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Risk of Cataract among Subjects with Acquired Immune Deficiency Syndrome Free of Ocular Opportunistic Infections

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Purpose: To evaluate the risk of cataract in the setting of AIDS.

Design: Prospective cohort study.

Participants: Subjects with AIDS free of ocular opportunistic infections throughout catamnesis.

Methods: From 1998 through 2008, subjects 13 years of age or older were enrolled. Demographic characteristics and clinical characteristics were documented at enrollment and semiannually.

Main Outcome Measures: Cataract was defined as high-grade lens opacity observed by biomicroscopy judged to be the cause of a best-corrected visual acuity worse than 20/40. Eyes that underwent cataract surgery during follow-up were considered to have developed cataract before the first visit when pseudophakia or aphakia was observed.

Results: Among 1606 participants (3212 eyes) at enrollment, 1.9% (95% confidence interval [CI]: 1.3%−2.7%) were observed to have cataract or prior cataract surgery. Among the 2812 eyes initially free of cataract and followed longitudinally (median follow-up, 4.6 years), the incidence of cataract was 0.37%/eye-year (95% CI: 0.26%−0.53%). In addition to age, significant cataract risk factors included prior cataract in the contralateral eye (adjusted hazard ratio [aHR], 21.6; 95% CI: 10.4−44.8), anterior segment inflammation (aHR, 4.40; 95% CI: 1.64−11.9), prior retinal detachment (aHR, 4.94; 95% CI: 2.21−11.0), and vitreous inflammation (aHR, 7.12; 95% CI: 2.02−25.0), each studied as a time-updated characteristic. Detectable human immunodeficiency virus RNA in peripheral blood was associated with lower risk of cataract at enrollment (adjusted odds ratio, 0.32; 95% CI: 0.12−0.80) but not of incident cataract (aHR, 1.58; 95% CI: 0.90−2.76). After adjustment for other factors, neither the then-current absolute CD4+ T-cell count nor antiretroviral therapy status showed consistent association with cataract risk, nor did an additive diagnosis of other comorbidities. Compared with the available population-based studies that used similar definitions of cataract, the age-specific prevalence of cataract in our cohort was higher than in 1 of 2 such studies, and the age-specific incidence of cataract surgery was higher.

Conclusions: Our results suggest cataract may occur earlier among patients with AIDS free of ocular opportunistic infections than in the general population. Cataract risk was associated most strongly with age and with other ocular morbidity in this population. With improved survival, the burden of cataract likely will increase for persons with the human immunodeficiency virus or AIDS. *Ophthalmology 2014;■:1−8 © 2014 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Cataract is the leading cause of visual impairment in the United States[1] and worldwide[2] and is the leading cause of legal blindness among African Americans.[1] Historically, cataract has not been viewed as one of the significant causes of ocular morbidity in patients with AIDS because such morbidity has been dominated by ocular opportunistic complications of immunodeficiency.[3] Furthermore, cataract typically is a disorder of older adults,[4] whereas the AIDS epidemic began predominantly among younger and middle-aged adults.[5,6]

In the era of highly active antiretroviral therapy (HAART), the incidence of opportunistic complications of AIDS has declined substantially,[7,8] including the incidence of ocular opportunistic complications.[8−13] Among persons who have a long-term favorable response to HAART, AIDS has evolved into a chronic disease wherein long-term survival is expected. This context provides an opportunity for ocular diseases of aging, including cataract, to develop in individuals with AIDS. In addition, there are indications that these individuals may experience accelerated aging,[14,15] of which cataract, and earlier onset of cataract, are potential indicators.[16]

In our investigations of the long-term ocular complications of AIDS, we found that patients with both AIDS and

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cytomegalovirus (CMV) retinitis are at high risk for cataract.[17] We also documented that cataract was the second leading cause of visual impairment in the Longitudinal Study of Ocular Complications of AIDS (LSOCA) cohort among subjects who did not have CMV retinitis at the time of enrollment.[18] To characterize better the risk of cataract among these subjects with AIDS, we report herein analyses of the prevalence and incidence of cataract in LSOCA subjects who were free of CMV retinitis and other intraocular opportunistic infections at the time of enrollment.

Methods

The methods of the LSOCA have been described extensively.[18–27] Briefly, patients with AIDS 13 years of age and older were enrolled at 19 United States centers specializing in ocular complications of AIDS beginning in 1998—entirely within the HAART era. The study respects the principles of the Declaration of Helsinki at all centers, operating under the ongoing approval of each site's governing institutional review board.

