

# Neuro-ophthalmological manifestations of tuberous sclerosis: current perspectives

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**Abstract:** Tuberous sclerosis complex (TSC) is a complex, multi-system disorder with a well-described underlying genetic etiology. While retinal findings are common in TSC and important in establishing the diagnosis, TSC also has many potential neuro-ophthalmology manifestations. The neuro-ophthalmology manifestations of TSC can have a significant impact on visual function and are sometimes a sign of serious neurological disease. The purpose of this review is to describe the neuro-ophthalmological manifestations of TSC. These manifestations include optic nerve hamartomas, elevated intracranial pressure, cranial nerve palsies, cortical visual impairment, visual field deficits, and ocular toxicity from vigabatrin treatment of infantile spasms. It is important to be aware of potential neuro-ophthalmological manifestations in these patients in order to detect signs of vision- or life-threatening disease and to optimize visual function and quality-of-life.

**Keywords:** astrocytic hamartoma, cortical visual impairment, intracranial pressure elevation, visual field defect, vigabatrin

## Plain language summary

Tuberous sclerosis complex (TSC) is a genetic disorder that can affect many different parts of the body. Benign tumors (called hamartomas) are a common manifestation of TSC. While these hamartomas are the most common finding in the eye, TSC can affect the visual system in many different ways. This review focuses on all of the potential effects of TSC on the visual system, including the effect of hamartomas on the optic nerve, high intracranial pressure due to hamartomas blocking the flow of fluid, injuries to the cranial nerves that move the eye, dysfunction of the visual processing systems in the brain, and various mechanisms that cause loss of peripheral vision. These manifestations are important to recognize because they can be a sign of life-threatening disease, or may have a significant effect on quality-of-life. Therefore, recognizing the effects of TSC on the visual system is critical to the care of these patients.

## Introduction

TSC is a complex, multi-system disorder. There are a wide array of clinical manifestations, including several that affect the neurological and visual systems. This review will focus on the neuro-ophthalmological manifestations of TSC.

## Overview of TSC Genetics

TSC is a multi-system disorder with a well-established genetic cause. The underlying genetic etiology is a mutation to either the TSC1 gene (chromosome 9q34) or the TSC2 gene (chromosome 16p13.3) and a disease-causing mutation can be identified in up to 90% of cases.<sup>1</sup> TSC is inherited in an autosomal dominant

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fashion and has very high (close to 100%) penetrance, so affected individuals have a 50% chance of passing the condition to their offspring.<sup>2</sup> However, about two-thirds of cases of TSC are due to new mutations in TSC1 or TSC2 (ie, sporadic). The estimated prevalence of TSC is 1 in 6,000 to 1 in 10,000, with approximately 50,000 affected individuals worldwide.<sup>3,4</sup>

A number of genotype–phenotype relationships have been identified in TSC. Those with TSC2 mutations are significantly more likely than those with TSC1 mutations to have angiomyolipomas, renal cysts, infantile spasms, subependymal giant cell astrocytomas (SEGA), and intellectual disability.<sup>5,6</sup> However, there are limitations on the prognostic value of genotype-phenotype correlations, and it has been well established that the clinical findings of TSC1 and TSC2 mutations overlap to a large extent.<sup>1</sup> As such, genetic testing plays an important role in diagnosis and prognosis of TSC, but cannot be used in isolation to accurately predict how a patient with TSC will ultimately be affected.

## Clinical manifestations

The diagnostic criteria for TSC are established by the International Tuberous Sclerosis Complex Consensus Group and were last updated in 2012.<sup>7</sup> The diagnosis can now be made based on genetic testing alone when a pathogenic mutation of TSC1 or TSC2 is identified. The diagnosis can also be made on clinical grounds based on the presence of major or minor features (Table 1).<sup>7</sup> The clinical manifestations of TSC vary widely between affected individuals and many systems can be involved,

with the most common being neurologic, dermatologic, renal, cardiac, pulmonary and ocular.<sup>8</sup>

## Neuro-ophthalmological manifestations

The only ocular manifestations of TSC that are part of the standardized diagnostic criteria are the retinal features. The current diagnostic criteria include “multiple retinal hamartomas” as a major feature and “retinal achromic patch” as a minor feature.<sup>7</sup> The major ocular feature, retinal hamartomas, is a very common ocular feature of TSC, being present in approximately 50% of affected individuals. However, these are not pathognomonic for TSC, as there are reports of retinal hamartomas in patients with neurofibromatosis and retinitis pigmentosa, or even as an isolated finding in otherwise healthy individuals.<sup>9–11</sup> Retinal hamartomas classically appear as flat/translucent or multi-nodular (“mulberry”) retinal lesions on dilated fundus examination.<sup>12</sup> These lesions usually have minimal impact on visual function, although rare cases of vitreous hemorrhage<sup>13</sup> and aggressive retinal hamartomas causing blindness have been reported.<sup>14</sup> The minor ocular feature, a retinal achromic patch, has been reported in approximately 5% of individuals with TSC.<sup>15</sup> These typically appear as small, flat areas of chorioretinal hypopigmentation in the midperiphery of the retina.

