The eye and phacomatoses

This article reviews the ocular and neuro-ophthalmic manifestations of phacomatoses, while emphasizing important differential diagnoses that exist based on their clinical features. Variations in the definition of phacomatoses do exist, but conditions not meeting the classical definition are also presented.

The phacomatoses form a collection of congenital and hereditary developmental abnormalities, characterized by multiple hamartomas of the central and peripheral nervous system, eye, skin and viscera (Nowak, 2007). Hamartomata are defined as localized overgrowths of a single tissue, or combination of tissues, that are indigenous to that particular site (Stricker and Kumar, 2010). Although they are regarded as benign tumours, they can lead to functional impairment.

Most phacomatoses have a Mendelian pattern of inheritance (as a result of a mutation in a single gene), but some have no clear patterns of inheritance or genetic susceptibility. They may be referred to as 'neurocutaneous' conditions, but some have no cutaneous manifestations (e.g. von Hippel–Lindau disease).

This article reviews the ocular and neuro-ophthalmic manifestations of phacomatoses, while emphasizing important differential diagnoses that exist based on their clinical features. Variations in the definition of phacomatoses do exist (Nowak, 2007) and although Wyburn–Mason and retinal-neurocutaneous cavernous haemangioma syndrome do not conform to the definition above they are presented here because of their ophthalmic and neurological manifestations.

Ophthalmic manifestations

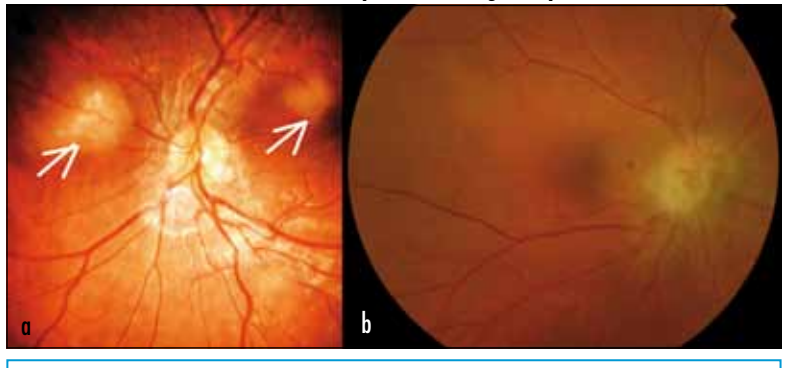
Depending on the structure affected, phacomatoses can lead to a variety of ocular symptoms and signs. Patients may be asymptomatic and ocular findings may have been noted on routine examination (e.g. retinal haemangioma or astrocytoma). Patients may present with blurred vision, monocular diplopia or metamorphopsia if the hamartoma affects the retina through the extravasation of fluid (e.g. retina haemangioma). Involvement of the cranial nerves or cerebellum may lead to binocular diplopia or nystagmus respectively.

Tuberous sclerosis

Tuberous sclerosis is an autosomal dominant disorder, although sporadic mutations can account for two-thirds of cases (Curatolo et al, 2008). The most commonly affected genes include TSC1 (encoding protein hamartin) and TSC2 (encoding protein tuberin), which are thought to be tumour suppressor genes and influence cell growth and proliferation. Its estimated prevalence is 1 in 12 000. There is a marked variation in the expression of the disease with lesions varying in size, location and number. A wide range of organs is affected. Neurological problems (seizures, cognitive impairment and behavioural problems) are the most common presenting feature, affecting up to 85% of children and adolescents. Dermatological features include hypomelanotic macules, facial angiofibromas (hamartomatous nodules of vascular and connective tissue distributed with a butterfly pattern over the malar region), shagreen patches (connective tissue naevi, generally located over the lumbosacral area). Renal complications are the most frequent cause of tuberous sclerosis-related death since angiomyolipomas can spontaneously bleed (Rakowski et al, 2006).

Retinal hamartomas can occur in up to 50% of people with tuberous sclerosis and a number of morphological types exist (Rowley et al, 2001). These include flat, salmon-coloured translucent lesions and multinodular calcified 'mulberry' lesions. A mixture of these two types can also occur (*Figure 1*). Mulberry-type lesions arise from within the nerve fibre layer of the retina and are composed of glial and astrocytic fibres. The growth of these lesions is uncommon and, unless the lesions affect the macular or optic nerve (*Figure 1*), they are typically asymptomatic.

