Visual loss in tuberous sclerosis

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**Article abstract**—Of 11 patients with tuberous sclerosis complex (TSC) treated from 1980 to 1990 for obstructive hydrocephalus secondary to subependymal giant-cell astrocytoma, four had adequate documentation to determine visual outcome. Despite surgical relief of elevated intracranial pressure in all cases, two patients sustained further visual loss. In one patient, visual loss was arrested, and in one patient, it was prevented. Although hydrocephalus is uncommon in TSC, its effects on the optic nerves are serious and eventually irreversible. Because TSC patients may not be able to express early symptoms of increased intracranial pressure, periodic ophthalmologic examination and brain imaging may be advisable when a subependymal lesion has been identified.

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Tuberous sclerosis complex (TSC) is a familial multisystem hamartomatous disorder with a reported overall prevalence of 1:10,000. Although the triad of seizures, mental retardation, and adena sebaceum has traditionally been considered diagnostic of TSC, one large study has shown that 71% of TSC patients lack one or more of these features. Moreover, imaging studies with newer modalities have disclosed tumors of various other organs in a surprisingly high proportion of TSC patients, leading to the consideration of TSC as a systemic disorder. Visual loss is unusual in TSC. The retinal hamartomas, present in 50% to 87% of patients, do not impair sight unless they involve the macula or cause vitreous hemorrhage, both very rare events. Visual loss is more likely to result from optic nerve damage secondary to chronic papilledema caused by increased intracranial pressure (ICP). The increased ICP is generated by obstruction of the foramina of Monro by subependymal giant-cell astrocytoma. The frequency of this phenomenon in TSC is believed to be under 5%, but its effects on vision may be devastating. Although isolated reports have described visual loss in TSC, documentation has been sparse. We present more detailed findings in four cases with the aim of alerting physicians to the need for careful monitoring and timely surgical intervention among patients who are often unable to communicate their distress.

**Methods.** In a chart review of TSC patients admitted to the University of Michigan Medical Center from 1980 to 1990, we encountered 11 patients who had undergone surgery for giant-cell astrocytoma. From these patients, the four who had adequate documentation of visual function are the basis of this report.

**Patient 1.** At his high school graduation, an 18-year-old boy diagnosed as having TSC in childhood complained of blackouts of vision, headaches, nausea, vomiting, and poor balance. His best corrected visual acuity was 20/200 in both eyes, and ophthalmoscopy revealed marked bilateral papilledema with distinct whitish retinal hamartomas remote from the macula. Neurologic examination was otherwise remarkable only for inability to perform a tandem gait. Brain CT and MRI disclosed massive enlargement of lateral ventricles by a third ventricular subependymal mass. Twelve months after partial surgical removal and radiotherapy of a giant-cell astrocytoma, his visual acuity had declined to finger counting in the right eye and 20/800 in the left eye. Ophthalmoscopy showed bilateral optic atrophy. Brain imaging revealed a dramatic reduction of the tumor size and no ventriculomegaly.

**Patient 2.** A 16-year-old severely retarded boy with early childhood seizures, characteristic skin findings of TSC, and subependymal calcifications on a brain CT performed at age 7 suffered a closed head injury. An emergency brain CT showed enlarged ventricles with a mass near the foramina of Monro. Ophthalmologic examination was not performed, but caregivers described no visual difficulties. He underwent a debulking of an intraventricular giant-cell astrocytoma and later placement of a ventriculoperitoneal shunt. Except for a left hemiparesis, present since his operation, he was stable until a year later, when he began to bump into objects. Ophthalmologic examination disclosed a relative afferent pupillary defect in the right eye and markedly impaired visual fields. Because of poor cooperation, visual acuity, formal visual fields, and ophthalmoscopy could not be adequately performed. A brain CT showed no hydrocephalus and minimal residual mass.

**Patient 3.** A 20-year-old female dental hygiene student consulted an ophthalmologist because of transient blackouts ("obscurations") of vision and headaches of 1 year's duration.

