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Is Zonal Occult Outer Retinopathy an Autoimmune Disease?

Grazyna Adamus

Ocular Immunology Laboratory, Casey Eye Institute, School of Medicine, Oregon Health & Science University, Portland, OR, USA

Acute zonal occult retinopathy (AZOOR) is a rare condition of unknown etiology characterized by an acute visual loss that may be related to rapid loss of one or more zones of the outer retinal function [1-3]. AZOOR typically manifests with asymmetrical visual field loss, persistent photopsia, acuity reduction and often with widespread photoreceptor dysfunction on the electroretinogram (ERG) [3]. This condition mostly affects young women and may be linked to female hormones, although such an association has not been reported.

The focus of my laboratory is on the autoimmunity of retinopathy, including cancer-associated retinopathy, melanoma-associated retinopathy, autoimmune retinopathy, and occasionally, AZOOR. I am often asked whether AZOOR is an autoimmune disease and whether this condition is associated with the presence of autoantibodies against retinal antigens. If so, do the autoantibodies play a role in pathogenicity of AZOOR? If one suspects an immunological or autoimmune involvement one should look for signs of inflammatory or autoimmune pathology as a result of failure in the mechanism of antigen-specific immunoregulation, typical of such diseases. AZOOR is a relatively new entity and has not been intensively studied. Two recent reviews suggested that AZOOR is a form of AR [4,5]. In 2003, Jampol and Backer proposed a hypothesis that AZOOR may originated from relatively common non-disease specific of "clusters" genes (at specific genetic loci) that predispose individuals to "autoimmune" diseases in a similar way to other inflammatory diseases of unknown etiology [6]. However, there is no strong evidence supporting this hypothesis. A history of AZOOR-associated immune-mediated inflammatory systemic disease was reported in only ~18% of patients [5]. Treatments with systemic corticosteroids and other systemic immunosuppressive agents have not been effective [5]. However, Grass et al. [1] reported inflammationthat typically develop within several weeks following the onset of AZOOR, possible as an effect of an inflammatory response to the dying photoreceptor cells. Occasionally, weeks or months later, narrowing of the retinal vessels, particularly the retinal arteries, perivascular sheathing and reactive changes in the RPE occur, including hypopigmentation and migration of RPE into the overlying retina similar to that occurring in the zones of receptor cell loss in RP. In such cases one would expect a generation of autoantibodies against components of these retinal cells.

Over last 10 years we have tested 53 patients diagnosed or suspected of AZOOR for anti-retinal autoantibodies. Table 1 summarizes the demographics of findings at the time of blood collection for anti-retinal autoantibody testing. Twelve patients had evidence of unilateral involvement at the time of antibody testing and the course was progressive in 14 reported cases. Depressed ERG was reported in 33 patients. Remarkably, more than a half of patients tested (52.8%) had circulating autoantibodies to various retinal proteins but the range of autoantibody specificity was relatively narrow. Anti-α-enolase autoantibodies occurred in fourteen patients (~27%), in seven as a singular anti-retinal autoantibody. Nine patients had autoantibodies against carbonic anhydrase II (CAII). Those autoantibodies are often associated with paraneoplastic and autoimmune retinopathies[7]. Autoantibodies of fifteen patients (~29%) recognized a single retinal antigen. Multiple autoantibodies were detected in 11 patients (21%), including anti-α-enolase, anti-CAII, anti-aldolase, anti-transducin and others, indicating a general activation of the immune system. In our cohort only two patients presented with inflammatory conditions (chronic uveitis and toxoplasmosis) that could contribute to the generation of autoantibodies. Those multiple autoantibodies represented extremely similar range of antigenic recognition. Although those antigens are components of retinal cells and they play important physiological functions the only antigen specifically related to photoreceptor cells was photoreceptor transducin α and β. One would argue that such autoantibodies are nonspecific to retinal degenerative disease therefore are not pathogenic.

Characteristic	Mean	Range
Age at testing	44.4	14-72
Female age (n=38)	42.4	14-65
Male age (n=15)	46.4	22-72
Years of presentation	3.6	6 months to 26 years
Ratio Male to Female	1 : 2.5	
Female with autoantibodies	18 (47%)	
Male with autoantibodies	10 (66%)	

Table 1: Patient Characteristic (n=53).

The incidence of autoantibody in AZOOR is high, much higher than in our control group of healthy subjects. It is known that autoantibodies are present in healthy individuals, usually in very low levels, indicating that these autoantibodies are not pathogenicas the levels are too low to rise to symptoms if the antigen is not preset, and they even may be protective. Depending on specificity, anti-retinal autoantibodies were found in 0-11% of normal subjects in our studies. Interestingly, in systemic diseases, about 25% of healthy relatives of SLE patients present with serum anti-DNA antibodies [8]. This would imply that, in some cases, pathogenicity of autoantibodies might depend on correct exposure of the autoantigen.

The presence of anti-retinal autoantibodies indicates an immunological involvement. The challenge is to understand regulatory mechanisms that induce autoimmunity against retinal antigens in AZOOR, and show that theseautoantibodies are involved in zonal destruction of the retinal cells like in other autoimmune retinopathies [9]. This will lead us to better understanding of pathogenicity of AZOOR and development of new immunotherapies for management of disease.

Corresponding author: Grazyna Adamus, Ph.D., Oregon Health and ScienceUniversity, Casey Eye Institute, 3181 SW Sam Jackson Park Rd., Portland, OR97239, USA, Tel: 503-418-2540; Fax: 503-418-2541; E-mail: adamusg@ohsu.edu

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