Figure 1. Retinal hamartomas in tuberous sclerosis. a. Two nodular pale retinal lesions can be seen (white arrows). b. An astrocytoma affecting the optic nerve.



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Retinal lesions that can have a similar appearance to retinal astrocytomas and also have systemic implications include retinoblastomas, toxocara and amelanotic choroidal melanoma. Myelinated nerve fibres may also appear similar to astrocytomas.

Uncommon ocular manifestations include early-onset cataracts, iris and ciliary body hamartomas. The ocular adnexae could also be affected with angiofibromas.

Neurofibromatosis

Neurofibromatosis is characterized by neuroectodermal tumours arising within multiple organs. Two clinically distinct forms exist. Some of the features can be apparent at birth, but most do not become apparent until late childhood or early adulthood. The severity of the syndrome varies markedly between patients and those with limited forms may not be diagnosed at all.

Neurofibromatosis 1 (von Recklinghausen's disease) is the most common phacomatosis (estimated prevalence 1 in 5000) and is an autosomal dominant disorder with high penetrance and expressivity (Reynolds et al, 2003). The neurofibromatosis 1 gene is thought to be a tumour suppressor gene and its inactivation in Schwann cells and other neural crest derivatives contributes to neuro-fibroma formation. Neurofibromatosis 1 is characterized by café au lait spots, axillary and inguinal freckling, Lisch nodules of the iris (*Figure 2*), cutaneous neurofibromas, optic nerve gliomas and CNS neurofibromas. Visceral lesions include phaeochromocytomas and neurofibromas of the intestines, liver or bladder.

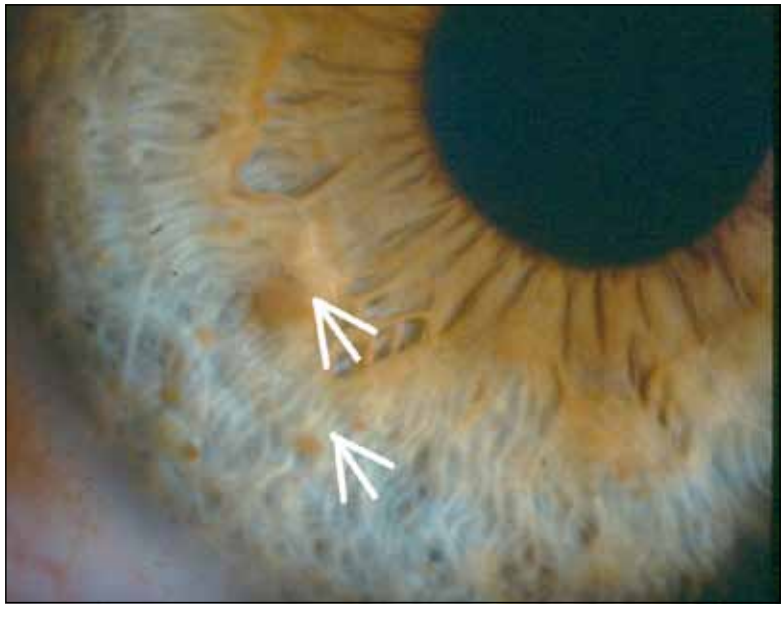
There are a number of ophthalmic features of neurofibromatosis 1. Lisch nodules (*Figure 2*) are melanocytic hamartomas of the iris stroma and develop by early adulthood in most patients with neurofibromatosis 1 (Reynolds et al, 2003). Optic nerve or chiasmal gliomas can affect the visual pathway in up to 20% of neurofibromatosis 1 patients and if diagnosed in patients aged <6 years have a worse prognosis and require frequent ophthalmic review and magnetic resonance imaging (Listernick et al, 2007). Optic nerve gliomas can also lead to proptosis. Low-grade astrocytic tumours of the cerebellum or brainstem can lead to nystagmus, abnormal saccadic or smooth pursuit movement, or diplopia (Albers and Gutmann, 2009). Meningiomas of the optic nerve sheath or sphenoid wing can also lead to visual loss. Although schwannomas (neuromas) in neurofibromatosis 1 are typically benign, they commonly affect cranial nerves such as the third, fourth and sixth resulting in diplopia. Dysplasia of orbital bones can also occur and lead to enophthalmos.