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Visual acuities were 20/20 in each eye, visual fields disclosed marked constriction, and optic fundi showed bilateral papilledema. Considered to have normal intelligence, she had no skin stigmata of TSC. Brain MRI disclosed marked enlargement of the lateral ventricles and a mass obstructing the foramina of Monro (figure). The patient underwent near total removal of a giant-cell astrocytoma. Postoperatively, her transient obscurations of vision disappeared immediately. The optic disks deturgesced gradually, leaving behind flat, slightly pale optic disks. One year after surgery, visual fields remained unchanged, sufficiently compromised to keep her from driving.

**Patient 4.** A 21-year-old man with childhood febrile seizures was diagnosed as having TSC at age 3 when he was found to have adenoma sebaceum. No brain imaging was performed. At age 7, his visual acuity was 20/20 in each eye. Ophthalmoscopic examination revealed a retinal hamartoma in the left eye and normal optic disks. At age 12, he developed headaches and vomiting and was noted to have papilledema. A brain CT revealed hydrocephalus and a mass indenting the third ventricle. Following excision of a giant-cell astrocytoma, residual hydrocephalus required bilateral ventriculoperitoneal shunts that were revised several times. At age 20, he presented with a 1-week history of headache and increased sleepiness associated with vomiting. When a brain CT showed a large cyst in the region of the third ventricle with a tumor nodule, he underwent further resection of a giant-cell astrocytoma from the wall of the lateral ventricle. Postoperatively, visual acuity was 20/15 in each eye, visual fields were full, and optic disks appeared normal.

Discussion. We have described four TSC patients who developed obstructive hydrocephalus from a third ventricular giant-cell astrocytoma. Two are blind, and one has severe visual field loss from the effects of chronic papilledema on the optic nerves. Early surgical decompression prevented visual loss in the fourth patient.

Patients with TSC may have three types of CNS abnormalities:10-12

1. **Cortical tubers** are areas of disordered lamination with gliosis. Tubers may not be visible grossly, but if so, they rise only slightly above the surface and are firm and slightly pale relative to surrounding tissue. Most common in the cerebral convexity but also rarely found in the brainstem, cerebellum, and spinal cord, they are much more easily seen with MRI than CT. Their frequency in and specificity for TSC are uncertain.

2. **White matter heterotopias**, consisting of disorganized, often very enlarged neurons, are extremely common but not specific to TSC. Generally found in cerebral white matter, they are believed to represent migration arrest.

3. **Subependymal giant-cell nodules** are encountered along all ventricular surfaces, but especially the basal lateral ventricles, in more than 90% of TSC patients defined by other criteria. Giant-cell astrocytomas are believed to arise from these nodules, which are filled with large, bizarre-shaped glial cells containing one or more convoluted nuclei ("giant cells"). The stroma of the nodules consists of densely webbed glial processes, blood vessels, and calcium. The distinction between nodules (also called "candle gutterings" because of the impression they make on the ventricular surface) and subependymal astrocytomas is one of size and position rather than histology. No histologic features of malignancy are found, even in reoperated or autopsied cases.10

Giant-cell astrocytomas are unique to TSC, but they may occur in patients without any other stigmata or family history of tuberous sclerosis (as in our patient 3).
Judging from our cases and those previously reported, the transformation from nodule to obstructive tumor appears to occur within the first two decades. In our patient 2, brain imaging documented the change over a 9-year interval; in our patient 4, the optic disks became swollen from increased ICP within a 5-year period.

The visual consequences of undetected elevation in ICP are serious, as our TSC patients exemplify. Increased ICP is believed to arrest axoplasmic flow within the optic nerve, causing optic disk swelling and eventually axonal death.\textsuperscript{13} If restoration of normal ICP comes too late, vision may not return,\textsuperscript{3-8} as in our patients one and two. On the other hand, timely intervention may arrest vision loss (patient 3) or prevent it (patient 4).

Usually the nonvisual symptoms of increased ICP (headache, nausea, vomiting, lethargy, diplopia, gait disturbance) will alert the physician to the diagnosis.\textsuperscript{10} Unfortunately, in the mentally impaired TSC patient, these signs and symptoms may be dismissed or misinterpreted. Moreover, by the time florid symptoms of increased ICP become manifest, irrevocable visual loss may have occurred. Accordingly, we recommend careful periodic ophthalmoscopic evaluation of the optic disks in all TSC patients within the first two decades who have imaging evidence of subependymal nodules. It may also be advisable to perform periodic brain imaging in the asymptomatic TSC patient to detect growth of these nodules.

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