

REMNANTS OF THE ANTERIOR TUNICA VASCULOSA LENTIS AND LONG ANTERIOR LENS ZONULES

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Abstract

Purpose: To investigate presence of remnants of the tunica vasculosa lentis, a possible indication of anterior segment dysgenesis, in subjects with the long anterior zonule (LAZ) trait. **Methods:** Retro-illumination photos of the pupil region had been collected in earlier study of the LAZ trait in African-Americans. Secondary image analysis was performed to assess the frequency of intact persistent pupillary membrane iris strands (PPMIS). **Results:** The analysis included 148 subjects, comprised of 74 LAZ subjects (median age=70 years, range=50-91 years; 64 females) and 74 controls (68 years, 50-83 years; 64 females). While controlling for age and gender, analysis showed that LAZ subjects were 3.1 times more likely than controls (OR=3.1; 95% CI =1.4 to 6.7; P=0.004) to exhibit PPMIS in at least one of their eyes. **Conclusions:** The LAZ trait, which is being studied as a potential risk factor for glaucoma, was associated with presence of PPMIS in our study population.

Keywords: Angle-closure glaucoma; crystalline lens; iris; long anterior lens zonules; pigment dispersion; tunica vasculosa lentis

Introduction

Long anterior zonules (LAZ) are characterized by zonular fibers occurring central to the normal insertion zone on the anterior lens capsule,⁽¹⁻⁵⁾ sometimes causing marked reduction in the zonule-free zone diameter^(6;7) (Fig. 1). LAZ may rub against the posterior iris, become pigmented (Fig. 2), and cause other pigment dispersion signs.^(2;4;8-10) There appear to be multiple etiologies for the LAZ trait, with one variety occurring in families manifesting late-onset retinal degeneration (L-ORD) in association with an S163R mutation in the CTRP5 (C1QTNF5) gene.^(11;12) In this situation, LAZ may clearly present in younger individuals within the third to fifth decades of life, but we have frequently encountered LAZ apart from L-ORD families, which we have only rarely detected in people <50 years old.^(9;10;13;14) Along with age in this form of the LAZ trait, there is also association with female gender, hyperopia, and shorter axial length.^(1;3;9;10;13;15) In addition to creating diagnostic confusion caused by its pigment dispersion signs, LAZ is also significant because of potential relationship to open- and narrow-angle forms of glaucoma,^(8;14;15) and because of concern for capsular tear formation occurring after cataract surgery.^(6;7)

The LAZ trait is understudied, and better understanding is needed, especially with its estimated prevalence near 2%.⁽⁹⁾ After observing persistent pupillary membrane iris strands (PPMIS) in people with LAZ (Fig. 2), we decided to test hypothesis of an association because it might further characterize the LAZ clinical syndrome and provide clues to related pathophysiology.

Subjects and Methods

Subjects were recruited from an urban, academic eye care facility, located in Chicago, Illinois, USA, and all presented for a broader investigation seeking to explore the clinical nature of the LAZ phenotype. Within the larger investigation, LAZ subjects and controls had been recruited over a 2.5 year period. Potential association of PPMIS with LAZ had not been recognized during initial data collection, so photo documentation was not obtained with this in mind.

LAZ subjects were recruited from a larger, database accumulated over 10-12 years, mostly through in-house referral. The criteria for LAZ was presence of zonular fibers ≥ 1.0 mm central to the normal zonule insertion zone on the anterior capsule (Fig. 1). To ensure definitive cases, subjects who did not have ≥ 5 LAZ fibers in at least one eye were excluded. Only African-Americans were recruited due to facility patient demographics. Race/ethnicity was determined by self-report.

Controls were recruited from an existing database of about 5,500 consecutive primary eye care patients examined over a two-year period by five study site practitioners, through in-house patient advertising, and through doctor referral. Controls were selected via frequency-matching on race, gender, and age.