Neurofibromatosis 2 is also an autosomal dominant disorder and has an estimated prevalence of 1 in 50 000 (Ferner, 2010). The neurofibromatosis 2 gene is also a tumour suppressor gene. Bilateral acoustic neuromas are the most common manifestation of neurofibromatosis 2. Meningiomas, schwannomas and gliomas can also occur. Cutaneous manifestations are uncommon.

Ophthalmic features of neurofibromatosis 2 are not as prominent as neurofibromatosis 1 but include posterior subcapsular cataracts, epiretinal membranes and retinal hamartomas (Kerrison, 2000). Diplopia can also result from the compression of the sixth cranial nerve by an acoustic neuroma.

The prominent and distinct cutaneous manifestations of neurofibromatosis 1 are almost diagnostic for this condition, but the cutaneous lesions, cranial nerve palsies, iris findings and optic nerve pathology should not be confused with sarcoidosis. In sarcoidosis, the most common ocular manifestation is uveitis and iris or optic nerve lesions include granulomas.

Figure 2. Lisch nodules (white arrows) in neurofibromatosis.



von Hippel–Lindau disease

von Hippel–Lindau disease is an autosomal dominant disease with incomplete penetrance. Its estimated incidence is 1 in 36 000 of live births in the UK (Maher et al, 2011). The genetic defect is caused by mutations in the VHL1 tumour suppressor gene. Mutations can arise de novo and approximately 20% of von Hippel–Lindau syndrome patients do not have a family history. The mean age of diagnosis is usually just before the end of the third decade of life. Characteristic tumours include retinal and CNS haemangioblastomas, clear cell renal cell carcinoma, phaeochromocytoma and pancreatic islet tumours. Affected individuals have a high risk of early death, usually as a result of intracranial haemorrhage from a haemangioblastomas or renal cell carcinoma.

Retinal angiomas (haemangioblastomas) are seen in up to 60% of patients with von Hippel–Lindau disease (Dollfus et al, 2002). Histologically, they have been shown to be benign lesions composed of endothelial-lined vascular channels in a stroma of polyhedral, spindle-shaped and vacuolated glial cells. Although these lesions are referred to as 'capillary haemangiomas', this is

not precisely correct. Initially, the retinal angiomas consist of a small feeder arteriole and draining venule but gradually enlarge and become globular (*Figure 3*). This may lead to haemorrhage, or extravasation of fluid (*Figure 3*) leading to a mound of macular exudate and, in some cases, exudative retinal detachment and eventual phthisis. The retinal angiomas can arise from all retinal sites, from the optic disc to the periphery, with at least 50% of patients having lesions that are bilateral, multifocal or both (Wong and Chew, 2008).

Early diagnosis and treatment can prevent visual loss or blindness and screening examinations with dilated fundoscopy are recommended at least once a year starting at the age of 1 year (Lonser et al, 2003; Wong and Chew, 2008). Most peripheral retinal tumours respond to laser photocoagulation or cryotherapy (Lonser et al, 2003; Wong and Chew, 2008). Tumours on the optic disc should be monitored without treatment because of the risk of damage that some treatments can cause. Case reports of successful treatment with systemic antiangiogenic agents have been reported for treating the exudative complications of the retinal angiomas, however, intravitreal therapy with the anti-vascular endothelial growth factor agent ranibizumab had minimal beneficial effect (Wong et al, 2008). If irreversible glaucoma with severe pain results from end-stage ocular angiomatosis, enucleation may be necessary.

Vision loss may also occur from haemangioblastomas involving the optic nerve and chiasm (Kerrison, 2000). Neuro-ophthalmological manifestations of haemangioblastomas include papilloedema, sixth nerve palsy, dorsal midbrain syndrome and downbeat nystagmus (Kerrison, 2000).

Although uncommon, patients with von Hippel–Lindau disease and phaeochromocytoma can present with malignant hypertension, thus hypertensive retinopathy can be observed in these patients.

Ataxia-telangiectasia

Owing to its progressive cutaneous features, ataxia-telangiectasia has often been grouped within the phacomatoses. Cerebellar ataxia, telangiectasiae, immune deficiency and susceptibility to neoplasms characterize this autosomal recessive condition. The condition is caused by mutations in the ATM gene, which encodes a protein involved in cell cycle control. It has an incidence of about 1 in 40 000 to 1 in 100 000 births (Mavrou et al, 2008). Affected patients are normal at birth but by the age of 3 years have lost muscle coordination and by 10 years old are confined to a wheelchair.

