

A Case of Tuberous Sclerosis Complicated by Bilateral Blindness

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Case Report

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Abstract

Tuberous sclerosis complex (TSC) is a rare autosomal dominant genetic disorder. Its primary clinical manifestations include facial angiofibromas, epilepsy, and intellectual disability. This article reports a case of a 16-year-old female patient with TSC. Genetic testing identified a heterozygous mutation in the TSC2 gene, a known pathogenic variant associated with TSC. The diagnosis was confirmed based on the presence of subependymal giant cell astrocytoma, facial angiofibromas, and other characteristic features. Additionally, the patient exhibited bilateral optic atrophy with no light perception. This case enhances clinicians' understanding of the diverse clinical manifestations and complications of TSC, providing valuable insights for the diagnosis of this disease.

1. Introduction

Tuberous sclerosis complex (TSC) is a rare autosomal dominant disorder characterized by multisystem involvement, primarily caused by pathogenic variants in the TSC1 (9q34) or TSC2 (16p13.3) genes. The estimated prevalence of disease-causing mutations ranges from 1/6000 to 1/10000 individuals, while the clinical incidence of manifest TSC falls between 1/20000 and 1/100000 live births^[1]. Tuberous sclerosis complex (TSC) manifests with heterogeneous multiorgan involvement, classically characterized by the triad of facial angiofibromas, epileptic seizures, and neurodevelopmental abnormalities. Approximately 30% of affected individuals exhibit all three hallmark features concurrently^[2]. However, patients with concurrent bilateral blindness are relatively rare. This article reports a case of tuberous sclerosis complicated by bilateral blindness.

2. Case Introduction

A 16-year-old female patient of Uygur ethnicity was admitted to the Department of Neurology V, The Second Affiliated Hospital of Xinjiang Medical University on July 19, 2024, presenting with "facial rash for 10 years and bilateral blindness for over 1 year".

2.1 Present Illness

Ten years ago, the patient developed idiopathic dense, millet-sized, dark red papules on the face (which have shown no significant change to date), without noticeable pain or pruritus. Subsequently, multiple elevated whitish plaques appeared on the back and lumbar region, but no medical attention was sought. (Figure 1) Starting in 2021, she experienced intermittent headaches, predominantly on the right side, without nausea or vomiting. In January 2022, she was hospitalized at an external hospital. Comprehensive genetic testing confirmed a diagnosis of Tuberous Sclerosis Complex (TSC). Further treatment was not pursued due to financial constraints. In December 2022, headaches recurred, accompanied by nausea and vomiting. This was followed by sudden onset blindness in the right eye and decreased light perception in the left eye. Complete bilateral blindness occurred within three months. In

February 2023, she underwent supratentorial deep lesion resection in the Department of Neurosurgery, The First Affiliated Hospital of Xinjiang Medical University. Postoperative pathological diagnosis confirmed: Left subependymal giant cell astrocytoma (SEGA) (WHO Grade I), with secondary hydrocephalus. Postoperative vision did not recover. The patient subjectively reports experiencing "colored gelatinous substance". Her academic performance remains average with no apparent intellectual disability. No similar symptoms have been observed in other family members.

2.2 Physical Examination

Neurological Examination (Visual System): The patient demonstrates no light perception bilaterally with unremarkable anterior segments in both eyes. Pupils are round with notable asymmetry (right ≈5mm, left ≈3mm), showing only intermittent sluggish light reflexes. Fundoscopy reveals bilateral optic discs with well-defined margins and distinct pallor, diffuse attenuation of retinal vessels, absence of retinal hemorrhages/exudates, and preserved foveal light reflex-all clinically consistent with optic atrophy. OCT confirms thinning of the peripapillary retinal nerve fiber layer across all quadrants and reveals nodular morphological changes, corroborating the diagnosis of bilateral optic atrophy(Figure 2). Visual evoked potential testing under full-field stimulation demonstrates complete absence of measurable P100 waveforms (Figure 3), confirming severe bilateral impairment of the visual pathways.