In addition to retinal features, there are a number of important neuro-ophthalmological manifestations of TSC. In contrast to the retinal manifestations of TSC, the neuro-ophthalmological manifestations are not part of the diagnostic criteria, but often have a significant impact on visual

**Table 1** Diagnostic criteria for tuberous sclerosis complex (TSC)<sup>7</sup>

|   |   |
|---|---|
| <b>Definite TSC</b> – Two major features or one major feature with $\geq 2$ minor features  |   |
| <b>Possible TSC</b> – Either one major feature or $\geq 2$ minor features   |   |
| <b>Major Features</b> <ol style="list-style-type: none"> <li>1. Hypomelanotic macules (<math>\geq 3</math>, at least 5-mm diameter)</li> <li>2. Angiofibromas (<math>\geq 3</math>) or fibrous cephalic plaque</li> <li>3. Ungual fibromas (<math>\geq 2</math>)</li> <li>4. Shagreen patch</li> <li>5. Multiple retinal hamartomas</li> <li>6. Cortical dysplasias (includes tubers and cerebral white matter radial migration lines)</li> <li>7. Subependymal nodules</li> <li>8. Subependymal giant cell astrocytoma</li> <li>9. Cardiac rhabdomyoma</li> <li>10. Lymphangiomyomatosis (LAM)</li> <li>11. Angiomyolipomas (<math>\geq 2</math>)</li> </ol> | <b>Minor Features</b> <ol style="list-style-type: none"> <li>1. “Confetti” skin lesions</li> <li>2. Dental enamel pits (<math>&gt;3</math>)</li> <li>3. Intraoral fibromas (<math>\geq 2</math>)</li> <li>4. Retinal achromic patch</li> <li>5. Multiple renal cysts</li> <li>6. Nonrenal hamartomas</li> </ol> |

**Note:** \*A combination of 10 and 11 without other features does not meet criteria for a definite diagnosis of TSC.

function. Neuro-ophthalmological findings may also be an indication of serious underlying neurological disease that requires urgent workup and treatment. The most important neuro-ophthalmological manifestations of TSC are optic nerve hamartomas, elevated intracranial pressure (ICP), cranial nerve palsies, cortical visual impairment, and visual field defects. Ocular toxicity from vigabatrin (a widespread and effective treatment for infantile spasms in TSC patients) is also an important neuro-ophthalmic issue in these patients.

## Optic nerve hamartomas

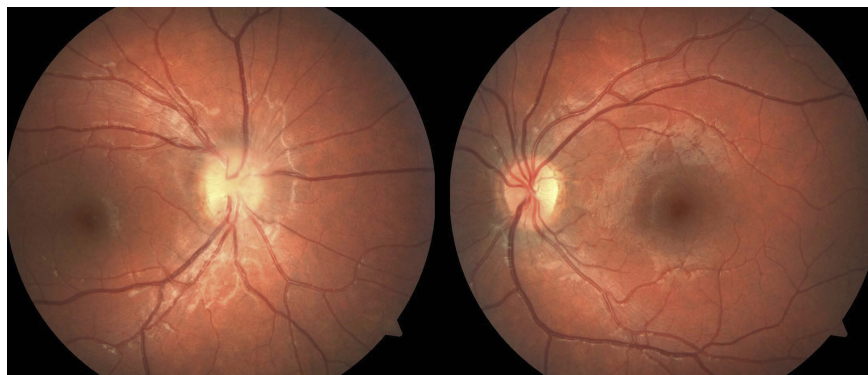
Although typically found in the retina, astrocytic hamartomas can also involve the optic nerve. Just like hamartomas elsewhere in the retina, astrocytic hamartomas of the optic nerve are generally benign and do not require treatment. The main clinical implication of optic nerve hamartomas is that they can be mistaken for other optic nerve pathologies. Therefore, it is important to differentiate optic nerve hamartomas from other optic nerve conditions which, unlike hamartomas, are often vision-threatening and treatable.