Telangiectasia (chronic dilation of capillaries) usually appears after the onset of ataxia and can lead to the development of dark red lesions on the skin. Conjunctival vessel telangiectasia is the classic ophthalmological manifestation (*Figure 4*). Cerebellar degeneration can lead to gaze-evoked nystagmus, impaired saccades and impaired smooth pursuit eye movements.

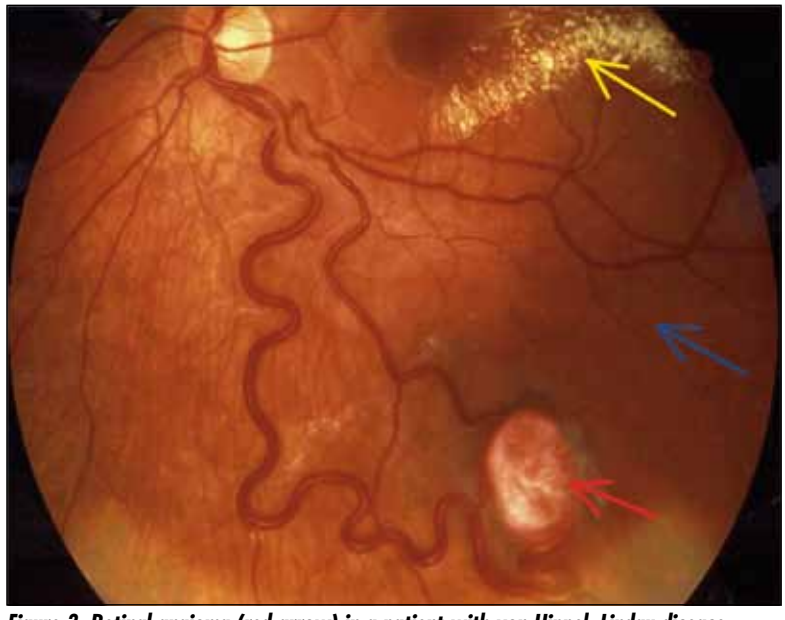


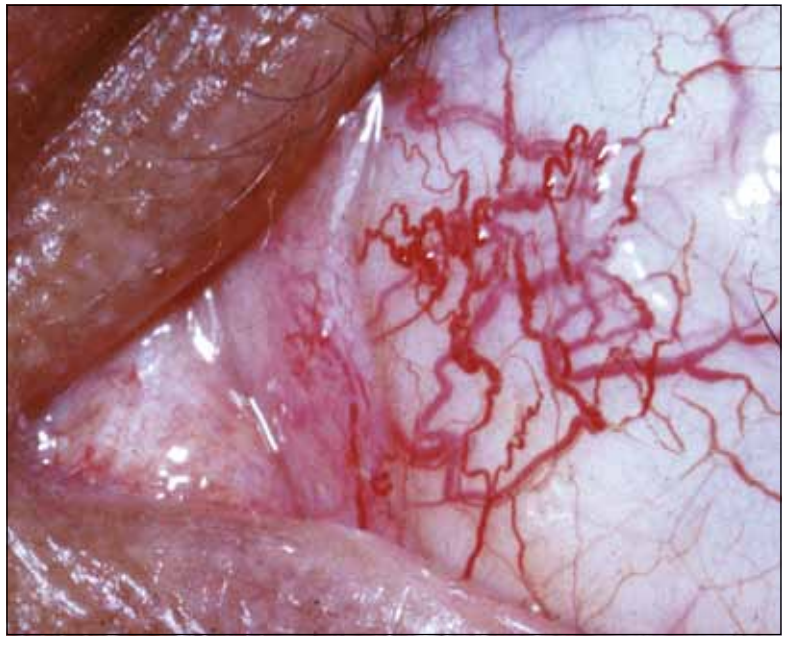
Figure 3. Retinal angioma (red arrow) in a patient with von Hippel–Lindau disease. There is associated extravasation of fluid (darker area of retina extending superiorly, blue arrow) with hard exudates at the edge of the fluid collection (yellow arrow).

Conjunctival telangiectasiae can occur in a number of other conditions with neurological manifestations, including Sturge–Weber syndrome, diabetes and Osler–Weber–Rendu syndrome (hereditary haemorrhagic telangiectasia).