None of the subjects in the case or control groups had familial relationship to each other, as determined via detailed pedigree analysis at time of examination. Except for <10% of the LAZ and control subjects, who were recruited while on-site for other examination, participants responded to a mailed invitation letter. Except for 7 LAZ cases (5 females, mean age=71.2 years, 60-76 years; 2 males, 76 and 79 years) who had prior laser iridotomy (6 bilateral) for incipient, chronic, or acute narrow angle-closure, subjects were excluded for this analysis if there was history of significant

trauma, intraocular inflammation, or intraocular surgery in either eye. Four LAZ subjects were taking topical medication for definitive glaucoma that was based on characteristic optic nerve cupping and visual field loss, and each of these had a history of intraocular pressure >22 mm Hg in the presence of open-angles at time of exam. However, two of these subjects also belonged to the group having prior laser iridotomy for concern of angle narrowing at some point in time. One LAZ subject had ocular hypertension with open angles and was taking a topical pressure-lowering medication.

Participants had ocular/medical history, pupil, motility, stereopsis and color vision testing, confrontation fields, keratometry, pre-dilation refraction, slit lamp exam, Goldmann tonometry, gonioscopy, dilated fundus evaluation, stereo fundus photography, corneal pachymetry, A-scan ultrasonography, optic nerve confocal scanning laser tomography, and Humphrey Field Analyzer II-Series threshold visual field testing. In attempt to document the presence/absence of LAZ in a standardized way, post-dilation retro-illumination photos (16x) were taken with focus on the anterior capsule using a digital photo slit lamp (Haag-Streit BX900). So the entire intra-pupillary lens could be viewed without obscuration, and so that lighting variation might enhance capture of subtle LAZ, three photos were acquired, i.e., two with a vertical light beam positioned just inside the lateral pupil borders and a third with a smaller beam inside the right border (photographer's view) (Fig. 3). The third beam was square or slightly rectangular with horizontal orientation. Adobe® Photoshop® Elements, Version 7.0 was used to merge the three photos, without other enhancement, into a single, column-oriented image file.

Since during the period of photograph collection we learned that LAZ could often not be adequately documented via the standardized retro-illumination method, we did not rely on a masked assessment of these photographs to establish the presence/absence of LAZ for purposes of this current investigation. Although we were able to document the presence of LAZ using direct illumination and high magnification, images could not be produced in such manner that they would be consistent in eyes with LAZ and in eyes without LAZ. Thus, as proof of LAZ, we ultimately relied on detection at the slit lamp along with high magnified, non-standardized images to demonstrate at least some LAZ lines in a given patient.

Regarding PPMIS, we found that subtle strands could go undetected unless there was very close scrutiny using high magnification at the computer screen. Therefore, in order to improve sensitivity of detection, we elected to have all photos assessed for the presence/absence of PPMIS by three different reviewers along with consensus discussion to establish definite PPMIS. Since LAZ presence could not be “hidden” during detection of PPMIS, we felt that this consensus approach also helped reduce the chance for bias in either direction. We considered PPMIS present when there was evidence of any intact PPMIS(s) bisecting the dilated pupil zone, with at least one strand having iris-to-iris or iris-to-lens attachment points.

Analyses were carried out using the SAS[®] Statistical Program, Version 9.2 for Microsoft Windows[®] (Cary, NC). The chi-square test, the Student's *t* test, or the Wilcoxon rank-sum test was used for simple group comparisons, multiple logistic regression was used to help check for confounding. Institutional Review Board approval was obtained for this investigation.

Results

At the time of data collection, our database contained 203 LAZ subjects, and there were 74 (36%) who responded to invitation and met the inclusion criteria for this analysis. Gender distribution of the inclusions was 64 females/10 males (86%/14%), which was similar ($P=0.95$) to the group not included (112 females/17 males, 87%/13%). The median age (range) of those included was slightly younger than those not included, i.e., 70 years (50-91 years) vs. 76 years (37-101 years) ($P<0.0001$).

