Original Article

Inter-ethnic variation of ocular traits——design and methodology of comparison study among American Caucasians, American Chinese and mainland Chinese

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Abstract

Purpose: To summarize the design and methodology of a multi-center study. With the existed ethnic differences of glaucoma, this survey will explore the differences with regard to anterior and posterior ocular segment parameters between Caucasians and Chinese.

Methods: In this study, four cohorts including American Caucasians and American Chinese from San Francisco, southern mainland Chinese from Guangzhou, and northern mainland Chinese from Beijing were prospectively enrolled for a series of eye examinations and tests from May 2008 to December 2010. A total of 120 subjects including 15 of each gender in each age decade from 40s to 70s were recruited for each group. Data of the following tests were collected: a questionnaire eliciting systemic and ocular disease history, blood pressure, presenting and best corrected visual acuity, auto-refraction, Goldmann applanation tonometry, gonioscopy, A-scan, anterior segment optical coherence tomography (ASOCT), ultrasound biomicroscopy (UBM), visual field (VF), Heidel berg retinal tomography (HRT), OCT for optic nerve, and digital fundus photography.

Conclusion: this study will provide insights to the etiologies of glaucoma especially PACG through inter-ethnic comparisons of relevant ocular anatomic and functional parameters.

The ethnic variations in ocular anatomy and in the prevalence and severity of eye diseases are widely recognized.Glaucoma, as a major cause of ocular morbidity and vision loss worldwide, has been reported to affect certain ethnic groups disproportionately with various subtypes[1,2]. Extensive researches have investigated the epidemiological characteristics of glaucoma among different racial groups.East Asians have been consistently found to have much higher prevalence of primary angle closure glaucoma (PACG) while people with African ancestry have a four to five times' higher prevalence of open angle glaucoma (POAG) than Whites[2,3]. The disparity of glaucoma across racial groups sparks widespread interests on underlying mechanism investigation. For PACG, anterior ocular segment biometry has been focuses of etiology exploration.The majority of studies suggested that small and crowded anterior segment represented as shallower anterior chamber depth (ACD) is predisposing factor for the increasing risk in East Asians[4]. However, the failure to detect interethnic difference of ACD in some studies indicated there might be factors other than ACD accounting for angle closure development[5].Iris is an important component of drainage angle construction. The iris insertion location on ciliary body assessed by gonioscopy was highly associated with narrow angle prevalence[6]. Asian Americans were found to have more anterioly located iris insertion than white and black subjects in a clinic-based study[7]. With the aid of ultrasound biomicroscopy (UBM), many angle related factors that are invisible by gonioscopy can be visualized and analyzed quantitatively, including ciliary body profile, spatial relationship of iris root insertion and angle apex/scleral spur and iris lens contact. Plateau iris configuration is one of the causes of narrow angle revealed by UBM[8]. The

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interethnic variation on ciliary body features and plateau iris has yet been studied. With the development of ocular imaging technique, anterior segment optical coherence tomography (ASOCT) brings a new era to anterior ocular structure exploration. Although not able to demonstrate ciliary body, ASOCT outperforms UBM in image resolution and non-contact exam style[9]. Combined with robust measurement software[10], numerous studies have identified a series of parameters that may contribute to narrow angle development by using this modality. It has been reported that narrow angle patients have thicker iris than people with open angles confirmed the important role that iris plays in angle closure[11].Meanwhile, this notion is further supported by the finding of thicker iris in Chinese than in Caucasians[12].

Glaucoma is a progressive optic neuropathy. The damage to optic nerve is the common ultimate pathological pathway of various subtypes of glaucoma[13].Evaluation of optic nerve appearance and function is critical for monitoring disease progression and establishing appropriate treatment plan. The size and cupping of optic nerve is another characteristic that varies among ethnic groups[14]. African Americans are reported to inherently have larger optic nerves and cups[14,15]. Considering the higher POAG prevalence in blacks compared with other ethnicities[16], it was hypothesized that individuals with larger optic disc will be more susceptible to the effect of IOP and therefore are at greater risk for developing glaucoma. Conflict results have also been indicated by the ocular hypertension study (OHTS). By using Heidelberg Retinal Tomography (HRT), the study found difference between Africans and other racial groups on optic disc parameters were nullified after controlling for disc area[17]. Similarly using HRT, a clinic-based study found parameters including disc area, cup volume, cup depth and vertical cup-disc ratio were largest in African Americans, intermediate in Asians and Hispanics and smallest in Whites[18].The discrepancy across various studies may subject to different design and methodology. Compared with the optic disc architecture analysis by HRT, information from retinal nerve fiber layer (RNFL) can manifest apoptosis of ganglion cells with enhanced sensitivity[19]. Peripapillary and macular RNFL measurement by OCT has become a robust method of recognizing axon loss in advance of visual field abnormality[20]. Ethnic variation also exists in RNFL thickness.A study performed among 6–12 children in Australia found East Asians tended to have thicker RNFL than Caucasians[21]. By using scanning laser polarimetry, Whites have been reported to have thicker RNFL than Afro-Caribbeans[22].