Sturge–Weber syndrome

A cutaneous hemifacial haemangioma (*Figure 5*) associated with angiomas of the meninges and brain characterize Sturge–Weber syndrome. No clear evidence of an inherited component of the condition has been demonstrated. The facial angiomas are usually found in the

Figure 4. Conjunctival telangiectasia.



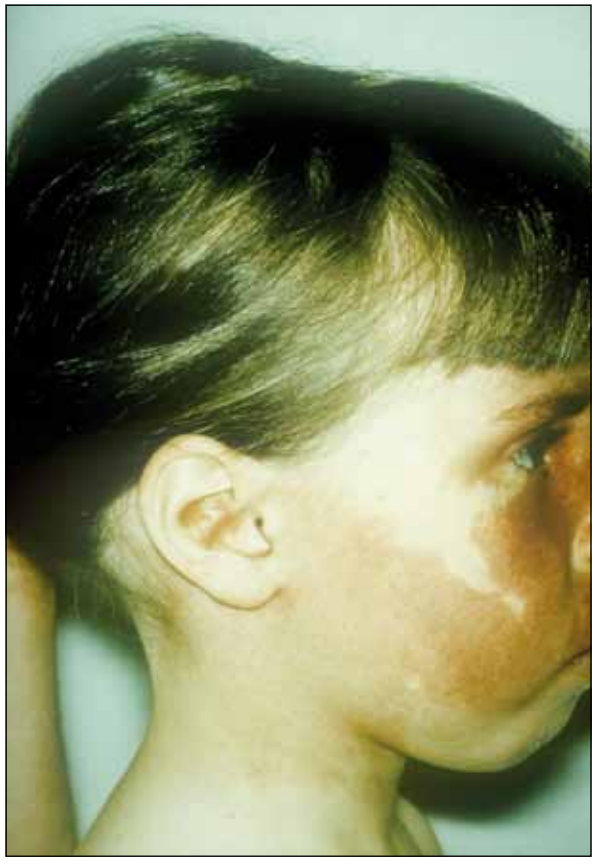


Figure 5. Facial angioma ('port-wine' stain) in a patient with Sturge–Weber syndrome.

distribution of the ophthalmic and maxillary divisions of the trigeminal nerve and are present at birth, unlike the variable picture in the phacomatoses described above. Histologically, these lesions are composed of a flat to moderately thick zone of dilated telangiectatic cutaneous capillaries lined by a single layer of endothelial cells in the dermis (Comi, 2011).

Diffuse choroidal haemangiomas are a classical ophthalmoscopic feature (*Figure 6*), being more pronounced near the optic disc and macula, with the area having a more saturated red appearance than the contralateral fundus. Retinal and conjunctival blood vessels may also be dilated and tortuous. Raised intraocular pressure may also be seen in these patients, with glaucomatous damage to the optic nerve being present in 60% of patients (Sujansky and Conradi, 1995). This may be the result of anomalous formation of the drainage angle or raised episcleral venous pressure as a result of abnormal cerebral venous drainage. If raised intraocular pressure occurs during infancy then buphthalmos can result. Medical therapy of the glaucoma in these individuals is sometimes unable to control the intraocular pressure and filtration devices or cyclodestructive procedures may be needed.

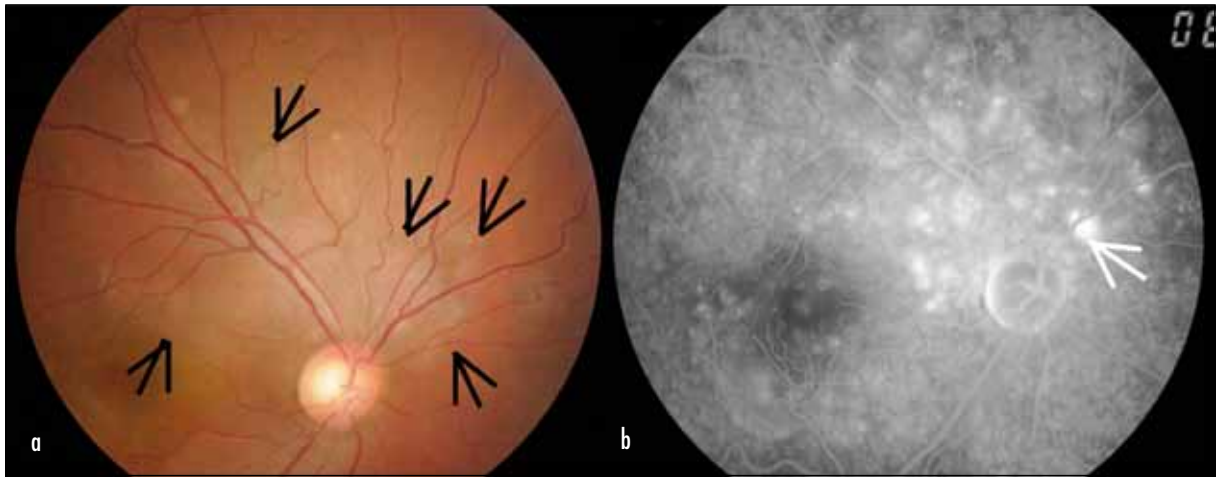
Other causes of visual loss in Sturge–Weber syndrome include exudative retinal detachment, cystic degeneration of the retina and homonymous visual field defects secondary to meningeal angiomas most commonly in the occipitoparietal region (Kerrison, 2000).