A hamartoma on the surface of the optic nerve can appear to elevate the nerve and obscure the borders, imitating the appearance of optic nerve edema (Figure 1). Given that there is a well-established risk of elevated ICP in individuals with TSC (see next section), it is important to differentiate a hamartoma on the surface of the optic nerve from papilledema. One important distinction is that optic nerve hamartomas are typically unilateral, while papilledema is usually (although not always) bilateral.<sup>16</sup> In addition, optic nerve hamartomas are generally asymptomatic, while patients with papilledema typically have symptoms of high ICP, such as severe daily headaches, nausea/vomiting, transient visual obscurations,

and pulsatile tinnitus. However, high ICP can be asymptomatic or the symptoms can be variable, especially in young children.<sup>17</sup> As such, if there is any suspicion of papilledema, a full workup is warranted. The workup for papilledema should start with urgent neuro-imaging of the brain and orbits. If neuro-imaging is unremarkable, a full neurological assessment and lumbar puncture should be performed. Prompt treatment and follow-up for papilledema are important for symptomatic relief and to minimize the risk of long-term vision loss.<sup>18</sup>

In addition to papilledema, an optic nerve hamartoma must also be differentiated from other causes of true optic nerve edema, such as inflammation, infiltration, or compression of the optic nerve. The first step is to perform a complete ophthalmological assessment, as other causes of optic nerve edema usually have a significant effect on optic nerve function, while hamartomas on the surface of the optic nerve do not.<sup>19</sup> In order to assess for optic nerve dysfunction, these patients should have a detailed check of visual acuity and color vision, a pupillary exam, and formal visual field testing. In TSC patients who are unable to cooperate with vision testing, the pupils should be checked for a relative afferent pupillary defect, as this is a sensitive test of unilateral or asymmetric optic nerve dysfunction. Any sign of visual impairment necessitates urgent neuro-imaging of the brain and orbits, since many causes of optic nerve edema can lead to severe and permanent vision loss if the diagnosis is missed or treatment is delayed.

When calcified, optic nerve hamartomas can closely resemble optic disc drusen. Indeed, the term “giant drusen” has been used to describe large calcified astrocytic hamartomas involving the optic nerve.<sup>20</sup> Optic disc drusen are acellular deposits that are usually buried in childhood and typically become superficial and calcified with time.



**Figure 1** Fundus photos showing pseudo-edema of the right optic nerve due to an astrocytic hamartoma on the surface of the nerve. Optic nerve function was normal and there was no evidence of high intracranial pressure.

Optic nerve drusen are found in approximately 2% of the population and commonly cause visual fields defects, with rare reports of other ocular complications including choroidal neovascular membrane, retinal vascular occlusion, and non-arteritic ischemic optic neuropathy.<sup>21,22</sup> Both optic nerve hamartomas and optic disc drusen are typically asymptomatic and often found incidentally. Differentiating drusen from hamartomas is usually possible based on a detailed eye examination, but the clinical features can overlap. In either case, the management is the same, involving regular eye examinations with dilated fundus examination, fundus photography if available, and formal visual field testing if possible.

Finally, although hamartomas on the surface of the optic nerve usually spare visual function, there is one published case of a hamartoma intrinsic to the optic nerve which gradually enlarged over a period of 10 years and eventually caused severe and permanent visual impairment. As such, it is prudent to follow all hamartomas involving the optic nerve regularly with serial fundus exams and testing of optic nerve function.<sup>23</sup>

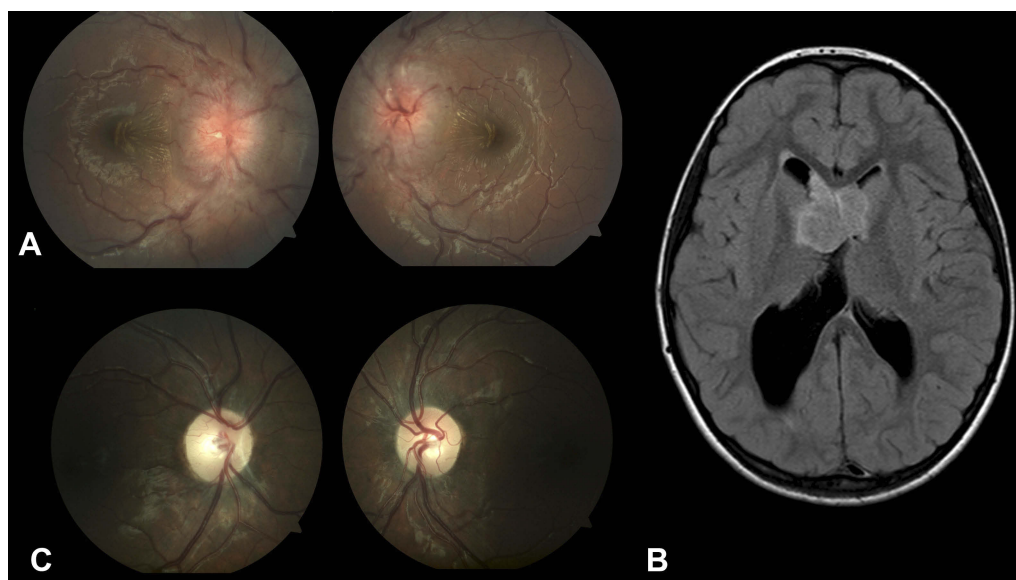
### Elevated intracranial pressure (ICP)