2.3 Laboratory Investigations:

Complete Blood Count: Hemoglobin 106 g/L (ref: 115-150 g/L); Platelet count 427×10⁹/L (ref: 100-300×10⁹/L); RDW-CV 15.00 fL; Plateletcrit 0.400%; Lymphocyte count 3.51×10⁹/L; MCH 23.30 pg; MCHC 283.00 g/L. Erythrocyte Sedimentation Rate (ESR): 30.00 mm/h (ref: <20 mm/h).Biochemical Profile: A/G ratio 1.36; Iron 5.1μmol/L (ref: 9-30 μmol/L); Bicarbonate 21.2 mmol/L (ref: 22-29 mmol/L); Total protein 63.3 g/L; Albumin 38.5 g/L; HDL 0.76 mmol/L (ref: >1.0 mmol/L); LDL 2.07 mmol/L; CK-MB 84.5 U/L (ref: <25 U/L). Thyroid Function:TSH 6.07 μIU/mL (ref: 0.27-4.2 μIU/mL).

Whole-Exome Sequencing Report (Beijing MyGenostics Medical Laboratory; High-Throughput Sequencing): A splice-site mutation (TSC2: Chr16:2122240; NM_000548; exon20; c.2098-2A>C) was identified, associated with phenotypes including lymphangi leiomyomatosis(unknown significance), tuberous sclerosis complex type 2(autosomal dominant), and possible focal cortical dysplasia (unknown significance). PCR-NGS validation confirmed this variant as a de novo mutation absent in the proband's mother. According to the ACMG(American College of Medical Genetics and Genomics) guidelines, this variant is classified as Pathogenic (PVS1 + PM2 + PP4).Table 1, Figure 4

Tab1 Patient genetic test results

Gene	Chromosome 1 Position	Transcript Exon	Nucleotide Change Amino Acid Change	Zygosity	Population Frequency	In Silico Prediction	ACMG Pathogenicity Classification	Disease/Phenotype (Inheritance)	Variant Origin
TSC2	chr16:212 2240	NM_0005 48;exon20	C.2098-2A>C (splicing)	het	-	-	Pathogenic	1.Lymphangioleiomyomatosis (-) 2.Tuberous Sclerosis Complex Type 2 (Autosomal Dominant) 3.? Focal Cortical Dysplasia Type II Somatic Mosaicism (-)	Paternal sample: Not received (-)
Summary of Genetic Variant Information: A heterozygous splicing mutation in the TSC2 gene was identified: c.2098-2A>C (splice acceptor variant).									

Whole-exome sequencing identified a heterozygous mutation in the TSC2 gene in this patient.

2.4 Imaging Studies

Brain MRI with contrast (December 2023, The First Affiliated Hospital of Xinjiang Medical University; Figure 5B) revealed bilateral nodular lesions isointense to gray matter on T2-weighted imaging projecting into the lateral ventricular bodies, alongside a 5.2-mm contrast-enhancing nodule adjacent to the left frontal horn surgical resection cavity. Subsequent non-contrast head CT (July 2024, The Second Affiliated Hospital of Xinjiang Medical University; Figure 5C) demonstrated postoperative calvarial changes with a left-sided cranial defect, poorly defined genu of the corpus callosum, widened septum pellucidum (approximately 10 mm), and multiple calcified subependymal nodules along the walls of bilateral lateral ventricles-collectively indicating progressive tuberous sclerosis complex (TSC) with evidence of prior subependymal giant cell astrocytoma (SEGA) resection, chronic calcified nodules, and developing hydrocephalus.

3. Discussion

The index patient manifested facial angiofibromas, one hallmark of TSC's classical triad. Beyond neurological manifestations, TSC commonly involves renal, cardiac, pulmonary, and ocular pathologies. Current therapeutic strategies for TSC-associated epilepsy include: mTOR inhibitors (mechanistic target of rapamycin; everolimus/sirolimus), first-line antiseizure medications, resective surgery, and vagus nerve stimulation (VNS). mTOR inhibitors (everolimus and sirolimus) now represent the cornerstone pharmacological intervention for TSC-related epilepsy. Notably, recent studies confirm that mTOR inhibitors are well-tolerated and efficacious for TSC patients with subependymal giant cell astrocytoma (SEGA)^[3].

