RETINITIS PIGMENTOSA AND PUNCTATE CATARACTS IN MEVALONIC ACIDURIA

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Background: Mevalonic aciduria, caused by deficiency of mevalonate kinase, was the first recognized defect in the biosynthesis of cholesterol and isoprenoids. Ophthalmic features of this potentially blinding disorder include blue sclera, cataract, uveitis, optic atrophy, and, importantly, a retinitis pigmentosa-like retinopathy. To date, ∼30 cases of this rare autosomal recessive disorder have been reported, with no full characterization appearing in the ophthalmic literature.

Methods: An 11-year-old white girl with mevalonic aciduria presented with decreasing peripheral vision and night blindness.

Results: Examination revealed decreased central vision, punctate cataracts, and a retinitis pigmentosa-like retinopathy. Goldmann visual fields confirmed severe constriction in both eyes. A full-field electroretinogram was performed. A-waves, B-waves, and oscillatory potentials were all nonrecordable in both eyes, indicating severe bilateral retinopathy, affecting both cone- and rod-mediated responses. Dark adaptation testing showed severely impaired cone and rod function under dark-adapted (scotopic) conditions. Farnsworth-Munsell hue discrimination (FM-100 hue) testing was abnormal in both eyes.

Conclusion: The ocular findings in patients with mevalonic aciduria are heterogeneous and include blue sclerae, cataracts, uveitis, retinopathy, and optic atrophy. Visual prognosis is guarded; several patients surviving to adulthood have progressed to apparent legal blindness caused by cataracts and/or retinopathy.

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Mevalonic aciduria, caused by deficiency of mevalonate kinase, was the first recognized defect in the biosynthesis of cholesterol and isoprenoids.1 To date, ∼30 cases of this rare autosomal recessive disorder have been reported, with no full characterization appearing in the ophthalmic literature. The clinical spectrum can include facial anomalies, psychomotor retardation, and progressive cerebellar ataxia.2 Recurrent febrile crises, which are also characteristic, are associated with hepatosplenomegaly, lymphadenopathy, arthralgia, and skin rash.2,3 Ophthalmic features of this potentially blinding disorder include blue sclera,1,4 cataract,1-3,5 uveitis,2,4 optic atrophy,3 and, importantly, a retinitis pigmentosa (RP)-like retinopathy.2-6 We now report a patient with mevalonic aciduria who has progressive degeneration of the retina and punctate cataractous changes.

Case Report

An 11-year-old white girl was diagnosed with mevalonic aciduria in infancy. Her family history is uncertain because of early adoption, but her biologic parents are believed to be genetically unrelated and unaffected.

The patient was known to have mild psychomotor retardation and recurrent febrile illnesses. Her parents stated that she had performed below average on previous cognitive testing. Her facial features were unremarkable. No ataxia of gait was noted.

She presented with complaints of a decrease in her peripheral vision over the past 1½ years and nyctalopia for 1 year. Her teacher reported that print size had needed to be enlarged by ∼150% over the past year.

Best-corrected visual acuity in both eyes was 20/60. Her anterior segments were largely within normal limits in both eyes, including
sclerae that were not blue. Her lenses, however, had punctate gray opacities in the posterior cortices and posterior capsules. There was no nuclear sclerosis and no posterior subcapsular opacification. Her optic nerves appeared pink without atrophy (Figure 1). Her foveae had normal contours with good light reflexes. The periphery of both fundi had retinal pigment epithelial mottling with rare bone spicule–like pigmentary changes and arteriolar narrowing (Figure 2). Her internal limiting membrane had uneven reflections, giving an almost fibrotic appearance.

Optical coherence tomography confirmed normal foveal architecture bilaterally. Although the thickness of her retinas appeared normal, normative data for comparison are not available in this age group. Goldmann visual fields showed severe constriction in both eyes in all isopters. A full-field electroretinogram was performed. Dark-adapted A-waves, B-waves, and oscillatory potentials were all nonrecordable in both eyes, indicating severe bilateral retinopathy, affecting both cone- and rod-mediated responses. Dark adaptation testing with the Scotopic Sensitivity Tester, model 1 (SST-1, LKC Systems, Gaithersburg, MD) showed severely impaired cone and rod function. None of the test lights were seen, even after 30 minutes of dark adaptation, indicating that cone sensitivity is reduced by at least 0.5 log units, and no measurable rod sensitivity can be demonstrated. Farnsworth-Munsell hue discrimination (FM-100 hue) testing was abnormal in both eyes, with errors that were not concentrated along any axis.

