Discordant Retinitis Pigmentosa in Monozygotic Twins

Retinitis pigmentosa (RP) is a diverse group of retinal dystrophies characterized by night blindness, progressive constriction of the visual field, and bone spicule deposition in the peripheral retina. All forms of inheritance have been described, including X-linked, autosomal dominant, autosomal recessive, and mitochondrial, but approximately 42% of cases are simplex (sporadic) with no known family history. An unusual case of monozygotic twin sisters discordant for simplex RP is reported here.

Report of a Case. Twin A was first seen by us at age 22 years with bilateral vitreous cells and cystoid macular edema (CME). Visual acuity was 20/70 OD and 20/40 OS. She had a moderate initial response to periocular and oral steroids and to oral acetazolamide. Findings from an extensive uveitis workup were unrevealing, and she was otherwise healthy with no evidence of malignancy or systemic autoimmune disorder. She subsequently developed continued visual loss, nyctalopia, visual field constriction, arteriolar narrowing, and pigmentary retinopathy with peripheral bone spicules consistent with a diagnosis of RP (Figure 1). Results of electroretinographic (ERG) studies were very...
abnormal under photopic and scotopic conditions (Figure 2), and serial Goldmann visual field examination revealed relentless progression over a 5-year period (Figure 3). There was no family history of any retinal dystrophies, and both parents and all siblings had normal findings from eye examinations. Special attention was paid to the patient's identical twin sister (twin B) who had no ocular symptoms. Results of a dilated fundus examination, ERG, and a visual field examination were all completely normal in twin B (Figures 1, 2, and 3).

Zygosity determination using DNA polymorphisms was performed at the University of Utah DNA Diagnostic Laboratory (Salt Lake City) using restriction enzyme HaeIII and probes ynh24, cmm101, tbq7, and edf52. The twins were concordant for all 4 DNA markers, yielding a monozygotic probability of more than 99%. Likewise, peripheral blood cell metaphase karyotyping and G-banding revealed no abnormalities or discordance. Both twins shared similar environments and preferences as children. The affected twin had her first child at an earlier age than her sister (age 18 years vs age 26 years). The affected twin was a non-smoker, whereas her unaffected twin sister smoked cigarettes for approximately 10 years.

Circulating serum antibodies to retinal proteins are commonly present in RP patients with prominent CME (90% prevalence), but they are uncommon in RP patients without CME (13% prevalence) and are rarely encountered in the unaffected population (6% prevalence). Peripheral blood samples from twins A and B at age 26 years were screened against human retinal proteins under standard Western blot assay conditions. Interestingly, both twins exhibited definite immunoreactivity against a variety of human retinal proteins (Figure 4). Among them, we have positively identified immunoreactivity against retinal enolase (46 kDa) and carbonic anhydrase II (30 kDa), antigens that have been previously reported in association with cancer-associated retinopathy (CAR) syndrome and RP with CME. Interestingly, twin B (the unaffected twin) had a higher titer of anti-enolase antibodies, whereas twin A had stronger anti-carbonic anhydrase immunoreactivity, as well as unique antibodies against proteins in the 37 to 42 kDa range. It is therefore possible that the detected antibodies to carbonic anhydrase II and to the 37- to 42-kDa proteins may have played an important role in the development of RP with CME in the affected twin. The identity of these other proteins is not known; however, retinal antigens of similar molecular weight have been previously reported in association with RP and autoimmune retinopathies. The 22-kDa protein labeled by our patients' sera has a similar size to the retinal protein recoverin, also known as CAR antigen. Antibodies to recoverin have been found in some patients with RP, but additional experiments using purified recombinant human recoverin showed that the immunoreactivity against the 22-kDa antigen was not specific for recoverin. A second Western blot assay of fresh blood samples from both twins 2 years later was unchanged for all protein bands.

Comment. Retinitis pigmentosa is ordinarily considered to be an inherited disorder, but more than 40% of patients with RP have no known family history, and a disproportionately large number of these simplex patients may exhibit clinically significant CME. The existence of a pair of monozygotic twins in which only one exhibits classic clinical findings of simplex RP (eg, nyctalopia, bone spicules, progressive visual field loss, and a severely attenuated ERG) is quite remarkable and might provide insights into the pathophysiological mechanisms of RP with CME. In fact, RP in monozygotic twins is itself a rare event—approximately 200 monozygotic pairs with RP would be expected in the United States based on a total population of 275 million people, a prevalence of RP of 1 in 3500, and a frequency of monozygotic twins of 3 per 1000 live births. According to a MEDLINE search, only 1 similar discordant RP pair has been reported—a pair of monozygotic sisters in which only one developed pigmented paravenous retinochoroidal atrophy, an atypical RP syndrome that has never been proven to have an inherited basis.