Elevated ICP is an uncommon but well-recognized neuro-ophthalmologic manifestation of TSC. The underlying cause is most commonly an enlarging SEGA. SEGAs are a major diagnostic feature of tuberous sclerosis with an

estimated prevalence of 20% in TSC patients.<sup>7,24</sup> Although histologically benign and slow-growing, SEGAs can cause significant complications due to their typical intraventricular location. An enlarging SEGA can block the foramen of Monro, obstructing the flow of cerebral spinal fluid and causing obstructive hydrocephalus (Figure 2).<sup>25</sup>

Patients who develop obstructive hydrocephalus usually present with typical signs and symptoms of high ICP, including headaches, nausea/vomiting, pulsatile tinnitus, transient visual obscurations, and papilledema (Figure 2). However, TSC patients can have more atypical clinical features of high ICP such as fatigue, decreased appetite, increased seizure frequency, cognitive decline, and behavioral problems.<sup>26</sup> Another potential manifestation of high ICP is a unilateral or bilateral cranial nerve VI palsy.<sup>27,28</sup> It is important to be aware that a cranial nerve VI palsy can be incomplete and a definite abduction deficit may not be appreciated on clinical exam. As such, any TSC patient with acute-onset esotropia or binocular horizontal diplopia, especially if worse in side gazes (compared to central) or at distance (compared to near), should be considered to have a cranial nerve VI palsy until proven otherwise.

When elevated ICP is suspected, urgent neuro-imaging with computed tomography (CT) or magnetic resonance imaging (MRI) should be performed to assess for obstructive hydrocephalus. If found, prompt treatment is crucial as chronic or severe papilledema can cause optic atrophy



**Figure 2** A patient with tuberous sclerosis complex presented with progressing worsening headaches associated with nausea/vomiting. The patient was found to have a mild left cranial nerve VI palsy on examination and papilledema with severe swelling of the optic nerve and macular exudates on dilated fundus exam (A). MRI revealed a subependymal giant cell astrocytoma with right univentricular hydrocephalus (B). After medical treatment with sirolimus, the papilledema resolved with mild pallor of both optic nerves (C).

and long-term visual impairment.<sup>29</sup> Patients with papilledema should undergo detailed ophthalmic exam including testing of visual acuity, color vision, and visual fields, as well as fundus photography and optical coherence tomography (OCT) of the optic nerves. The testing should be done at baseline and repeated serially post-treatment until the papilledema has resolved.

Formal visual field testing is crucial as visual field loss is the earliest sign of visual compromise due to papilledema.<sup>30</sup> Standard automated perimetry (SAP) is the gold standard for visual field testing and should be obtained in all patients with papilledema who are able to reliably perform the test. Dynamic visual field testing (eg, Goldmann kinetic visual fields) is useful in patients who are unable to fully cooperate with automated perimetry testing, such as younger children or those with neurological deficits.<sup>31</sup> If formal visual field testing is not possible, there are other objective measures of visual function which have been proposed as techniques to monitor vision in patients with papilledema.<sup>32</sup> These tests include visual evoked potentials (VEP), pattern electroretinogram (ERG), and full-field ERG. However, access to these tests is often limited to large centers and the correlation with visual function has not been fully validated.

In the context of obstructive hydrocephalus due to a SEGAs, surgical resection was historically the standard of care.<sup>26</sup> Since SEGAs are histologically benign and rarely recur, complete surgical resection is curative. However, the surgery is technically challenging and there is a significant risk of serious complications, including hemiparesis, cognitive decline, and even death.<sup>33</sup> Recently, a class of medications has emerged as an alternative treatment for SEGAs causing obstructive hydrocephalus. Mutations to TSC1 or TSC2 that cause TSC have been shown to activate the pathway involving mTOR, a kinase that helps to regulate cellular growth.<sup>34</sup> Medications that inhibit mTOR, including sirolimus and everolimus, can shrink SEGAs which may relieve the blockage of cerebrospinal fluid flow at the foramen of Monro and treat obstructive hydrocephalus without the need for surgical resection (Figure 2).<sup>35</sup> The Federal Food and Drug Administration (FDA) approved everolimus for the treatment of SEGAs in TSC in 2010 based on a study of 28 patients.<sup>36</sup> In the study, there was a reduction in the size of SEGAs by at least 30% in 21 of 28 (75%) patients, and by at least 50% in 9 of 28 (32%) patients. A subsequent multicenter, randomized, placebo-controlled phase 3 trial showed that 35% of patients treated