Genetic testing in January 2022 identified a heterozygous TSC2 mutation in this patient. Maternal analysis confirmed absence of this variant at the same locus. In accordance with the 2021 International TSC Diagnostic Criteria^[4], the diagnosis of sporadic tuberous sclerosis complex was established by major clinical features: facial angiofibromas, subependymal giant cell astrocytoma, hypomelanotic macules and negative family history.

The multiple elevated hypopigmented plaques observed over the patient's lumbar region likely stem from TSC2 mutation-induced hyperactivation of mTOR signaling. Mechanistically, inhibition of TSC1/2

expression reduces tyrosinase activity and melanogenesis by suppressing the microphthalmia-associated transcription factor (MITF) and its downstream pigmentary targets: TYR (tyrosinase), TYRP1 (tyrosinase-related protein 1), PMEL (premelanosomal protein), and DCT (dopachrome tautomerase). This impaired melanogenesis operates through mTORC1/GSK3 β -mediated regulation of pigmentation: Enhanced mTORC1 activity phosphorylates GSK3 β , subsequently suppressing nuclear translocation of β -catenin and thereby downregulating MITF and its target gene expression^[5].

The patient was pathologically confirmed with subependymal giant cell astrocytoma (SEGA) following surgery at The First Affiliated Hospital of Xinjiang Medical University in 2023. SEGA represents a pathognomonic central nervous system manifestation of tuberous sclerosis complex (TSC), occurring in approximately 5%–14.3% of TSC patients^[6]. Gradual tumor growth obstructs cerebrospinal fluid (CSF) pathways, triggering obstructive hydrocephalus. This manifests clinically as progressive symptoms of elevated intracranial pressure (ICP), including headache, nausea, vomiting, and visual deterioration. In severe cases, acute brain herniation may precipitate sudden death^[7]. Preoperatively, the patient developed progressive symptoms including headache, nausea, and vomiting, which were later complicated by bilateral blindness. Postoperative diagnostic evaluations revealed secondary hydrocephalus as an associated complication. A study by Jerry et al.^[8] demonstrated that subependymal giant cell astrocytomas (SEGAs) may exhibit aggressive behavior in select cases, precipitating acute elevations in intracranial pressure (ICP) and irreversible vision loss. Dotan et al.^[9] documented four tuberous sclerosis complex (TSC) patients with visual impairment: three cases attributed to papilledema secondary to obstructive hydrocephalus and elevated intracranial pressure (ICP), and one resulting from mechanical impact following intraventricular giant cell astrocytoma debulking surgery. Notably, ophthalmic evaluation in our patient revealed neither elevated intraocular pressure nor papilledema. Globally, reports of TSC2 mutation-associated optic atrophy remain scarce, and its precise pathogenesis is unelucidated. Based on progressive clinical deterioration, we hypothesize multifactorial etiology for this patient's optic atrophy: combined effects of subependymal giant cell astrocytoma (SEGA), retinal nodular lesions, chronic hydrocephalus, and the pathogenic TSC2 variant. Emerging evidence indicates that non-calcified subependymal nodules (SENs) may undergo gradual transformation into subependymal giant cell astrocytomas (SEGAs), with Erk pathway activation identified as a critical molecular driver facilitating this malignant progression^[10]. This process is also associated with upregulation of genes involved in the MAPK signaling pathway^[11].

