Clinical & Experimental Ophthalmology
RANZCO The Royal Australian and New Zealand College of Ophthalmologists
Clinical and Experimental Ophthalmology 2017; 45: 81–86 doi: 10.1111/ceo.12806

Review

Ophthalmic manifestations of tuberous sclerosis: a review

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Abstract

Tuberous sclerosis or tuberous sclerosis complex (TSC), one of the phakomatoses, is characterized by hamartomas of the heart, kidney, brain, skin and eyes. Ophthalmologic examinations are required in all cases of TSC. Retinal hamartomas are the most common ocular finding in tuberous sclerosis. The majority of hamartomas are non-progressive; however, lesions with subretinal fluid and progression have been reported. This paper details the genetics, clinical features and ocular findings of TSC and reviews potential therapeutic options for ophthalmic manifestations.

Key words: ophthalmic, tuberous sclerosis, review.

Introduction

Tuberous sclerosis is an autosomal dominant disorder characterized by benign tumours or hamartomas of the brain, kidney, lung, heart and eyes. Bourneville is frequently recognized as describing tuberous sclerosis complex (TSC) in 1880 after a post-mortem autopsy of a girl with mental retardation, epilepsy and sebaceous adenoma revealed cerebral tubers.[1,2] In 1908, Heinrich Vogt described the diagnostic triad of 'epilepsy, idiocy and adenoma sebaceum' (now termed angiofibromatosis).[3] Van der Hoeve first described the retinal hamartomas associated with TSC in 1921.[4] Van der Hoeve is also credited with coining the term 'phakomatoses' (Greek: *phako* lens, *oma* tumour, *osis* condition) for neuro-oculo-cutaneous syndromes, specifically tuberous sclerosis and neurofibromatosis.

Pathophysiology and Genetics

Tuberous sclerosis is an autosomal dominant disorder with near complete penetrance that results from mutations in tuberous sclerosis-1 (TSC1) or tuberous sclerosis-2 (TSC2).[5] TSC1 is due to a heterozygous mutation of TSC1 on chromosome 9q34, which encodes for the gene hamartin. TSC2 is caused by a heterozygous mutation of TSC2, which encodes for the gene tuberin. Two-thirds of cases represent *de novo* events. TSC2 mutations (75–80%) are more common than TSC1 (10–30%).

Tuberin and hamartin are tumour suppressor genes that inhibit the mammalian target of rapamycin (mTOR) pathway. TSC has variable expressivity because TSC1 and TSC2 produce a phenotype according to Knudson's two-hit hypothesis.[6] The first hit is a mutation of TSC1 or TSC2, and the second hit is loss of heterozygosity. Loss of function of the tuberin or hamartin genes results in unregulated cell growth.[7] TSC affects cell growth in different germ layers causing hamartomas in affected organ systems. In retinal hamartomas, glial astrocytes and blood vessel growth is unregulated leading to characteristic retinal astrocytic hamartomas.

Genotype/phenotype association

TSC2 mutations produce a more severe phenotype then TSC1 mutations.[8–10] Further, TSC2 mutations are correlated with a higher rate of retinal findings. Patients with retinal findings are more likely to have

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Received 9 March 2016; accepted 29 June 2016.

Competing/conflicts of interest: None declared.

Funding sources: Supported in part by an unrestricted grant from Research to Prevent Blindness (New York, NY).

associated cognitive impairment, epilepsy, renal angiomyolipoma and giant cell astrocytomas.[11]

Epidemiology

Several population-based studies have reported the incidence of TSC as approximately 1 in 5000 to 10 000 live births. TSC occurs equally in men and women and in all ethnic groups.[12–15]

Diagnosis

The diagnosis of tuberous sclerosis has classically been based on clinical criteria with definite diagnosis of TSC requiring either two major features or one major feature with two minor features of TSC (Table 1). A probable TSC diagnosis requires one major feature and one minor feature. Possible TSC requires one major feature or two or more minor features.[16]

A pathogenic mutation of TSC1 or TSC2 is sufficient for diagnosis of TSC, regardless of clinical features, according to revised consensus criteria.[17] A pathogenic mutation is defined as a deletion, frame shift or missense mutation affecting protein synthesis of function of TSC1 or TSC2 proteins. Detecting a mutation on genetic testing may allow for improved surveillance and early detection in patients prior to the development of clinical features. A genetic mutation is not required for diagnosis as 10–25% of patients with TSC have no identifiable mutation and therefore should not preclude diagnosis by clinical features.