with everolimus had a 50% reduction in the volume of SEGAs compared to none in the placebo group, with only mild to moderate adverse events.<sup>37</sup> In studies on everolimus for SEGAs, it was incidentally noted that there were also reductions of comorbid skin lesions, renal angiomyolipomas, and retinal astrocytic hamartomas.<sup>38,39</sup> As such, in rare cases when retinal or optic nerve astrocytomas cause vision-threatening complications, mTOR inhibitors may be a potential treatment option.

## Cranial nerve palsies

Cranial nerve palsies are a rare but important neuro-ophthalmic manifestation of TSC. Cranial nerve III and VI are most commonly affected, but palsies of other cranial nerves have been reported. It is important to be aware of the underlying mechanisms and clinical implications of cranial nerve palsies in the context of TSC.

A cranial nerve VI palsy in a patient with TSC is most commonly due to elevated ICP (see previous section). A cranial nerve III palsy in TSC is most concerning for an intracranial aneurysm. Although rare, cranial nerve III palsies due to aneurysms have been reported in both children and adults with TSC.<sup>40,41</sup> A complete cranial nerve III palsy usually presents acutely with severe ipsilateral ptosis, mydriasis, and a hypotropic/abducted eye (ie, the eye is “down and out”).<sup>42</sup> However, similar to cranial nerve VI palsies, a cranial nerve III palsy can be partial or incomplete. A partial cranial nerve III palsy may be much more difficult to diagnose as some of the signs can be subtle or not present at all. Since the parasympathetic pupillary fibers run on the outside of cranial nerve III, compression from an intracranial aneurysm causes ipsilateral pupillary dilation in the majority of cases. However, it is not uncommon for there to be incomplete or absent ptosis and/or mild or absent ophthalmoplegia.<sup>43</sup> Since intracranial aneurysms are treatable and potentially life-threatening, a patient with TSC presenting with any signs of a cranial nerve III palsy should be urgently evaluated with neuroimaging (eg, CT or MRI) including angiography.

Cranial nerve III palsies in TSC are usually caused by direct compression from an enlarging, un-ruptured posterior communicating artery aneurysm. When detected, intracranial aneurysms can be successfully treated with coil embolization to minimize the risk of future rupture.<sup>41,44</sup> A ruptured aneurysm can also rarely manifest as an isolated cranial nerve III palsy, but more commonly presents acutely with a myriad of neurological findings, including

severe headache (“worst headache of my life”), nausea/vomiting, neck stiffness, seizures, and loss of consciousness.<sup>45</sup> A ruptured intracranial aneurysm has a high mortality rate and should be treated emergently in a high-acuity setting.

Finally, multiple simultaneous cranial nerve palsies can occur in patients with TSC. While rare, this is a medical emergency whenever it occurs. The potential causes of multiple simultaneous cranial nerve palsies include severely elevated ICP, a ruptured intracranial aneurysm, and an internal carotid artery aneurysm in the cavernous sinus, all of which are life-threatening.<sup>46</sup>

## Cortical visual impairment (CVI)

CVI is one of the most common ophthalmological manifestations of TSC. CVI is a broad and evolving term. The definition of CVI currently includes all types of visual dysfunction caused by damage and/or dysfunction of the retrochiasmatic visual pathways and cerebral structures in the absence of major ocular disease (or visual deficits out of keeping with the ocular disease alone).<sup>47</sup> As such, instead of a single condition, CVI is best thought of as a large number of conditions, each of which with the potential to have different effects on the visual system and a wide spectrum of severity.