From the beginning of the study on September 2, 1998, through March 27, 2008, the period of the observations reported here, subjects free of intraocular opportunistic infections were evaluated at semiannual study visits. Demographic and clinical data about AIDS diagnosis, current and nadir CD4+ T-cell count, current and zenith human immunodeficiency virus (HIV) load in peripheral blood, anemia, the presence of systemic opportunistic complications of AIDS, past and present use of medications, and the presence of comorbidities were obtained at enrollment and were updated at each study visit. A complete ophthalmologic examination including both binocular biomicroscopy and dilated ophthalmoscopy was performed by a study-certified ophthalmologist at each visit, including grading of lens opacities as normal or trivial opacities (less than grade 1), peripheral vacuoles (grade 1), peripheral opacity (grade 2), central opacity (grade 3), central opacity affecting vision (grade 4), or surgical aphakia or pseudophakia. A total of 158 examiners at 20 clinics evaluated cataract status. The median number of assessments per examiner was 13 (range, 1–1670; interquartile range, 3–50). The median number of examiners per clinic was 10 (range, 1–23; interquartile range, 7–14). Best-corrected visual acuity with a logarithmic chart was measured at every visit by gold standard methods.[28] For purposes of these analyses, eyes were defined as having a cataract if they met the following 3 criteria: (1) graded as having a lens opacity, (2) best-corrected visual acuity worse than 20/40; and (3) reduction of best-corrected visual acuity attributed to cataract by the examining ophthalmologist. Eyes that had undergone cataract surgery before the first study visit also were considered to have had a cataract. Among phakic eyes free of cataract at the time of enrollment, the incidence of cataract was counted as occurring on the first follow-up visit at which either cataract, pseudophakia, or aphakia was noted. Anterior segment inflammation was defined as present for eyes with anterior chamber cells, anterior chamber flare, a diagnosis of anterior uveitis or keratitis, the presence of posterior synechiae, or a combination thereof. Posterior segment inflammation was defined as present for eyes with vitreous cells, vitreous haze, or both; eyes with a diagnosis with intermediate uveitis, posterior uveitis, or panuveitis or with endophthalmitis also were considered to have posterior segment inflammation.

Most population-based studies of cataract in both the United States and Australia have diagnosed cataract based on masked gradings of lens photographs by a reading center, independent of the effects of any opacities on visual acuity.[29–32] However, slit-lamp biomicroscopy-based grading methods comparable with those used here have been applied to estimate the prevalence of cataract in 2 population-based studies in the United States, each of which studied Hispanics predominantly of Mexican origin.[33,34] One of these, the Los Angeles Latino Eye Study (LALES),[35] provided data on the incidence of individual-level cataract surgery for comparison with the data from the LSOCA cohort in this analysis.

Sensitivity analyses were performed to determine whether risk factor associations with incident cataract were consistent across 2 possible alternative definitions of cataract: (1) presence of a "central opacity affecting vision (grade 4)" and (2) the ophthalmologist's indication that "based solely on lens status . . . [the eye would] be a candidate for cataract surgery." The prevalence of either present or prior cataract was evaluated at the time of enrollment in LSOCA. Logistic regression models were fit via generalized estimating equations to estimate the prevalence of cataract and to compare the prevalence and the 4-year incidence in the LSOCA cohort with the population-based studies. Staggered entry Kaplan-Meier curves were constructed to show the cumulative probability of incident cataract over time. Cox proportional hazards models evaluated risk factors for incident cataract. All time-to-event analyses were anchored on age to account for this potent cataract risk factor and were clustered by individual to account for intereye correlation. Subscripts before and after estimates of adjusted odds ratios (aORs) and adjusted hazard ratios (aHRs) indicate the upper and lower bounds of 95% confidence intervals. Statistical analyses were performed with SAS software version 9.1 (SAS Inc., Cary, NC), Stata software release 10 (StataCorp, College Station, TX), and R software version 2.11.1 (The R Project for Statistical Computing; available at: http://www.r-project.org/; accessed April 14, 2014).

Results

A total of 2121 subjects with AIDS were enrolled into the LSOCA cohort between September 2, 1998, and March 28, 2008. Twenty-six subjects were excluded from the analysis for the following reasons: (1) they had been diagnosed with a non-CMV herpetic retinitis, toxoplasmosis involving the retina, or syphilitic eye disease (n = 21) before enrollment or during follow-up; (2) they did not complete the enrollment visit (n = 3); or (3) they had unknown cataract status (n = 1) or unknown CMV retinitis status (n = 1) at the time of enrollment. Among the remaining 2095 subjects with complete cataract and CMV retinitis data, 1606 (88%) were free of intraocular opportunistic infections in both eyes at enrollment and intraocular opportunistic infections did not develop during follow-up. The prevalence and incidence of cataract were evaluated in the 3212 eyes of these 1606 patients.

Characteristics of the analyzed population at enrollment are given as Table 1 (available at www.aaojournal.org). Most patients were young and middle-aged male adults, 46% of whom were white, 36% of whom were African American, 15% of whom were Hispanic, and the rest of whom were another race or ethnicity. By inclusion criteria of LSOCA, all met the then current Centers for Disease Control and Prevention definition of AIDS,[36] 63.2% based on a systemic opportunistic infection and the remainder based on CD4+ T lymphopenia. As of the enrollment visit, the median time since AIDS diagnosis was 4.2 years. Although 84% were receiving HAART, 56% had a detectable HIV load in peripheral blood at enrollment. Although for 53% the nadir CD4+ T-cell count at or before enrollment was less than 50 cells/μl, at enrollment 82% had a CD4+ T-cell count of 50 cells/μl or more. A substantial