Initial workup in a patient with suspected TSC on clinical exam or confirmed TSC1 or TSC2 mutation should include dilated retinal evaluation, dermatologic exam with a Wood's lamp, echocardiogram, renal ultrasound and brain MRI or CT.

Table 1. Clinical criteria for diagnosis of tuberous sclerosis

Major criteria	Minor criteria
Cardiac rhabdomyoma	Pits in dental enamel
Cortical tuber	Hamartomatous rectal polyps
Facial angiofibroma	Bone cysts
Lingual fibroma	Cerebral white matter radial migration lines
Hypomelanotic macule	Gingival fibromas
Subependymal nodule	Renal cysts
Subependymal giant cell tumour	Confetti skin lesions
Retinal hamartoma	Retinal achromic patch
Renal angiomyolipoma	–
Lymphangiomatosis	–

Definite diagnosis of tuberous sclerosis complex (TSC) requires either two major features or one major feature with two minor features. Revised consensus criteria have identified mutations in TSC1 or TSC2 as independent criterion for diagnosis.[16,17]

Brain lesions are classified into three types: (i) cortical tubers; (ii) subependymal nodules; and (iii) subependymal giant cell astrocytomas.[18] These lesions can have calcifications and cystic components, and lesions may lead to hydrocephalus. Most patients with TSC will develop seizures. Approximately one-half to two-thirds of patients will have developmental delays and/or autism spectrum disorders, although many patients will only have mild symptoms.[19,20]

Approximately 70–80% of patients will develop renal cysts or angiomyolipomas.[17] Angiomyolipomas, commonly asymptomatic, can cause anaemia and renal failure if very large.[21,22] Adult polycystic kidney disease occurs with a contiguous polycystin-1 deletion and can result in progressive renal failure.[23]

Cardiac rhabdomyomas are frequently detected on prenatal ultrasound. Therefore, this is often the seminal finding leading to greater workup and diagnosis. These tumours have been described to regress over time[16,17] but can lead to death if large and obstructing cardiac outflow.[24]

There are many dermatologic features including hypomelanotic macules or 'ash leaf' spots, angiofibromatosis, previously called adenoma sebaceum (Fig. 1a), thickened shagreen (shark skin) patches typically on the low back (Fig. 1b) and ungual (nail) fibromas.[18]

Pulmonary lesions such as lymphangioleiomyomatosis are more common in women with TSC and can vary from asymptomatic to severe.[25]

Ophthalmic Manifestations of Tuberous Sclerosis

Retinal hamartomas

Retinal hamartomas or retinal astrocytic hamartomas, one of the major criteria for diagnosis of TSC,[16,17] occur in approximately 50% of patients in an American cohort.[26] Bilateral hamartomas occur in 30% of patients.[27] These are categorized into flat and translucent lesions, nodular lesions and transitional type lesions, which display a combination of features. Most lesions remain stable over years, and there is no definite association with the type of lesion and age.

Flat lesions are the most common type of hamartoma and are often light grey or yellow and translucent with indistinct margins (Fig. 2). The lesions do not have calcifications. Because they are faint in colour, these lesions can be subtle and therefore missed on examination. They are often located near the end of the arcades and are characterized by obscuration of vessels. Flat hamartomas occur in 50–70% of patients with tuberous sclerosis.[28]

The classic multinodular type hamartoma is a sharply demarcated, elevated, nodular lesion often

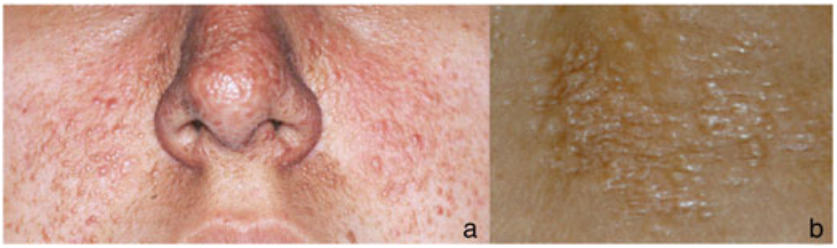

Figure 1. Dermatologic features in tuberous sclerosis complex (TSC). (a) Angiofibromatosis (adenoma sebaceum) in a male patient with TSC. (b) Shagreen patch on the low back of a female patient with TSC.

