Asteroid Hyalosis in an Autopsy Population

The University of California at Los Angeles (UCLA) Experience

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Objectives: To study the prevalence and associations of asteroid hyalosis (AH) in a series of autopsy eyes.

Methods: Retrospective review of the University of California at Los Angeles (UCLA) autopsy eye database from 1965 to 2000 yielded 10801 patients. The patients’ medical histories were reviewed for evidence of diabetes mellitus, hypertension, hyperlipidemia, alcohol abuse, hypercalcemia, hypothyroidism, and chronic renal failure. Autopsy records were searched for evidence of optic atrophy, macular degeneration, posterior vitreous detachment, atherosclerosis, and chronic renal failure. Asteroid hyalosis was diagnosed by examination of the autopsy eyes. Univariate and multivariate statistical methods were used to analyze our data.

Results: The prevalence of AH was 1.96% in this autopsy population. By χ² analysis, AH was significantly correlated with age (P<.001), male sex (P=.006), age-related macular degeneration (P=.02), hypertension (P=.03), atherosclerosis (P<.001), and posterior vitreous attachment (P<.001). After adjusting for age in a multivariate logistic regression analysis, statistical significance was found only for posterior vitreous attachment (P=.002) and male sex (P=.046). No statistically significant association was found with diabetes mellitus or alcohol abuse by univariate or multivariate analysis. Analysis of the odds ratio showed a strong age effect that increased from 5.0 (95% confidence interval, 2.2-11.3) in age group 41 to 50 years, compared with 25.4 (95% Wald confidence interval, 8.2-77.9) in the age group of patients older than 90 years.

Conclusions: A unique epidemiological autopsy cohort study of AH and its systemic associations yielded a higher prevalence of AH than previous studies. Asteroid hyalosis was strongly correlated with age and inversely correlated with posterior vitreous detachment. Unlike some previous reports, we found no statistically significant correlation between AH and diabetes mellitus.

However, that report surveyed a population from Beaver Dam, Wis, that was predominantly restricted to a white northern European background (99.4%). In addition, AH was diagnosed retrospectively by inspection of fundus photographs. The photographs were not interpretable in 3.6% of patients, most of whom were older (mean age, 71 years) and more likely to have a history of DM and cardiovascular disease. The authors indicated that AH was likely to be underestimated because photographs did not include the periphery and the camera focused on the posterior retina rather than on the vitreous.3

The limitations of the previous studies prompted us to study the prevalence of several systemic diseases in association with AH. Our study population was large enough to permit multivariate analyses, included a wide cross-sectional population reflective of the United States in general, and, to our knowledge, is the only cohort study of the prevalence of AH in human autopsy eyes.

**METHODS**

Retrospective review of the University of California at Los Angeles (UCLA) autopsy eye database from 1965 to 2000 included 10 801 patients (Figure 1). The patients’ medical records were reviewed for evidence of DM, hypertension, hyperlipidemia, alcohol abuse, hypercalcemia, hypothyroidism, and chronic renal failure, in addition to autopsy evidence of optic atrophy, glaucoma, age-related macular degeneration, posterior vitreous detachment (PVD), atherosclerosis, and renal diseases. Racial backgrounds were categorized according to the classification provided in the report of the US census for 2000.

**EXAMINATION OF AUTOPSY EYES**

Autopsy eyes were processed and examined using previously described methods.15 Posterior vitreous detachment was diagnosed by suspension of the eyes in air as reported previously.19 For analysis, 20 227 eyes were studied as a subgroup in which PVD was scrutinized.

**STATISTICAL METHODS**

Univariate χ² analysis and multivariate logistic regression statistical methods were used to analyze our data. In the multivariate analysis, several models were tested using factors that were found to be statistically significant on χ² analysis (hypertension, atherosclerosis, DM, hyperlipidemia, age-related macular degeneration). We adjusted for age and sex in all of these models. In addition to studying AH cases overall, bilateral AH cases were specifically studied in several models in an attempt to explore whether there were inherent differences between unilateral and bilateral AH. Age-specific prevalence of AH was calculated using 10-year interval age groups (Figure 2). Statistical analysis was done using SAS statistical package (SAS Institute, Inc, Cary, NC).

Review of our autopsy database yielded 212 cases (1.96%) of AH, of whom 42 cases (0.4%; 42 of 212 patients [19.8%]) were bilateral. In addition to the bilateral cases,
there were 97 cases with only the right eye affected and 73 with only the left eye affected.

AGE

In the autopsy population, the ages ranged from 0 (stillbirth) to 109 years, with a mean and median of 48 and 55 years, respectively. There were a total of 4274 patients (39.59%) older than 60 years, of whom 619 (5.73%) were 81 years or older, and 74 patients (0.69%) were 90 years or older. The age of patients with AH ranged from 9 to 97 years, with a mean and median of 67 years. By χ² analysis, age was highly associated with AH whether unilateral (P < .001) or bilateral (P = .001), an effect that persisted after adjusting for sex in a multivariate model (P < .001). Age-specific prevalence increased from 0.27% in patients younger than 40 years to 6.76% in patients older than 90 years (Figure 2).