The final analysis included 148 people (Table 1), comprised of 74 LAZ subjects (median age=70 years, range=50-91 years; 64 females) and 74 controls (68 years, 50-83 years; 64 females). All of the case subjects had bilateral LAZ except for 3 of them, and 29 (39.2%) had PPMIS (12 bilateral, 17 unilateral). Among controls, 15 (20.3%) had PPMIS (5 bilateral, 10 unilateral). Among the LAZ subjects, 27 of 64 (42.1%) females and 2 of 10 (20%) males had PPMIS in at least one eye, and among controls, 13 of 64 (20.3%) females and 2 of 10 (20%) males had PPMIS in at least one eye. Among LAZ subjects, the median age was 67 years in those with PPMIS and 71 years in those without PPMIS. Among controls, the median age was 64 years in those with PPMIS and 70 years in those without PPMIS. Controlling for age and gender, logistic regression analysis showed that LAZ subjects were 3.1 times more likely than controls ($OR=3.1$; 95% CI =1.4 to 6.7; $P=0.004$) to exhibit PPMIS in at least one eye.

Although the LAZ subjects were more hyperopic on average than the controls ($P<0.0001$), the refractive errors were similar between subjects who did and did not have PPMIS in both the case and control groups ($P>0.1$). Among the 29 LAZ subjects

with PPMIS in either eye, median spherical-equivalent refractive error was +1.75D in the right eyes and +1.50D in the left eyes. Among the 45 LAZ subjects without PPMIS in either eye it was +2.00D in the right eyes and +1.75D in the left eyes. Among the 15 controls with PPMIS in either eye, median refractive error was +0.13D in the right eyes and 0.00D in the left eyes. Among the 59 controls without PPMIS in either eye it was +0.50D in the right eyes and +0.38D in the left eyes. While controlling for the average refractive error of both eyes of each subject, as well as gender and age, the LAZ subjects were 3.7 times more likely than controls (OR=3.7; 95% CI=1.6 to 8.8; P=0.003) to exhibit PPMIS in at least one eye.

Dilated pupil size was clinically similar between the case and control groups. For the LAZ subjects, mean horizontal diameter of the pupil as a proportion of the overall iris diameter (calculated by a masked observer using the Haag-Streit BX900 digital photo slit lamp instrument software) was 63% among right eyes and 63% among left eyes. For controls it was 65% among right eyes and 65% among left eyes.

Discussion

The anterior portion of the tunica vasculosa lentis forms part of the vascular net that completely surrounds the lens during fetal development. It occurs along with the beginning of the capsule formation, it is closely associated with the development of the iris stroma, and it gives rise to the “pupillary membrane” that atrophies and usually disappears completely before birth or soon afterwards. Not infrequently, a small portion of the pupillary membrane sporadically persists in the otherwise normal eyes of adults.⁽¹⁶⁾ Sometimes persistent pupillary membranes can be pronounced, and they can

also be accompanied by other anterior segment abnormalities including goniodysgenesis and aniridia.⁽¹⁷⁻²⁰⁾ Familial presence of pupillary membranes, without other anterior segment abnormality, has been reported.⁽¹⁹⁾ Most likely, there are many different etiologic processes that can influence their formation.⁽²¹⁾

Our data indicate that at least subtle remnants of pupillary membranes might sometimes be part of the constellation of clinical characteristics associated with the LAZ phenotype that we are encountering. This may suggest that although this LAZ variety isn't detected early, it may still be part of an underlying congenital syndrome whereby eventual LAZ clinical manifestation may be influenced by certain "aging requirements" and other exposures. Certainly, this study does not prove that LAZ and PPMIS have a related etiology, but observation of an association can be informative toward future work nonetheless.

Even prior to this current study, we have found it curious that we have rarely observed LAZ in people younger than 50 years of age in our clinical population,⁽⁹⁾ and this has led to speculation as to whether the LAZ we have detected are actually present at younger age but not visible due to lack of pigment, etc., or whether there is actual growth (lengthening and/or hypertrophy) of zonular fibers over time. Since we have rarely seen LAZ in younger people, despite concerted search for them,⁽⁹⁾ and since LAZ are detectable even when not pigmented, we believe that latter may be the case.