How can the discordance be explained? There is no evidence that this is a pseudoretinitis pigmentosa syndrome such as syphilis, a toxic drug reaction, or CAR. Non Mendelian inheritance mechanisms, such as uniparental disomy, or a postfertilization translocation or mutation resulting in somatic mosaicism in one or both twins are possible but ex-
ceedingly rare events. Uneven lyonization (skewed X-chromosome inactivation) is a possible explanation, but the discordance between these twins is extreme, and there is no history of X-linked RP in the family. Their prominent antiretinal antibodies provide an intriguing clue because it has been speculated that environmental factors may trigger expression of retinal degenerations in individuals harboring antiretinal antibodies. Perhaps the early pregnancy of twin A caused an immune alteration that initiated such a reaction.

This case report demonstrates that discordant RP can occur in monozygotic twins and that the presence of antiretinal antibodies such as antienolase that have previously been described in patients with RP does not always correlate with the expression of clinically detectable RP. Furthermore, it suggests that noninherited environmental modifier factors may play an important role in RP and macular dystrophy kindreds that manifest incomplete penetrance or variable clinical phenotypes.

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Management of Retinal Detachment in Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) is an inherited disorder of connective tissue resulting from mutations in genes coding for type I collagen. The condition was first described in 1788 by O. J. Ekman in Sweden, and the term osteogenesis imperfecta was first used by Willem Vrolik in 1849. The disease is manifested in tissues in which the principal matrix protein is type I collagen: bone, ligaments, dentin, and sclera. Biochemical and molecular genetic studies have shown that most affected individuals have mutations in either the COL1A1 or COL1A2 genes that encode the chains of type I procollagen. Osteogenesis imperfecta is clinically characterized by increased bone fragility with a propensity to fracture, often resulting in skeletal deformity and variably associated with hearing loss, dental abnormalities, and blue sclera.

The skeletal manifestations are usually the most prominent. There is a continuum of varying severity, ranging from asymptomatic forms with subtle osteopenia, to moderately severe forms with deformity and propensity to fracture, to a perinatal lethal form consisting of innumerable fractures in utero and at birth. For most patients, the presence of multiple fractures early in life, with or without blue sclera, is usually sufficient to establish the diagnosis. Multiple fractures during childhood and adolescence often lead to short stature and spinal abnormalities. Thoracic scoliosis is the most common deformity, resulting from osteoporosis, compression fractures, and ligamentous laxity. Pes planus is also a common feature.

Otologic manifestations of OI occur in approximately 50% of patients and include hearing loss, the most common problem, as well as tinnitus, vertigo, middle ear infections, and sinusitis. Dental involvement, termed dentinogenesis imperfecta, is present in 30% of patients and typically consists of soft, translucent brownish teeth. The enamel wears easily, and the teeth are carious, shortened, and susceptible to cracking. The skin is often thin, translucent, and easily distensible. Surgical scars may heal with widening and prominence. Cardiovascular involvement is less common but may include mitral valve prolapse and non-progressive aortic root dilatation. Intelligence is usually normal.

The ocular manifestations of OI are not usually sight threatening and typically consist of blue sclerae; however, the sclerae can vary in color from normal to a slightly bluish or slate color to a bright blue. The blue sclerae result from thinning of the abnormal sclera, leading to the transmission of the uveal tissue to the observer. The treatment of retinal detachment in patients with OI is challenging owing to the abnormal morphologic characteristics of the sclera. In this study, we report the successful treatment of retinal detachment in 4 eyes of 3 patients with OI.

Report of Cases. Case 1. A 57-year-old man with a recent complaint of hazy vision and floaters in his left eye came to the Kresge Eye Institute (Detroit, Mich). The patient denied photopsia. His medical history was significant for OI, diagnosed when he suffered multiple bone fractures during childhood as a result of minor trauma. There was no known history of OI in the family. Best-corrected visual acuity was 20/25 OD and 20/30 OS with a −11.0-diopter correction in both eyes. Slitlamp examination was remarkable for bilateral blue sclerae. In the right eye, a posterior vitreous detachment was present with mild myopic fundus changes. In the left eye, there was a posterior vitreous detachment with vitreous hemorrhage. A funduscopic examination of the left eye showed a supertemporal retinal detachment secondary to a large retinal tear, with vitreous traction at the apex of the flap. The macula was spared. Because of the generalized thinning of the sclera, demarcation laser photoocoagulation was elected. Four hundred sixty-seven spots of argon green laser at 500 µm, 0.10 seconds, and 530 mW was applied...