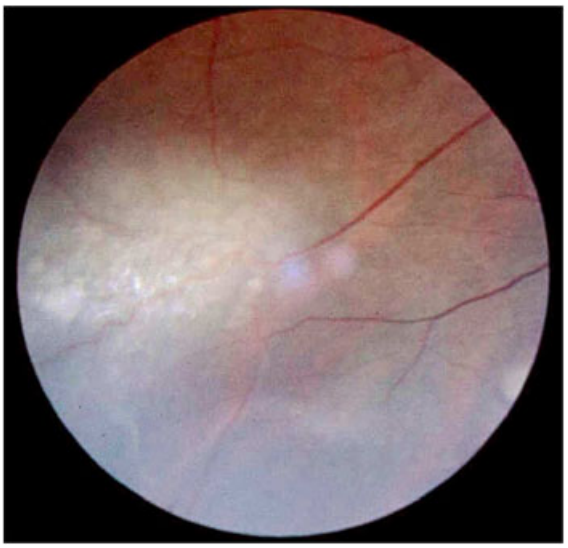

Figure 2. Colour fundus photo demonstrating flat type lesion. Note the obscuration of retinal vasculature.

described as a 'mulberry' 'lesion' or 'fish eggs' (Figs 3 and 4). These lesions have calcifications that can be demonstrated on B-scan ultrasonography as hyperechogeneic with posterior shadowing (Fig. 5) and CT scan. Multinodular hamartomas are found in the posterior pole and near the disc. These elevated lesions occur in approximately 50% of patients.[26,28,29]

Transitional lesions are less common occurring in 9–12% of patients. These lesions have a combination of features typical to the flat and multinodular astrocytic hamartomas. The base of the tumour may be translucent and flat with a central elevated, nodular appearance.[26,28,29]

Although most retinal hamartomas in TSC are stationary, aggressive hamartomas with progressive growth can occur. Shields *et al.* reported a series of four patients with TSC complex and retinal neoplasms with progressive growth.[30] These tumours were peripapillary and demonstrated slow persistent growth with development of neovascular glaucoma and exudative retinal detachment. Despite surgical and laser therapy in two of the cases, all four cases required enucleation for a blind and painful eye. Figure 6a demonstrates a peripapillary aggressive type astrocytic hamartoma in a patient with TSC. Despite treatment with Photodynamic therapy (PDT), the patient developed an exudative retinal detachment 2 years later (Fig. 6b) and required vitrectomy with retinal reattachment.

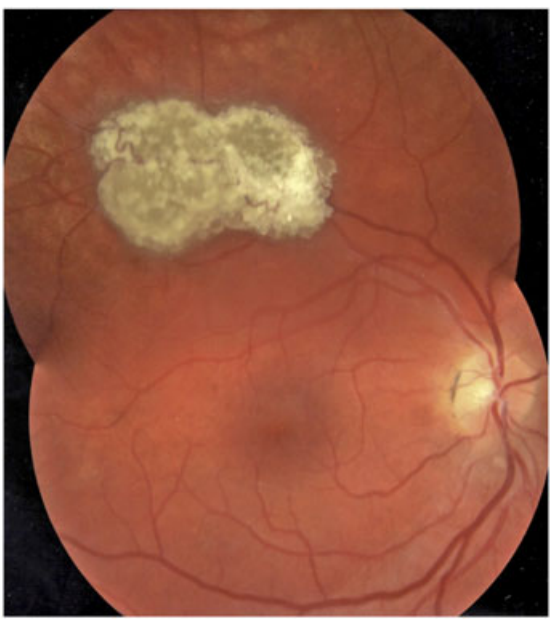

Figure 3. Colour mosaic photo of the right eye with 'mulberry' or multinodular lesion appearance.