Retinal neurocutaneous cavernous haemangioma syndrome

The retinal neurocutaneous cavernous haemangioma syndrome (Weskamp–Cotlier syndrome) is rare and characterized by cavernous haemangiomas of the retina, CNS and small telangiectatic vascular lesions of the skin. Both sporadic and inherited familial forms of the disease have been reported (Sarraf et al, 2000). The CNS lesions can lead to seizures, hemiparesis or intracranial haemorrhage.

The typical retinal cavernous haemangioma is a cluster of small retinal vascular saccules associated with a back-branching retinal venule. These lesions can have a prominent white fibrous component (gliosis) and some

Figure 6. a. Choroidal haemangioma in a patient with Sturge–Weber syndrome (boundaries of lesion marked by black arrows). Although the lesion does not have the typically 'strikingly-red' appearance, instead having an orange appearance, (b) fluorescence angiography demonstrates areas of hyperfluorescence (white arrow) which reflect filling of vascular spaces within the tumour and also staining of vascular structures.



cases may also have associated retinal exudates (Sarraf et al, 2000). Most patients tend to have good visual acuity throughout life.

Wyburn–Mason syndrome

Arteriovenous malformations of the retina and ipsilateral CNS characterize Wyburn–Mason syndrome (Schmidt et al, 2008). A hereditary pattern has not been identified. Intracranial arteriovenous malformations can lead to intracranial or subarachnoid haemorrhage and oro-nasal lesions can also bleed.

The classic ophthalmic findings in Wyburn–Mason syndrome are markedly dilated and tortuous retinal vessels, which may be isolated to one or more quadrants. The anomalous arterial limb extends from the optic disc and the anomalous venous limb extends back towards the disc, but distinction between the two may not be possible. Ocular complications that have been reported from retinal arteriovenous malformations in Wyburn–Mason syndrome include central retinal vein occlusion and neovascular glaucoma (Schmidt et al, 2008). In these cases, pan-retinal photocoagulation or cyclodestruction may be needed. Direct laser photocoagulation to close vessels can be difficult and lead to the risk of intraocular bleeding. Complications such as vitreous or macular haemorrhage should be managed conservatively, with a vitrectomy being considered if it fails to resolve. Orbital arteriovenous malformations can also occur and can lead to pulsating exophthalmos.

Retinal lesions with dilated and tortuous vessels can be seen in Sturge–Weber syndrome, von Hippel–Lindau disease and hereditary haemorrhagic telangiectasia, thus these should be considered in the differential diagnosis of Wyburn–Mason syndrome (Schmidt et al, 2008).

Conclusions

This article has reviewed a number of conditions which may be regarded as phacomatoses; however, not all conditions are characterized by hamartomas or cutaneous manifestations. If ocular lesions are detected, referral to and workup by other specialists is warranted as a result of neurological and systemic implications. Some of these conditions can have similar features (e.g. dilated and tortuous retinal vessels), but the associated retinal findings are usually characteristic. **BJHM**

Conflict of interest: none.

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KEY POINTS

- The phacomatoses form a collection of congenital and hereditary developmental abnormalities.
- They are characterized by multiple hamartomas of the central and peripheral nervous system, eye, skin and viscera.
- They may be referred to as 'neurocutaneous' conditions, but some have no cutaneous manifestations (e.g. von Hippel–Lindau disease).
- The ophthalmologist can play an important role in the diagnosis and the management of sight-threatening complications.