Additionally, approximately 80% of children with tuberous sclerosis complex (TSC) aged 5 years and older have facial angiofibromas. These lesions represent hamartomatous nodules composed of vascular and connective tissue, clinically presenting as bilateral, coarse, erythematous papules with a characteristic cobblestone appearance. Unilateral involvement is exceptionally rare. The index tuberous sclerosis complex (TSC) patient exhibits characteristic facial angiofibromas. Hyperactivation of mTORC1 serves as a central pathogenic driver for these lesions, alongside hypomelanotic macules, forehead fibrous plaques, and shagreen patches. Clinical evidence confirms partial regression of these dermatological manifestations following mTORC1 inhibitor therapy. Genetically, TSC tumorigenesis-including

angiofibroma development-adheres to Knudson's "two-hit" tumor suppressor model: Germline TSC1/2 mutation (first hit), Acquired somatic second hit (UV radiation-induced mutagenesis in skin).

Additionally, the incidence of epilepsy in pediatric patients with tuberous sclerosis complex (TSC) reaches up to 90%^[13]. Concurrently, research by Peter et al. ^[14] demonstrated that approximately 73% of TSC patients develop epilepsy before 1 year of age. Infantile spasms peak in incidence between 3 and 9 months, while focal seizures exhibit a relatively constant onset pattern persisting up to 21 months. Other seizure types may emerge as late as 26 months. Notably, this 16-year-old patient has never manifested seizures, representing a distinctive phenotype despite carrying a pathogenic TSC2 mutation.

4. Conclusion

This case exhibits classic tuberous sclerosis complex (TSC) manifestations, including facial angiofibromas and subependymal giant cell astrocytoma (SEGA), alongside distinctive phenotypic features: bilateral blindness without light perception (NLP) and complete absence of epilepsy despite carrying a pathogenic TSC2 mutation. This constellation represents a notable clinical divergence from the expected TSC phenotype, particularly given: 1. Neurological Rarity: <5% of TSC2 patients remain seizure-free beyond adolescence 2. Ophthalmological Severity: Acute bilateral blindness without preceding papilledema

Declarations

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Author contributions

QL: Organize clinical materials, Writing-original draft. AK: Participated in diagnosing cases, Revise and polish articles. XYZ and FFF: Revise and polish articles. ZQW: Proposed key diagnostic insights and treatment plans; Revised, Polished, Critically reviewed articles.

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Ethics approval and consent to participate

The guardians of the pediatric patients have been informed and provided consent, and they have signed the informed consent form.

Consent to Publish

Written informed consent was obtained from the parents of the patient for the publication of this case report and any accompanying images.

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the NCBI Sequence Read Archive repository, PRJNA1356500.

Competing interests

The authors declare no competing interests.