At the extreme end of the spectrum is profound CVI (ie, cortical blindness), the total loss of vision with a very poor prognosis for recovery. Cortical blindness presents as severe vision loss in the presence of a normal structural eye exam, usually accompanied by other neurological deficits. The diagnosis of profound CVI can usually be made with a comprehensive eye exam in the context of relevant clinical and neuroimaging findings. However, the diagnosis can sometimes be challenging, especially in young children, as there can be significant overlap in clinical signs with other conditions such as autism spectrum disorder and delayed visual maturation.<sup>48</sup> In uncertain cases, an abnormal visual evoked potential can help to confirm the diagnosis.<sup>49</sup> Fortunately, cortical blindness is rare in TSC, and many more individuals have less severe, but still significant, forms of CVI.<sup>50</sup> The prevalence of CVI in general is difficult to estimate given the broad and evolving definition. This is particularly true in patients with TSC, as many have moderate to severe intellectual disability and are unable to fully cooperate with testing. It is known that approximately 90% of TSC patients have epilepsy, cortical brain malformations, and/or neuropsychiatric disorders.<sup>8,51</sup> These manifestations

imply some degree of neurological dysfunction, which is highly correlated with CVI. As such, it is likely that many, if not most, patients with TSC have some degree of CVI.

CVI can manifest with a myriad of visual deficits. Typically, vision is significantly subnormal for age and visual function and attention fluctuate widely from day to day. Both visual acuity and visual field (typically the lower hemi-field) can be affected. Visual function with CVI is usually best in familiar environments with minimal crowding and there is a tendency to view objects of interest very close or with eccentric gaze.<sup>52,53</sup> On examination, common findings include a horizontal conjugate gaze deviation and exotropia, with absence of nystagmus and normal optic discs.<sup>54</sup> By definition, to be diagnosed with CVI, the structural eye exam must be normal, or if there are ocular abnormalities, the visual deficits must be significantly greater than can be explained by ocular abnormalities alone.

In addition to visual acuity and visual field deficits, which can be detected on standardized tests, there is increasing recognition that CVI causes deficits in higher-order visual processing.<sup>55</sup> These deficits can have significant impacts on learning, mobility, interactions, and overall quality-of-life.<sup>56</sup> Despite the high prevalence, deficits in higher-order processing due to CVI are often difficult to recognize. The deficits may only manifest in complex real-life situations, such as difficulty with perceiving complex moving scenes or recognizing faces and objects.<sup>57</sup> Having these patients assessed outside of the typical clinical environment (eg, at home or at school), ideally with occupational therapy support, can be very helpful in trying to assess the effect of visual processing deficits on daily function.

The prognosis of CVI is highly variable. Improvement of vision can occur to varying degrees in up to half of individuals with CVI, although most never achieve completely normal visual function.<sup>58</sup> Management is primarily supportive, with regular eye examinations, refractive correction if needed, and referral to vision support services as early as possible. Given the complexity of these cases, interdisciplinary specialized care is the preferred model, with coordination between ophthalmology, neurology, psychiatry, occupational therapy, and primary care.<sup>59</sup>

## Visual field deficits

There are several possible mechanisms for visual field loss in TSC. The main mechanisms of visual field loss in individuals with TSC include astrocytic hamartomas, CVI, and vigabatrin treatment.

Astrocytic hamartomas of the retina and optic nerve and SEGAs are all potential causes of visual field deficits in TSC patients. Large astrocytic hamartomas of the retina can cause arcuate visual field defects corresponding to the anatomical location of the hamartoma.<sup>11</sup> For instance, a peripheral inferonasal retinal astrocytic hamartoma can cause a superotemporal visual field defect. However, the visual field defect is typically small and often functionally compensated for by the overlapping visual field of the other eye. As such, although retinal astrocytic hamartomas are very common in TSC, the corresponding effect on peripheral vision is usually so minor as to be functionally insignificant. In contrast, ocular complications of retinal astrocytic hamartomas, such as vitreous hemorrhage and exudative retinal detachments, are uncommon but generally cause significant visual field loss when they do occur. Astrocytic hamartomas of the optic disc generally do not affect visual function when on the surface of the optic nerve. However, when intrinsic to the optic nerve, hamartomas can gradually enlarge and cause progressive loss of visual field.<sup>23</sup> Finally, SEGAs associated with high ICP can rarely cause visual field defects as a result of severe or chronic papilledema and ultimately optic atrophy.<sup>60</sup>

CVI is another cause of visual field loss in TSC. CVI can affect any part of the visual field with a variable degree of severity. In general, visual field defects in CVI are typically in the lower hemi-field, although there is no evidence that this association specifically applies to TSC.<sup>52,61</sup> If possible, visual field testing should be performed in patients with TSC suspected of having CVI, although detailed