Discussion

Mevalonic aciduria is an autosomal recessive disorder involving an error of cholesterol biosynthesis caused by mevalonate kinase deficiency. Blue sclerae have been reported in severely affected patients who also had congenital malformations, such as microcephaly, dolichocephaly, low-set and posteriorly rotated ears, and downslanted palpebral fissures. Cataracts, which can develop during the first few months of life, up to elementary school age, have been reported as nuclear sclerosis. Mevalonic aciduria is characterized by marked accumulation of mevalonic acid in plasma and urine, and plasma levels of mevalonic acid in patients with mevalonic aciduria approach the millimolar range. Hoffmann et al theorized that the cataracts seen in these patients were caused by an osmotic consequence of mevalonate accumulation in the lens. A study by Cenedella and Sexton, however, suggested that the cataracts associated with mevalonic aciduria were caused by direct toxicity from mevalonic acid. Young rat lenses were cultured in increasingly elevated mevalonic acid concentrations and subsequently developed nuclear cataracts. Lenses exposed to mevalonic acid accumulated water and sodium and lost potassium and soluble crystalline proteins. These changes were preceded by a loss of the lens’s ability to concentrate a potassium analog, suggesting poisoning of the cation pump, direct effects on membrane integrity, or both. Cortical punctate changes, such as those found in our patient, have not previously been reported in patients with mevalonic aciduria. Given that these changes were subtle, they may have been previously overlooked in other patients. Furthermore, the authors recognize that these cortical changes are not unique to mevalonic aciduria and may represent an incidental finding.

After preschool age, short stature, ataxia, and ocular involvement, with cataracts, uveitis, and retinopathy,
become more noticeable. Uveitis has been reported in two patients, which worsened during recurrent crises characterized by fever, vomiting, and diarrhea. The features of uveitis, such as anterior versus posterior locations, have not been characterized to date.

The associated retinopathy has been described as a tapetoretinal or RP-like degeneration. The findings include bone spicules, narrowing of retinal vessels, and countless minute defects of the retinal pigment epithelial throughout the periphery that create a “pepper and salt” appearance. One patient reported by Prietsch et al had uneven retinal surface reflections, retinal vessel narrowing, and optic atrophy of moderate extent, but no RP-like bone spicule pigmentation. Given the RP-like appearance, vitamin A has been administered in some patients without confirmed efficacy. Related findings, such as field constriction, lack of normal dark adaptation, and abnormal electroretinogram, have also been reported.

Many other inherited retinal conditions, which are phenotypically somewhat similar to mevalonic aciduria with pigmentary retinopathy and cataracts, have been described. For example, Alström disease is associated with infantile cardiomyopathy, diabetes mellitus, obesity, deafness, renal failure, acanthosis nigricans, baldness, hypogenitalism, and hypertriglyceridemia. Cockayne syndrome (Neill-Dingwall syndrome) is associated with dwarfism, deafness, mental deterioration, precocious senility, and intracranial calcifications. Flynn-Aird syndrome includes progressive deafness, ataxia, peripheral neuritis, epilepsy, dementia, dental caries, skin ulceration, baldness, and bone changes. Refsum syndrome is characterized by accumulation of phytanic acid and mental retardation, hepatomegaly, and skeletal changes. Bassen-Kornzweig disease is associated with abetalipoproteinemia, acanthocytosis, and ataxic neuropathy.

Visual prognosis seems to be guarded to poor in mevalonic aciduria. Simon et al reported that 4 of 5 adults, ranging in age from 30 to 54 years, had progressed to blindness caused by retinopathy and cataracts. This report did not, however, define what was considered blindness and did not state whether the decreased vision was caused by retinopathy, cataracts, or a combination of both. Our patient meets the typical legal definition for blindness because of the severely constricted visual fields. Her cataracts did not seem extensive enough to account for the reduced central vision.

Mevalonic aciduria, which is caused by an inherited deficiency of mevalonate kinase, causes a defect in the biosynthesis of both cholesterol and isoprenoids. Balgobind et al noted that patients with Smith-Lemli-Opitz syndrome, an inborn error in cholesterol biosynthesis, have slowed phototransduction (but no features of RP). They suggested that the RP-like retinopathy in mevalonic aciduria may not necessarily be caused by impaired cholesterol biosynthesis but instead may be caused by the unique isoprenoid metabolism found in the retina, which is abnormal in mevalonate kinase deficiency.

Balgobind et al explained that, under normal circumstances, the retina, unlike most tissues in the body, predominantly produces nonsterol isoprenoids, which are required for posttranslational protein isoprenylation. Several proteins important in phototransduction require isoprenylation, including RP GTPase regulator protein, which has been implicated in the pathogenesis of X-linked RP. Impaired isoprenoid biosynthesis could interfere with the function of other proteins that are needed for normal photoreceptor function, causing diseases such as choroideremia and one type of Leber’s congenital amaurosis.

In summary, the ocular findings in patients with mevalonic aciduria are heterogeneous and include blue sclerae, cataracts, uveitis, retinopathy, and optic atrophy. Visual prognosis is guarded; several patients surviving to adulthood have progressed to apparent legal blindness caused by cataracts and/or retinopathy. No systemic treatment has been proven to be efficacious to date.

References