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Figures



Figure 1

Patient Skin Symptoms

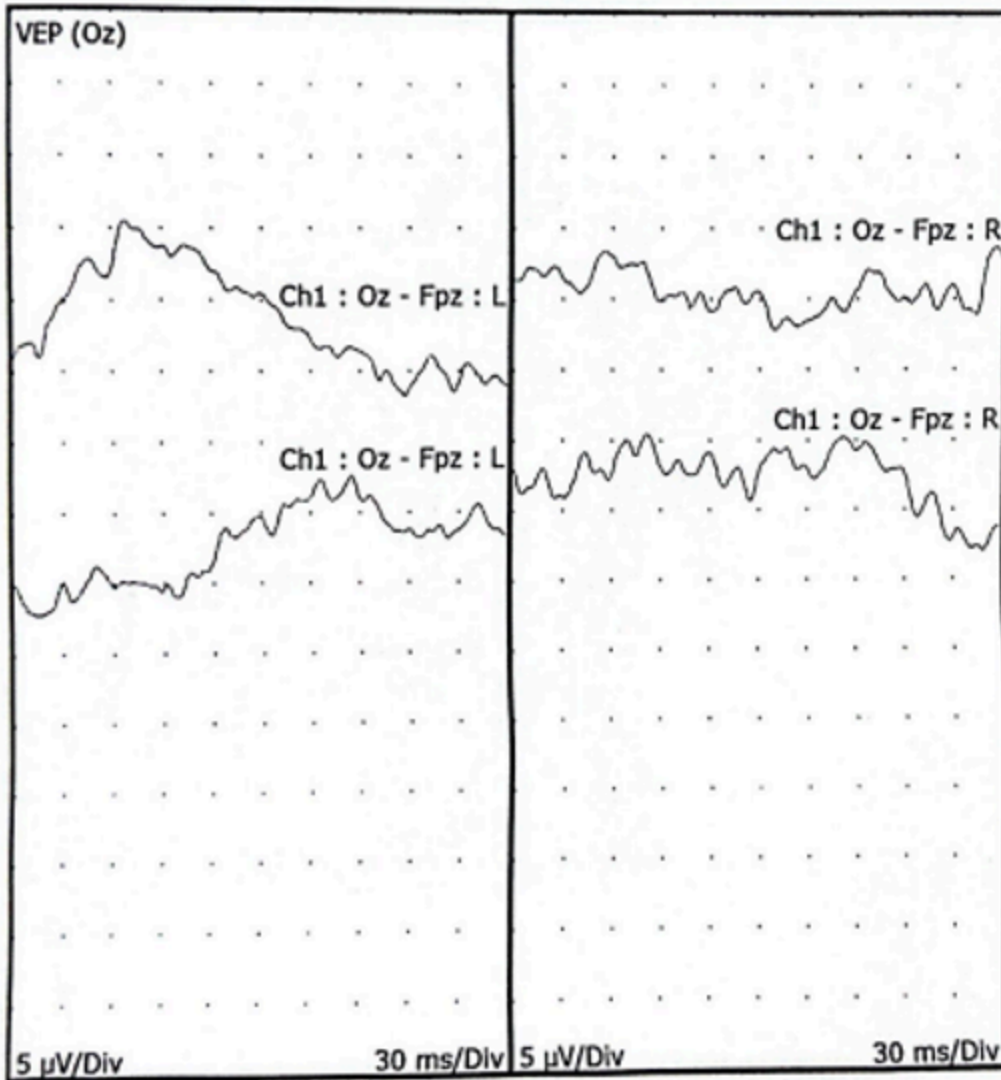


Figure 3

Visual evoked potential results