SEX

There were 6725 males (62%) in the autopsy population. Of the patients with AH, 151 (71.2%) were male, which was statistically significant on χ² analysis (P = .006) and was less significant after adjusting for age in a multivariate model (P = .046).

RACE

The racial backgrounds of patients in the autopsy reports revealed that 8081 patients were white (75%); 1368, African American (13%); 216, Asian (2%); and 1119 were categorized as other racial backgrounds (10%). Of the patients with AH, 156 were white (73.6%); 29, African American (13.7%); 4, Asian (1.9%); and 22 other (10.4%). There was no statistical significance for an association between AH and race whether in univariate or multivariate models.

DIABETES MELLITUS

Diabetes mellitus was reported in 780 patients (7.22%). Of those patients, only 20 had AH; this was not a statistically significant association by either χ² or multivariate analysis. Diabetes mellitus was statistically associated with bilateral AH on χ² analysis but not after adjusting for age and sex. On subgroup analysis for the different age groups, we found specific age subgroups (51-60 years, P = .006; 41-60 years, P = .004) that showed a statistically significant association between AH and DM. The age groups with the lowest association were age groups younger than 40 years, 81 to 90 years, and 91 years and older; P = .50, .53, and .73, respectively.

POSTERIOR VITREOUS DETACHMENT

Of the 20,227 eyes studied for PVD, 243 were found to have AH. The prevalence of AH in eyes with PVD was only 1.39%. No association was found for AH and PVD in our population. However, AH was associated with the absence of PVD, after adjusting for age and sex (Table 2). There was no association of partial PVD with AH after adjustment for age (P = .89).

OTHER CONDITIONS

Age-related macular degeneration, hypertension, and atherosclerosis showed apparent statistically significant associations with AH by χ² analysis but not after adjusting for age and sex in the multivariate model (Table 2). No other conditions, including hypercalcemia, hyperlipidemia, alcohol abuse, hypothyroidism, chronic renal failure, and optic atrophy, showed statistically significant association with AH, whether by χ² or multivariate analysis (Table 2).

COMMENT

The population surveyed in this study of AH represents a large cross-sectional population of Los Angeles. The racial backgrounds surveyed match the demographic characteristics of the US population based on the 2000 cen-
The wide distribution obtained is the result of a broad-based autopsy eye program that included several hospitals with varying demographic populations and no selection bias for eye diseases. The largest previous study surveyed an eye clinic population in Philadelphia, Penn, of 12205 patients and provided little demographic information. The second largest previous study surveyed the population of Beaver Dam, and included 4926 patients, but 99.4% of patients were white.

The broad representation of the demographic groups in our study provides a basis to study the relationship of race to AH. Five previous studies compared the prevalence of AH in African American patients with white patients but not with other racial groups. The largest of these reports surveyed a largely white population (99.4%) and did not report any racial difference. In their population, Potter and Newcomb similarly found no racial difference. In contrast, Jervey and Anderson reported a 2-fold higher prevalence of AH among their white patients; however, no details are provided regarding the overall racial distribution of their surveyed population. Similarly, Rodman et al found a predominance of white individuals among patients with AH, in cases selected from the Armed Forces Institute of Pathology Registry, Washington, DC. Interestingly, Luxenberg and Sime criticized the conclusions of Jervey and Anderson, noting that the 2-fold higher prevalence of AH in white patients in their study correlated with a 2-fold higher prevalence of white individuals in their population. In these reports, little is conveyed about the baseline characteristics of the population surveyed. Any survey of the racial characteristics of a population is subject to error because racial heterogeneity in the United States is often underreported. In any case, we found no association of AH with any racial category, in either multivariate or univariate models.

We found a statistically significant higher prevalence for AH among males, which became of borderline statistical significance after adjusting for age. The association of AH with male sex has been reported previously, although the results were not adjusted for age. One of the studies included a large population base but only 83.1% of the population participated in the survey. The majority of nonparticipants were older men, which may have led to underestimation of AH and its sex association. Of the other reports, little is known about the baseline characteristics of the population surveyed, apart from 1 report that originated from a veterans affairs ophthalmology clinic with a 13:1 predominance of males among patients with AH.

The design of an autopsy eye study offers distinct advantages compared with previous studies. Because the data for AH and the associated diseases are collected at autopsy, the results reflect the lifelong prevalence of AH and its associations. To our knowledge, AH has never been documented to spontaneously disappear, consistent with the observation that prevalence dramatically increases in each advancing decade of life (Figure 1). The second advantage of this autopsy study is that eyes were methodically examined for AH, PVD, and other associated pathologic findings. Prior studies have relied on fundus photographs or clinical examination by multiple examiners. These methods are severely limited, especially in patients with media opacity, and may not be reliable or provide an examination of the entire eye for AH. This is reflected by the fact that in the Beaver Dam Eye Study, only 96.4% of the fundus photographs were gradable for AH. Retrospective reports suffer several limitations, including incomplete data acquisition, in addition to the nonstandard methods of data collection and examination methods. This may explain why the largest clinical report to date, which surveyed 12205 subjects, yielded only 101 cases of AH (0.83%). The authors report that junior residents, who consulted with senior residents or attending physicians, screened the study patients. In our study, one of 2 ocular pathologists thoroughly examined all autopsies eyes with the same methods. These factors may account for the nearly 2-fold higher prevalence of AH in our study compared with previous reports.

