Subsequent genetic testing revealed a POMGnT1 mutation, consistent with MEB disease. Specifically, the mutation was in POMGnT1 intron 17. This resulted in a DNA substitution of c1539+1 G>A, which is a common founder mutation in Finnish patients. Mutations in POMGnT1 near the 5’ terminus, as is the case with c1539+1 G>A, have been suggested to correlate with more severe cerebral malformations.

Comment. Both MEB disease and Walker-Warburg syndrome have underlying deficiencies in posttranslational glycosylation of α-dystroglycan that lead to severe defects in organogenesis and neuronal migration. Brain and eye phenotypes in MEB disease and Walker-Warburg syndrome likely involve defective glycosylation in proteins other than α-dystroglycan since chimeric mice deficient in α-dystroglycan develop congenital muscular dystrophy but not brain or eye phenotypes of MEB disease or Walker-Warburg syndrome. In both diseases, there can be hypoplasia of the retina, choroid, optic nerve, and iris. Specifically, Zervos et al performed a histopathologic examination of 2 siblings with MEB disease and found loss of the inner nuclear layer, thinning of the outer nuclear layer, absence of rod and cone outer segments in midperipheral portions of the retina, and localized nerve fiber layer schisis nasal to the optic nerve head. They also noted focally atrophic retinal pigment epithelium and diffuse chorioidal atrophy.

In our patient, with genetic testing results supportive of an MEB disease diagnosis, we describe the previously unreported clinical findings in early disease. A peripheral avascular retina led to extraretinal fibrovascular proliferation with subsequent contracture and combined tractional and rhegmatogenous retinal detachment with multiple perforating holes in the right eye. The underlying defect in glycosylation in MEB disease, which results in a severe defect in neuronal migration and possibly in hypoplasia of various structures, may be the cause of these retinal findings.

Quan V. Hoang, MD, PhD
Michael P. Blair, MD
Bahram Rahmani, MD, MPH
John M. Galasso, MD, PhD
Michael J. Shapiro, MD

Author Affiliations: Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago (Drs Hoang, Blair, and Shapiro) and Department of Ophthalmology, Children’s Memorial Hospital, Northwestern University (Dr Rahmani), Chicago, and Retina Consultants, Ltd, Des Plaines (Drs Galasso and Shapiro).

Correspondence: Dr Shapiro, Department of Ophthalmology and Visual Sciences, University of Illinois at Chicago, 1855 W Taylor St, M/C 648, Chicago, IL 60612 (michaelj.shapiro@gmail.com).

Author Contributions: Dr Shapiro had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Financial Disclosure: None reported.

Funding/Support: This work was supported by an unrestricted grant from Research to Prevent Blindness, New York, New York (Dr Blair).


Diffuse Infiltrating Retinoblastoma With Central Nervous System Metastasis

A diffuse infiltrating pattern of growth seen in 1% to 2% of retinoblastomas is associated with horizontal growth of tumor cells along the retinal tissue as well as retinal thickening. Vitreous and anterior segment seeding simulate uveitis. We describe a child who developed acute onset of headache and vomiting followed by visual loss in his right eye. Findings on clinical examination led to a diagnosis of diffuse infiltrating retinoblastoma with central nervous system involvement, which was confirmed following discovery of malignant cells in the cerebrospinal fluid (CSF).

Report of a Case. A 10-year-old boy visited the pediatric emergency department with headache, vomiting, and altered sensorium of 3 days’ duration. There was no history of fever or upper respiratory tract infection. The next day, he developed acute, painless diminution of vision in the right eye. Systemic examination results were unremarkable. Full blood cell count and workup for infectious diseases yielded negative results. Magnetic resonance imaging of the brain and orbit showed diffuse thickening and enhancement of the right optic nerve and meninges (Figure 1A and B). Lumbar puncture revealed normal opening pressure; CSF analysis showed low glucose and high protein content. With a tentative diagnosis of right optic neuritis with meningoencephalitis, the child was referred for ophthalmic examination. Findings on examination of the right eye showed visual acuity of no light perception, anterior chamber flare 1+, clumps of vitreous cells, a swollen optic disc, and a thickened superonasal retina (Figure 1C and D). B-scan ultrasonography of the right eye revealed medium-amplitude vitreous echoes, disc swelling, and thickened retina (Figure 2A). Repeated lumbar puncture showed clumps of malignant cells (Figure 2B), confirming the clinical suspicion of diffuse infiltrating retinoblastoma with CSF metastasis. The child was referred to the pe-
diatric oncology department, where 15 cycles of intra-
thechal chemotherapy (12 mg of methotrexate, 30 mg of 
hydrocortisone acetate, and 25 mg of cytarabine) and 8 
cycles of systemic chemotherapy (intravenous vincris-
tine sulfate, 1.5 mg/m², carboplatin, 560 mg/m², and eto-
poside, 150 mg/m²) were administered. The child also 
received craniospinal radiation. With CSF becoming free 
of tumor cells and the optic nerve size reverting to nor-
mal (Figure 2C), enucleation of the right eye was per-
formed. Histopathological examination of the globe re-
vealed retinoblastoma cells diffusely infiltrating the retina 
and the optic nerve (Figure 2D). The cut end of the op-
tic nerve and choroid were free of tumor cells.