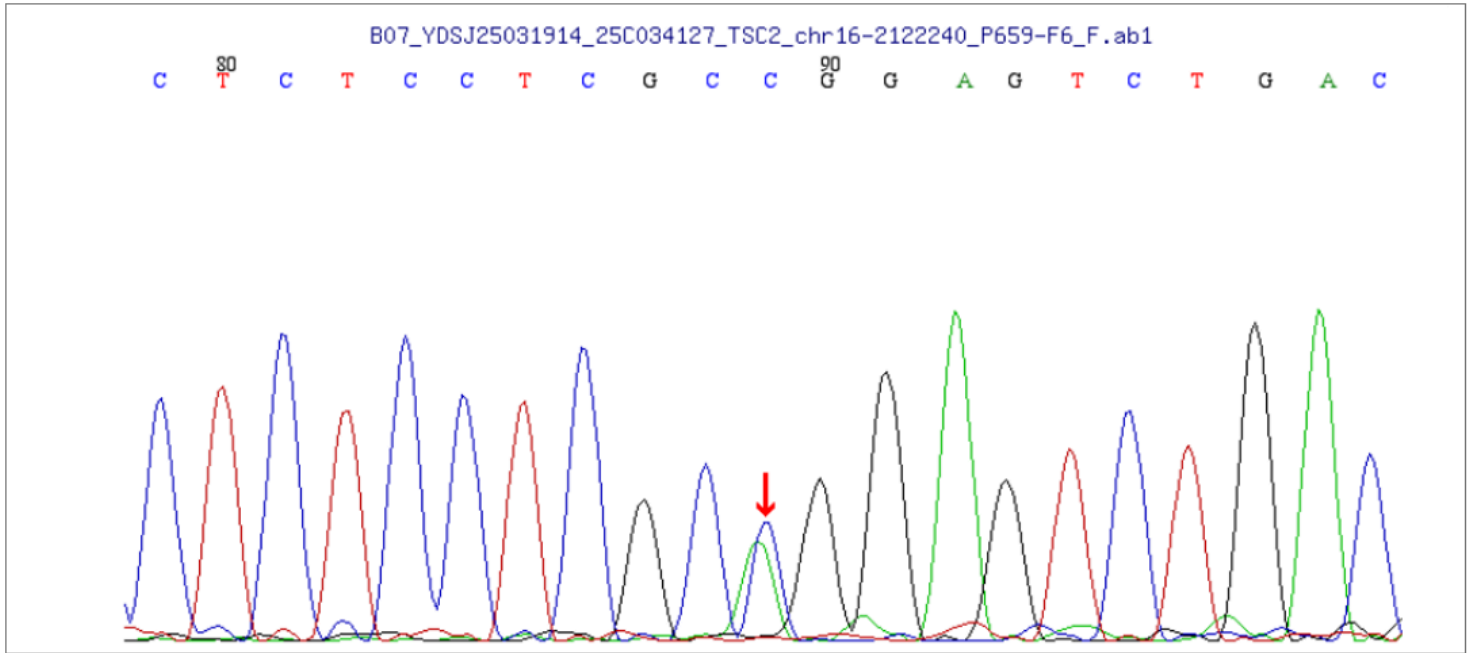


Figure 4

sanger validation results

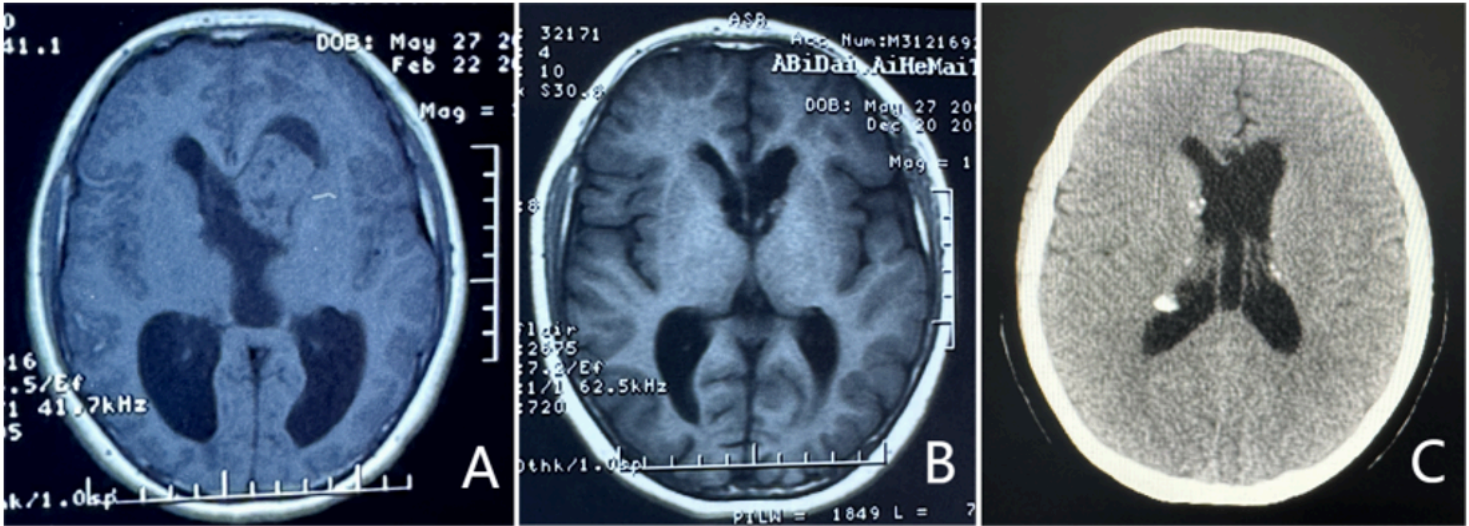


Figure 5

Cranial image of the patient