An association of AH with DM has been proclaimed in several previous reports, many of which were small case series. These reports have prompted the proposal that increased permeability of basal membranes found in the eyes of patients with DM might lead to the release of anions and macromolecules that could initiate development and growth and asteroid bodies. When evaluating the association of these 2 diseases that are both highly prevalent in the older population, it is imperative to control for age in any statistical analysis to exclude reporting chance association. Recent estimates of the prevalence of diagnosed and undiagnosed DM in the elderly population approach 1 in 5 people 65 years or older. An additional 23% of the elderly population meet the diagnostic criteria for impaired glucose tolerance, yielding an incidence that approaches 50%. The reports that found a positive correlation of DM and AH were not controlled and/or did not adjust for age. Similar to our report, the Beaver Dam Eye Study failed to confirm a correlation between DM and AH.

An association of AH with DM was found in studies derived from eye clinic populations. The eye clinic population is biased toward patients with DM and with vision problems. Yazar et al surveyed an eye clinic population ranging in age from 50 to 89 years. In all of these reports, excluding patients who are younger than 40 years could bias results toward finding an association, especially if patients are clustered in the 40- to 60-year age group. In the age group of 40 to 60 years, we had the highest prevalence of DM in our population and found a statistical association with asteroid hyalosis.

One obvious limitation to an autopsy study is the inability to confirm the diagnosis of associated diseases by prospective clinical blood tests or studies. However, general autopsy findings were available to confirm the history and clinical findings. It is also likely that our methods overlooked cases of early or undiagnosed DM, which represent a large proportion of individuals with DM. The prevalence of DM in our study was slightly lower (7.2%) than others (8.9% in the Beaver Dam Eye Study). A recent report found the proportion of undiagnosed DM to range from 35% to 44% of total persons with diabetes aged 40 to 74 years between 1988 and 1994, depending on the diagnostic methods used. However, the reports by Ber-
guren et al.,2 Wasano et al.,12 and Potter and Newcomb13 used history of prior diagnosis or treatment as their criteria for diagnosis of DM. The diagnostic criteria for DM are continually updated. For our study and several clinical studies, the diagnosis of DM reflects the changing criteria used by health care professionals during the period in which the patients lived.

Unlike previous studies, we did not find an association of AH with partial PVD. We limited the scope of this investigation to include cases that had been carefully examined for PVD as part of another study.26 Wasano et al.12 compared 59 consecutive cases of AH with 46 age-matched, healthy controls in an eye clinic setting. The authors found a lower prevalence of complete PVD in the AH population compared with controls and a significantly higher incidence of partial PVD in the AH population. They used slitlamp biomicroscopy to diagnose PVD, which can be limited in patients with cataract, media opacity, poor cooperation, narrow pupils, or intraocular liquid lacunae (syneresis). Our study confirms that there is a lower prevalence of PVD in patients with AH. However, unlike Wasano et al., our data show a lower prevalence of partial PVD in patients with AH after correcting for age.

The most statistically significant association with AH is advancing age (P < .001). Only 1 previous report1 studied age-specific prevalence of AH. The population surveyed ranged from 43 to 86 years, and they found a progressively increasing prevalence with advancing age (P < .001). Our study covered a wider age range of a more broadly distributed population, which would explain the higher age-specific prevalence found in our study (Figure 1).

The definite association of AH with age invites speculation as to the mechanism of AH. The asteroid bodies feature a multilamellar structure comprising a mineral compound containing calcium, phosphorus, and oxygen, presumably a calcium apatite-like material.27 There is chondroitin-6-sulfate at the periphery and hyaluronic acid in the inner matrix.24 The stacks of parallel crystaline lamellae of asteroid bodies are closely associated with irregular collagen fibrils. It has been suggested that the aggregation of collagen fibers into parallel fibrils with aging26 in combination with an anionic field produced by N-acetylglucosamine found in hyaluronic acid may serve as a matrix on which calcium-apatite crystals could form.22 The reason for the lower prevalence of AH in patients with PVD is not readily apparent. Perhaps AH is less likely to form in the presence of vitreous detachment. Alternatively, the composition of the fibrils and vitreous in patients with AH may somehow prevent PVD. This raises fundamental questions about the composition of the vitreous fibrils and biochemical changes associated with aging. The biomolecular composition of the vitreous and asteroid bodies has only recently been explored, and many questions remain unanswered.

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REFERENCES


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