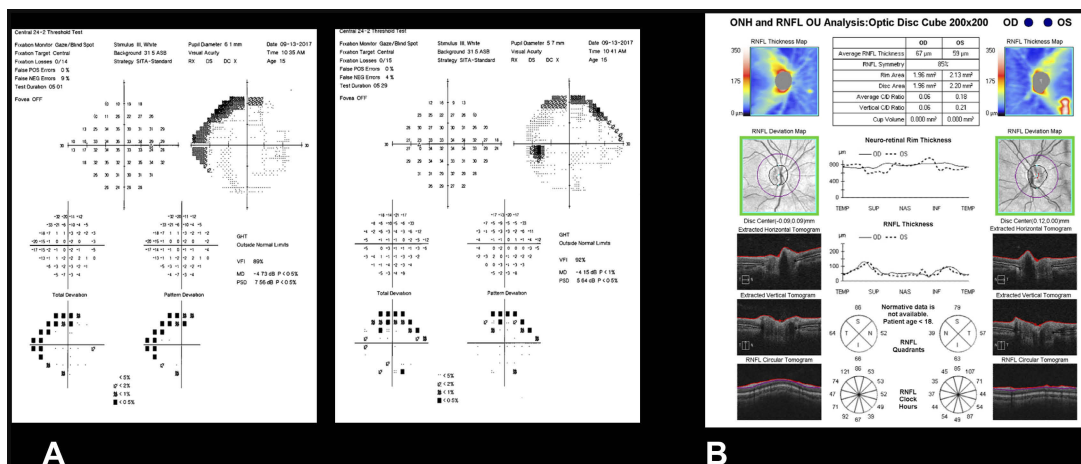
testing may not be possible as CVI is often associated with intellectual impairment.

Although not directly related to TSC, patients with TSC can develop visual field defects as a complication of vigabatrin treatment. Vigabatrin treatment is effective for the infantile spasms and complex partial seizures that affect many individuals with TSC. Long-term treatment with vigabatrin is associated with concentric constriction of peripheral vision (see next section).<sup>62</sup>

If possible, formal testing of visual fields should be performed in all individuals with TSC suspected of having a visual field deficit. SAP is the most frequently used method for measuring the visual field (Figure 3A). In TSC patients with neurological deficits or intellectual disability unable to perform SAP, dynamic visual field testing may be a suitable alternative.<sup>31</sup> OCT is a useful adjunctive test, as the extent of the nerve fiber layer thinning has been shown to correlate with the extent of visual field loss (Figure 3B).<sup>63</sup> Unfortunately, OCT is also not possible in very young or uncooperative patients without sedation or general anesthesia. In TSC patients unable to perform visual field or OCT testing, there are quantitative measures of visual function that may correspond with visual fields, including visual evoked potentials and multifocal ERGs.<sup>49</sup> However, these tests are not widely available and more research is needed to fully characterize the clinical implications of abnormal test results.

### Ocular toxicity of vigabatrin

Many patients with TSC suffer from infantile spasms, a type of epilepsy usually identified before age one and



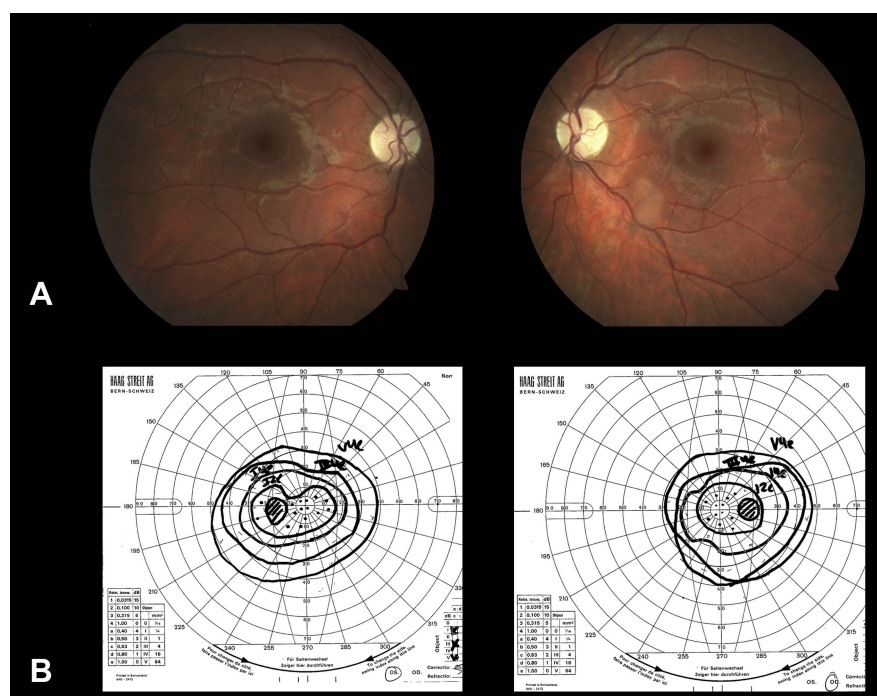
**Figure 3** Standard automated perimetry (SAP) testing in a patient with tuberous sclerosis complex and vigabatrin toxicity (A). The reliability indices (top left) indicate an acceptable visual field test. There is evidence of peripheral visual field loss in both eyes (the visual field defects are concentric, but this is not apparent on this visual field test because it only assesses the central 24 degrees). In the same patient, optical coherence tomography (OCT) of the optic nerve showed diffuse loss of retinal nerve fiber layer thickness in both eyes (B).

