Unilateral Retinitis Pigmentosa Occurring in an Individual With a Germline Mutation in the RP1 Gene

Retinitis pigmentosa (RP) is a heterogeneous group of monogenic retinal disorders characterized by progressive rod and then cone photoreceptor degeneration. Although female carriers of mutations in the X-linked genes RP2 and RP3 show asymmetry, cases due to mutations of autosomal genes show a high degree of symmetry between eyes. Patients with unilateral RP have been described, but none of these cases have been reported to be familial or associated with a gene mutation and the cause of these cases remains unclear. We describe the phenotype of a patient with entirely unilateral disease despite the inheritance of a germline mutation.

Report of a Case. The study adhered to the tenets of the Declaration of Helsinki and was approved by the local ethics committee.

A 63-year-old woman was visually asymptomatic but was found to have retinal signs as an incidental observation. Subsequent review showed best-corrected visual acuity of 20/30 OU. Anterior segment examination of both eyes revealed posterior subcapsular cataracts. Dilated funduscopcopy revealed narrow arterioles, retinal pigment epithelial atrophy, and bone-spicule intraretinal pigment deposition in all quadrants of the peripheral retina in the right eye with sparing of the macular region (Figure 1). The left fundus was completely normal. There was no abnormality of color vision (Hardy-Rand-Rittler and Ishihara pseudoisochromatic charts) in either eye.

Goldmann peripheral fields were normal in the right eye but showed generalized constriction to 10° trans-
versely with a III4e target in the left. Fundus autofluorescence of the right eye showed patchy hypofluorescence in the midperipheral retina and a hyperfluorescent ring in the macular region; the left eye was normal. Optical coherence tomographic findings of the left eye were normal. The right eye showed preservation of the outer retinal architecture in the foveal and parafoveal regions with loss in the more peripheral macula (Figure 1).

The full-field electroretinogram (ERG) of the left eye was normal. The ERGs in the right eye showed undetectable rod-specific findings; a delayed and markedly subnormal bright-flash ERG a-wave and proportional b-wave; and markedly subnormal but not delayed results on 30-Hz flicker and single-flash photopic ERGs. Pattern ERG results were bilaterally normal. Electro-oculogram light rise was undetectable on the right and normal on the left.

Figure 2. Pedigree and electropherogram. A, Pedigree showing dominant inheritance. Squares indicate males; circles, females; diamond, unknown sex; diagonal lines, deceased; open symbols, unaffected; solid symbols, affected; and arrow, proband. B, Electropherogram displaying the heterozygous c.2029C>T change in forward and reverse strands as compared with the reference sequence (top line).

The patient is part of a family showing dominantly segregating RP (Figure 2). Sequencing exon 4 of the RPI gene revealed a p.R677X mutation, which segregated with the disease in the family.

Comment. We describe the clinical findings in the first case, to our knowledge, of unilateral RP in a person carrying a germline mutation. Detailed evaluation confirmed the dysfunction to be confined to one eye.

The heterozygous nonsense mutation p.R677X, detected in RPI from the leukocyte DNA of the patient, is one of the most common causes of autosomal dominant RP. Although all of the mutations in RPI causing dominant RP result in truncation of the protein, in human cultured lymphoblasts the p.R677X allele is shown to be expressed. Therefore, haploinsufficiency is unlikely and
Comment. Prior to the era of molecular diagnosis, it was known that vision loss in the SCAs could result from primary optic neuropathies or, less commonly, retinal degeneration. Detailed studies of vision in the different SCA genotypes have not yet been performed, although it is well established that SCA7 is the only genotype in which retinal degeneration commonly occurs. In a prior series of patients with genetically confirmed SCA1, decreased visual acuity, dyschromatopsia, and optic atrophy were reported, but no other funduscopic abnormalities were noted. All 6 patients in that series had attenuated oscillatory potentials on full-field electroretinography (ERG) also reported in 6 patients. We describe a patient with genetically confirmed SCA1 who developed progressive painless binocular vision loss and had evidence of rod and cone photoreceptor dysfunction on full-field ERG.

Report of a Case. A 56-year-old woman had an 8-year history of progressive painless binocular vision loss, blepharospasm, and cerebellar ataxia. There was a strong history of cerebellar ataxia with associated vision loss on the paternal side of her family.

On examination, best-corrected visual acuity was 20/70 OU. She identified only the control Ishihara color plate bilaterally. Confrontation visual fields revealed bilateral central scotomas. External examination revealed blepharospasm and occasional facial grimacing. Anterior segment examination findings were unremarkable. The pupils were normal. Ocular motor examination revealed slow saccades and impaired smooth pursuit, without nystagmus. General neurologic examination revealed dysarthria, head titubation, and appendicular, truncal, and gait ataxia. Funduscopic examination revealed absent foveal light reflexes, drusen and subtle pigmentary changes in the posterior poles, and retinal arteriolar attenuation (Figure 1). The optic discs were normal and no pigmentary changes were noted in the retinal peripheries (Figure 1).

Goldmann visual fields showed central depression and constriction of all isopters. Brain magnetic resonance imaging showed brainstem, cerebellar, and cervical spinal cord atrophy. Full-field ERG showed attenuated responses to all stimuli in both eyes, with prolonged implicit times for dim white flashes and maximal white b-waves (Figure 2 and eTable, http://www.archophthalmol.com). Genetic testing revealed an increased CAG repeat number of 46 (normal <34) in 1 SCA1 allele, confirming the diagnosis of SCA1. Genetic testing results for SCA7 were negative. Other laboratory studies were unrevealing.

Rod-Cone Dystrophy in Spinocerebellar Ataxia Type 1

Spinocerebellar ataxia type 1 (SCA1) is a rare autosomal dominant neurodegenerative disease caused by a CAG triplet repeat expansion in the SCA1 gene on chromosome 6, encoding for a protein called ataxin-1.1 Spinocerebellar ataxia type 1 typically produces a progressive cerebellar syndrome, with prominent ataxia, dysarthria, and bulbar palsy. Early ophthalmologic manifestations include saccadic hypermetria, gaze-evoked nystagmus, and rebound nystagmus, with saccadic slowing and ophthalmoplegia developing in the later stages of the disease.2,3 Decreased visual acuity, dyschromatopsia, and optic atrophy are less commonly reported, with attenuation of oscillatory potentials on full-field electroretinography (ERG) also reported in 6 patients.4 We describe a patient with genetically confirmed SCA1 who developed progressive painless binocular vision loss and had evidence of rod and cone photoreceptor dysfunction on full-field ERG.