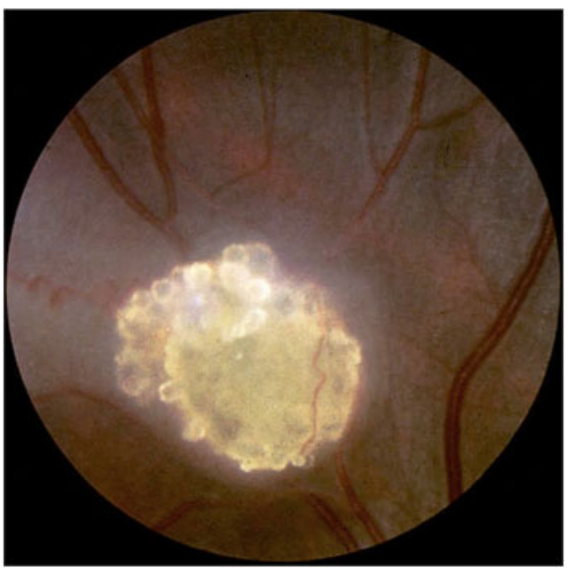

Figure 4. Colour fundus photo high magnification of another multinodular astrocytic hamartoma.

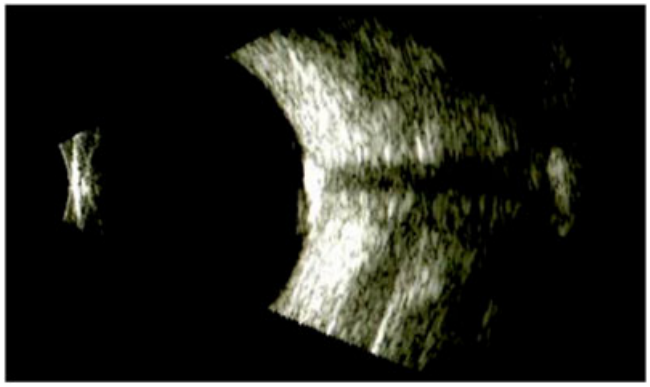

Figure 5. B-scan ultrasonography demonstrating a hyperechogeneic mass (hamartoma) with posterior shadowing due to calcifications.

Optical coherence tomography of astrocytic hamartomas characteristically show dome-shaped hyperreflective masses with retinal disorganization, posterior shadowing and moth-eaten spaces associated with calcifications (Fig. 7).[31,32]

Retinal hamartomas can occur in neurofibromatosis and have also been described in cases of retinitis pigmentosa.[33] Retinoblastoma should be considered in the differential.[28] Optic nerve head drusen may mimic multinodular lesions near the disc. Features of tuberous sclerosis as described in Table 1 support the diagnosis of TSC and associated retinal astrocytic hamartoma.

Non-retinal findings

There are several case reports of hypopigmented sectoral lesions of the iris and ciliary body as well as colobomas of the iris and choroid.[34–37] Hamartomas of the iris and ciliary epithelium have also been described.[38] Angiofibromas of the eyelids can occur. In patients with tuberous sclerosis, the prevalence of myopia was found to be 27% compared with 25% in a National Health and Nutrition Examination survey, the prevalence of hyperopia was 22% compared with 57% in the Blue Mountains Eye Study, and the prevalence of astigmatism was 27% compared with 20% in a Danish population.[29] Additionally, obstructive hydrocephalus secondary to giant cell astrocytomas can occur and produce papilloedema. Papilloedema in a patient with TSC complex warrants CT imaging to evaluate for obstructive hydrocephalus and may require ventroperitoneal shunt.[39,40]

Histopathology

Astrocytic hamartomas are composed of a network of glial astrocytes and blood vessels. Lesions develop in the nerve fibre layer or the optic nerve head. Multinodular lesions form hyaline and calcium deposits that are basophilic.[41,42]

Management and Treatment

Studies in mouse models have indicated sirolimus (mTOR inhibitor) and interferon-gamma may serve as a potential therapy for TSC.[43] A clinical trial using sirolimus for angiomyolipoma found some regression while on treatment; however, the tumours increased in volume after discontinuation of therapy.[44] Everolimus is approved to treat subependymal giant cell astrocytomas and angiomyolipomas.[45]

Most patients will require anti-epileptics. Vigabatrin is commonly used for the treatment of associated infantile spasms.[46] Everolimus and sirolimus have been effective in patients with intractable epilepsy.[47,48]