characterized by muscle contractions that occur in clusters over minutes.<sup>64,65</sup> Infantile spasms correlate with poor cognitive outcomes for children with TSC, thus motivating aggressive treatment.<sup>66</sup> The anti-epileptic vigabatrin is very effective at treating infantile spasms in children with TSC. In five trials reviewed by the American Academy of Neurology/Child Neurologic Society, 41 of 45 TSC patients treated with the drug achieved cessation of spasms.<sup>67</sup> In addition to infantile spasms, vigabatrin is also FDA-approved for the treatment of complex partial seizures in individuals 10 years old or older who have responded inadequately to alternative treatments.<sup>68</sup> Therefore, older patients with TSC may also require vigabatrin for the treatment of refractory complex partial seizures. Despite its efficacy, the use of vigabatrin has been challenging in TSC patients due to concerns about the drug's ocular toxicity.

Beginning in the 1990s, visual field constriction was observed in adult epilepsy patients on vigabatrin, and cohort studies soon established that ocular toxicity was related to the cumulative dose of the drug.<sup>69–71</sup> Vigabatrin toxicity presents clinically with visual field loss, optic atrophy and diffuse loss of retinal nerve fiber layer (Figure 4).<sup>72</sup> However, clinical ophthalmologic signs are often not apparent until the visual field loss is

advanced and may be under-reported in children and patients with intellectual disability. As many TSC patients could not cooperate with the conventional visual field testing in which toxicity was first identified, an alternative mechanism to monitor infantile spasm patients on the drug was needed. Electroretinography (ERG) does not require patient cooperation and was found to correlate with visual field loss in vigabatrin patients. As a result, ERG has become a means to monitor for retinal toxicity in infants on vigabatrin, but the capacity to perform sedated ERGs is generally confined to large centers.<sup>73</sup>

A systemic review of early studies on vigabatrin toxicity estimated that visual field loss occurred in 52% of adults and 34% of children treated with vigabatrin.<sup>62</sup> The FDA approved vigabatrin in 2009 with a black box warning of permanent visual loss. The approval was accompanied by a Risk Evaluation and Mitigation Strategy (REMS), a program designed to monitor the use of vigabatrin and reduce the risk of permanent vision loss.<sup>74</sup> Through REMS, ophthalmologic testing results were analyzed for 1,509 patients on vigabatrin from 2009 to 2016 and it was found that 37% had had pre-existing pathology affecting the visual system, while only 2% had a potential vigabatrin-associated effect on vision.<sup>75</sup> These results suggest that the rate of retinal toxicity from vigabatrin is likely significantly lower than previously



**Figure 4** Fundus photos (A) and Goldmann visual fields (B) in a patient with tuberous sclerosis complex who had been on vigabatrin for over 10 years. On fundus photos, there is bilateral optic atrophy and diffuse loss of retinal nerve fiber layer. There is also a retinal astrocytic hamartoma in the left eye along the inferior temporal arcade. Corresponding visual fields show concentric constriction of peripheral visual fields in both eyes.



reported and emphasize the importance of carefully assessing patients for pre-existing pathology before initiating vigabatrin therapy. In contemporary practice, neurologists often seek to limit the length of vigabatrin treatment to minimize the risk of significant retinal toxicity, although longer treatment durations are often justified based on a balance of the risks and benefits.<sup>76</sup>

## Conclusion

TSC is a complex disease with a multitude of potential neuro-ophthalmological manifestations. Certain findings, such as papilledema or a cranial nerve III palsy, can indicate potentially life-threatening underlying conditions that need urgent workup and treatment. Other manifestations, such as cortical visual impairment, can have a significant impact on visual function and need to be recognized in order to optimize quality-of-life. The signs of disease can be subtle and the assessment of TSC patients is often challenging. Therefore, it is crucial to know how to diagnose and manage the potential neuro-ophthalmological manifestations of TSC in order to optimize the care of these patients.

## Disclosure

Dr Asim Ali reports personal fees from Santen Inc., outside the submitted work. The authors report no other conflicts of interest in this work.

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