The child was followed up at monthly intervals and 
has since received 3 cycles of systemic and intrathecal 
chemotherapy. Cytological analysis of the CSF after 6 
months of radiation and chemotherapy showed no ma-
lignant cells.

Comment. Diffuse infiltrating retinoblastoma poses a di-
agnostic challenge. Any interventional procedure such
as a diagnostic tap is contraindicated while a diagnosis
of retinoblastoma is being considered,1 and therapeutic
decisions have to be made based on clinical diagnosis.
In our patient, retinoblastoma was not on the initial list
of potential diagnoses. It was only after referral to the on-
cology service that the diagnosis of retinoblastoma with 
CSF spread was made. Although the CSF was clear after 
systemic treatment, owing to the possibility of live tu-
mor in the eye, enucleation and examination of the cut 
end of the optic nerve were considered essential.

Metastasis to the CSF in retinoblastoma is difficult to
treat. Intensive chemotherapy has been reported to be suc-
cessful in obtaining a cure;2 however, metastatic retino-
blastoma shows multidrug resistance and the blood-
brain and blood-retinal barriers impede access to tumor 
cells. Orbital and craniospinal radiation is often resorted 
to in these patients.3 The cut end of the optic nerve in our 
patient was found to be free of tumor cells. However, the 
possibility of residual tumor cells in the central nervous 
system cannot be ruled out. Our patient continues to re-
ceive chemotherapy and is under close follow-up.

Figure 1. Composite images. A, Magnetic resonance image of the brain showing a thickened and enhanced optic nerve (arrow) in the right eye. B, Magnetic resonance image of the brain showing meningeal thickening and enhancement (arrows). C, Fundus photograph of the posterior pole showing disc swelling, macular edema, and vitreous seeds (arrows). D, Fundus photograph showing a thickened superonasal retina (arrows).
To our knowledge, diffuse infiltrating retinoblastoma with central nervous system spread at the initial visit has not been previously reported.

Author Affiliations: Departments of Oncology and Vitreoretina (Dr Khetan) and Ocular Pathology (Drs Biswas and Kumar), Sankara Nethralaya, and Department of Medical Oncology, Apollo Hospitals (Dr Raja), Chennai, India; and Departments of Ophthalmology (Drs Al-Kharusi and Ganesh) and Child Health (Dr Al-Futaisi), Sultan Qaboos University Hospital, Sultanate of Oman. Correspondence: Dr Khetan, Department of Ocular Oncology, Retina, and Vitreous, Medical Research Foundation, Sankara Nethralaya, 18 College Rd, Chennai, Tamil Nadu 600006, India (drvk@snmail.org).

Financial Disclosure: None reported.


Figure 2. Results from B-scan ultrasonography, repeated lumbar puncture, fundus photography, and histopathological examination. A, B-scan ultrasonogram of the right eye showing vitreous clumps and a thickened retina (arrow). TGC indicates time gain control. B, Repeated lumbar puncture showing round, multinucleated cells in the cerebrospinal fluid (hematoxylin-eosin, original magnification ×20). C, Fundus photograph of the right eye showing resolution of disc swelling after treatment. D, Photomicrograph of the enucleated globe showing diffuse infiltration of retinal layers (arrow) with tumor cells (hematoxylin-eosin, original magnification ×20). V indicates vitreous.

Topical Timolol for Periocular Hemangioma: Report of Further Study

Childhood superficial capillary hemangiomas of the eyelid may lead to amblyopia or anisometropia. Although benign, such tumors can cause irreversible visual loss if not treated promptly. Treatment options for infantile hemangioma include both systemic...