Retinal hamartomas generally remain stable over years and rarely affect vision. Patients should be seen yearly as hamartomas can develop subretinal fluid

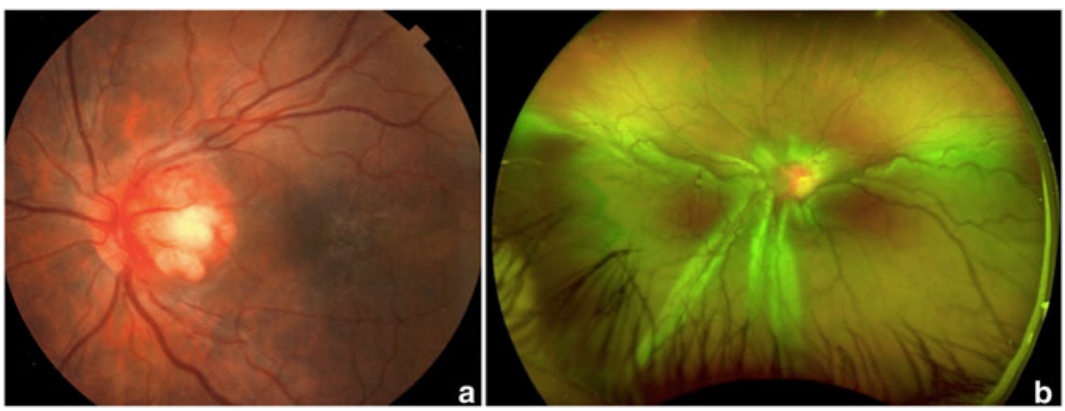

Figure 6. (a) Colour fundus photo of early stage of aggressive type peripapillary astrocytic hamartoma. (b) Optos ultra-widefield photo of aggressive astrocytic hamartoma 2 years later showing enlargement of astrocytoma and exudative retinal detachment despite treatment with PDT.

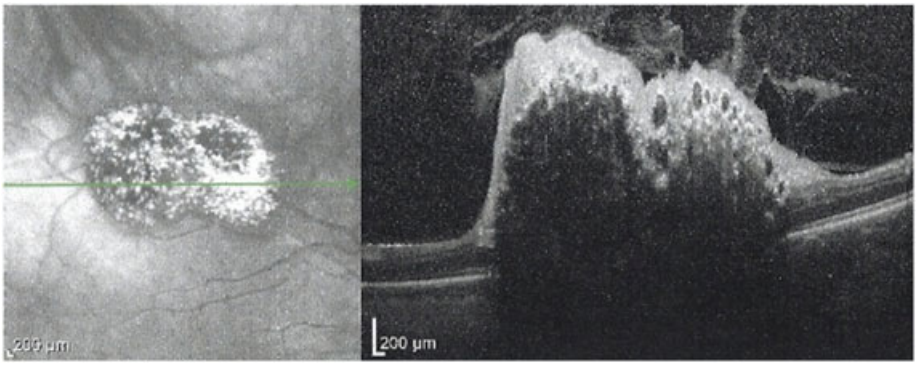

Figure 7. Spectral domain optical coherence tomography of the left eye demonstrating retinal disorganization, 'moth eaten' spaces and calcifications associated with multinodular-type lesion.

and rarely cause retinal detachment. Mennel *et al.* reported that most fluid resolved spontaneously.[49,50] If fluid persists, treatment with argon laser photocoagulation may be effective; however, recurrent laser treatment has been shown to induce choroidal neovascularization. PDT is an effective alternative with fewer reported complications.[51] Recent case reports have described the efficacy of intravitreal bevacizumab and combined bevacizumab and triamcinolone in patients with macular oedema and intraretinal haemorrhage associated with hamartomas.[52–54] Aggressive lesions are rare and do not respond well to vitrectomy or laser and may require enucleation for a blind painful eye.

Conclusions

This review details the ophthalmic manifestations of TSC. If features of TSC are detected on prenatal ultrasound or clinical examination, a full ophthalmologic examination is warranted. Further, a retinal hamartoma found on ophthalmologic exam should prompt a workup for TSC including brain imaging, echocardiogram and renal ultrasound. The majority of retinal hamartomas remain stable, although can develop subretinal fluid that may respond to PDT and intravitreal bevacizumab.

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