Slight shifting of the anterior zonular insertion zone occurs with age,⁽²²⁻²⁴⁾ but not enough to explain the small zonule-free zone found in many LAZ patients. Although age-related growth of zonular fibers may be unfamiliar, evidence supports there being a more dynamic environment than realized. For example, zonular fibers can show

branching patterns at their lens insertion that are different in younger eyes compared to older eyes.⁽²⁵⁾ Furthermore, the thickness of the capsule, the structure with which zonular fibers merge,⁽²⁵⁻²⁷⁾ changes with age, and the amount of change varies with location on the lens.⁽²⁸⁾ Perhaps genetic mutation, with effects that are also susceptible to environmental influences, could play a role in certain clinical manifestations associated with the age-related LAZ phenotype, e.g., unusual contraction of anomalous zonules that contribute to forward rotation of the ciliary body/processes and narrowing of the iridocorneal angle.

Since understanding the nature of the LAZ phenotype we describe could be important toward elucidating mechanisms related to a unique form(s) of secondary glaucoma, it is useful to summarize evolving hypotheses. One version could be as follows: Perhaps not everyone has the potential to develop LAZ, but those who do may require underlying genetic predisposition, which may also influence the development of axial hyperopia. As predisposed subjects age, there is eventual growth of zonular fibers that can become visible along the mid-peripheral anterior capsular surface. In addition to age, other factors such as gender and environmental influences may hasten the development of LAZ or affect the likelihood of clinical LAZ altogether.

Strength of this analysis includes the fact that participants were not recruited with PPMIS status in mind, because this could bias results if there were any differential recruitment efforts of subjects with PPMIS. Although a potential weakness includes the fact that photos were not taken specifically to capture the presence of PPMIS strands, study strength lies in the fact that all subjects had three separate images of each eye taken in the same manner for both the LAZ and control groups. Also, if subtle PPMIS

were not detectable due to depth of focus, etc., this would be expected to be similar between the LAZ and control groups.

Although only African-Americans were included in this study due to institutional demographics, it is not our intent to imply that a LAZ-PPMIS association might be limited to African-Americans because we have observed LAZ in other race/ethnicity groups as well.⁽⁹⁾ Nonetheless, our results cannot be generalized to other groups without further investigation.

Conclusions

The LAZ trait, which is being studied as a potential risk factor for glaucoma, was associated with presence of PPMIS in our study population.

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Figure Legends

- Figure 1. Termination of normal anterior zonules along a well-demarcated zone (arrows, top photo) vs. LAZ (bottom).
- Figure 2. Pigmented LAZ (top photo, arrows). LAZ subject with persistent pupillary membrane iris strands (arrows).
- Figure 3. Retro-illumination slit lamp images of the pupil and crystalline lens, with three different light beam positions, were reviewed for each study eye. Images like these had been used in earlier study to help document the presence or absence of LAZ. The lighting variation allowed for full inspection of the entire pupillary zone without obscuration, while also providing brightness variation that sometimes enhanced LAZ visibility.

TABLE 1
SUBJECT CHARACTERISTICS (N=148)

		[†] LAZ Subjects	Controls
N		74	74
Females/Males		64/10	64/10
[‡] Median Age (Range)		70 (50-91)	68 (50-83)
LAZ Present (%)	Either Eye	74 (100%)	-
	Right Eye	73 (98.7%)	-
	Left Eye	72 (97.3%)	-
	Both Eyes	71 (96.0%)	-
PPMIS Present (%)	Either Eye	29 (39.2%)	15 (20.3%)
	Right Eye	23 (31.1%)	9 (12.2%)
	Left Eye	18 (24.3%)	11 (14.9%)
	Both Eyes	12 (16.2%)	5 (6.8%)

[†]Abbreviations: LAZ, long anterior zonules; N, number; PPMIS, persistent pupillary membrane iris strands.

[‡]Age in years.