reflect those of any tumour surgery within the cerebral ventricles and around the foramen of Monro. Transient or permanent motor deficits, haemorrhage or compressive subdural collection have

been reported in about 10–20% of surgical patients [67, 70]. Major complications tend to occur more frequently in patients who are symptomatic for raised intracranial pressure or major hydrocephalus before surgery [71], such that a SEGA should be removed as soon as clear evidence of growth on two subsequent images has been determined [68]. Early resection of the tumour before the onset of irreversible neurological deficit is critical to improve the quality of life of this population, and it is associated with a low recurrence rate and low morbidity.

Symptomatic renal tumours previously have been treated surgically with nephrectomy or selective embolization for size greater than 4 cm. With the availability of medical interventions that may slow growth of angiomyolipomas and preserve renal function, embolization or resection is reserved for acute situations of haemorrhage [72].

In a meta-analysis of the literature for cardiac rhabdomyomas, Verhaaren et al. [73] concluded that surgical intervention immediately after birth is only necessary when severe cardiac outflow obstruction occurs. This tumour is generally believed to have no haemodynamic effects in the majority of cases. Exceptions may surface such as a report case of severe obstruction of the left ventricular outflow tract by a solitary tumour during pregnancy. Cardiac arrhythmias can be treated by medication or ablative surgery.

Medical treatment: In animal models, mTOR inhibitors showed that mTORC1 blockade alone and PI3K-mTOR blockade lead to suppression of tumour development and a longer survival of the treated animals [74]. Rapamycin, the first mTOR inhibitor used in individuals with TSC-associated lesions, was able to cause regression of SEGAs [75]. Its efficacy has been subsequently confirmed in later studies and even in lesions other than SEGAs, such as angiomyolipomas [76–79].

Actions of mTOR inhibitors within the mTOR pathway result in decreased protein synthesis and cell-cycle arrest, as well as decreased angiogenesis. EXIST-1 (examining everolimus in a study of TSC) was a phase III international, multicentre, double-blind, randomized, placebo-controlled trial that evaluated the efficacy and safety of everolimus in 117 patients (median age 9.5 years; range 0.8–26.6 years) with SEGA associated with TSC [80]. Everolimus was associated with a significantly greater overall SEGA response rate to shrink or stabilize growth, compared with placebo (35% vs. 0%; $p < 0.0001$); this benefit was consistent across all patient subgroups analysed [80]. Medical management with mTOR inhibitor such as everolimus can be considered for tumours that are multiple, recurrent or not amenable to gross total resection based on location or size [69, 81].

Common, typically self-limited, side effects are mostly linked to the immunosuppressive action of mTOR inhibitors and include aphthous ulcers, acneiform rash, diarrhoea, arthralgias, thrombocytopenia and non-infectious pneumonitis and may require temporary dose reduction or cessation. Severe adverse events may include upper respiratory tract infections and a potentially dramatic elevation of serum cholesterol and lipoproteins, sometimes requiring dietary adjustment or even an adjunctive pharmacological treatment [81].

Cutaneous manifestations in the form of facial angiofibromas can warrant intervention such as pulsed dye laser therapy. Systemic mTOR inhibitors have not been

approved for primary cutaneous indication, but patients with TSC taking these treatments for other indications report improvement in skin findings. Nonsystemic formulations of topical mTOR inhibitors have been compounded but are not commercially available. In topical formulation, localized irritation is a possible side effect. Ungual fibromas and cephalic plaques may warrant surgical intervention [82]. The Tuberous Sclerosis Association has released clinical guidelines for the care of patients and families with TSC (www.tuberous-sclerosis.org). In the United States, similar guidelines and resources are available through the Tuberous Sclerosis Alliance (www.tsalliance.org). In addition to medical surveillance, families with TSC and their care providers should screen for TSC-associated neuropsychiatric disorders (TAND) as these comorbidities often are underrecognized. Early recognition can facilitate interventions in homes, schools and communities [83].

Prognosis

The prognosis varies depending on the type and severity of the disease but generally reflects poorly on the psychomotor progress of the child. In oligosymptomatic cases, the prognosis is encouraging. Early screening for a diagnosis of autism is necessary [84, 85]. The onset of seizures in the neonatal period predicts moderate to severe developmental delay in more than 1/3 of cases. Most patients develop partial focal seizures that secondarily generalize or advance to Lennox-Gastaut syndrome during the course of the disease. The presence of infantile spasms due to TSC strongly correlates with the number of cortical tubers. Infants with transient IS and isolated cortical tubers located in the parietal and Rolandic regions may have normal intelligence. In contrast, children with persistent IS preceded or followed by focal seizures and with multiple bilateral tubers often develop refractory epilepsy and severe intellectual disability. Intellectual disability is a common comorbidity accompanying leading causes of death such as CNS tumours, renal insufficiency or epilepsy as in the cases of status epilepticus or sudden, unexpected death in epilepsy (SUDEP). Renal complications evolve over the lifespan. Female patients in particular are vulnerable to fatal complications of LAM [56]. Early recognition of these distinctive features appears worthwhile for therapeutic and prognostic implications [25, 86, 87].

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