Despite the extensive studies on inter-ethnic comparison of glaucoma-related indices in both the anterior and posterior ocular segments, there has been limited data on comparisons of these parameters between American Caucasians and mainland Chinese with identical exam protocol[12]. To further elucidate the possible environmental impact on ocular traits among these two ethnic groups, we also included an American Chinese group who lives in the same geographic area as the American Caucasians.To adjust for the possible confounders for the target ocular parameters, a series of various eye exams and tests were also conducted for each participant.Considering the diversity of mainland Chinese, we enrolled native Chinese from both north and south China to detect potential subtle differences among various Chinese groups.

Subjects enrollment

From May 2008 to December 2010, subject enrollment for four cohorts was performed at three sites, including San Francisco in the United States for American Caucasians and American Chinese, Guangzhou in China for southern mainland Chinese, and Beijing for northern mainland Chinese.San Francisco (SF), located on the west coast of America, has one of the highest proportions of residents with Chinese ancestry amongst American cities. This makes it an ideal location for a representative sample of Chinese immigrants in North America. As economic and cultural centers of south and north China, respectively, Guangzhou (GZ) and Beijing (BJ) are suitable cities for samples representing southern and northern mainland Chinese. Each cohort was designed to comprise 120 people, including 15 of each gender in each age decade from the 40 s to the 70 s and above. Subjects in SF were consecutively recruited in comprehensive ophthalmology clinics of the U-

niversity of California, San Francisco (UCSF). Subjects in Beijing were enrolled in the general ophthalmic clinic of Peking University Eye Center.Subjects in Guangzhou were drawn from an ongoing population-based study organized by the preventive division of Zhongshan Ophthalmic Center (ZOC). Age, self-report of Caucasian or Chinese ancestry (both parents)and willingness to participate were inclusion criteria. Exclusion criteria included:

1.Bilateral pseudophakia or aphakia, any previous intraocular surgery, or laser treatment likely to alter the natural anterior segment anatomy.

2.Corneal or conjunctival abnormalities precluding an adequate view of anterior chamber on ASOCT images.

3.Patients who were on any glaucoma medications.

4.Active ocular infection in which contact exams might be contraindicated.

5.Patients with extreme refractive error defined as spherical equivalent(SE)less than-8 or greater than 4.

Institutional Review Board/Ethics Committee ap proval was obtained from UCSF, ZOC in Guangzhou, and Peking University Eye Center in Beijing.This study adhered to the Tenets of the Declaration of Helsinki and the Health Insurance Portability and Accountability Act (HIPAA). Informed consent was obtained for all individuals who participated in the study.

Examination methods

Questionnaire

A brief questionnaire was administrated to each participant. Information on age, gender, date of birth, place of birth, nationality of both parents, duration of residency in America, and history of systemic and ophthalmic diseases and related treatments were recorded.

Systemic examination

Participants of posterior segment exam underwent tests for systolic and diastolic blood pressure, heart rate, height and weight.

Ocular examinations and parameters measurement

1.Presenting vision acuity (VA), non-cycloplegic auto-refraction (Automatic Refractor/Keratometer, Model 599, Humphrey Zeiss, Dublin, CA) (spherical and cylindrical refraction)and corneal radius (CR). Spherical equivalent(SE)was calculated (spherical+1/2 cylindrical)to represent the refractive status of the eye. The average of the CR on horizontal and vertical meridians was calculated for data analysis. This test was performed for both eyes.

2.Intraocular pressure(IOP) was measured by Goldmann applanation tonometry.The median of three consecutive measurements was recorded.This test was performed for both eyes.

3.Gonioscopy was performed and the angle was graded according to the Shaffer system. Angle width was classified as grade 0, 1, 2, 3 or 4 with 0 denoting a closed angle and 4 for a wide open (> 45 degrees)angle. This test was performed for the study eye.

4.ASOCT(Visante OCT, Zeiss Meditec, Dublin, CA)was used to acquire five horizontal images of the anterior chamber, including in darkness (<1 Lux ambient illumination), in light (350-400 Lux ambi ent illumination), and 1 second, 15 seconds and one minute after the lights were turned off. The ASOCT images were analyzed by custom software.Related indices include angle opening distance (AOD), angle recess area (ARA), trabecular meshwork iris space area (TISA), iris thickness (IT), iris area (IArea), iris curvature(ICurv), pupil diameter(PD), anterior chamber width (ACW), and lens vault (LV). This test was performed for the study eye.

5.UBM (Model P45, Paradigm Medical, Inc, Salt Lake City, UT, USA) images were collected in a dark room with the patients in a supine position. An eye cup was put in the conjunctival sac to hold methylcellulose for UBM probe immersion.Images of the superior, nasal, inferior and temporal quadrants of the study eye were acquired. Standardized UBM images were used as references to semi-quantitatively grade the iris root insertion, ciliary process profile and rotation, iris convexity, iris thickness and presence of appositional closure. This test was performed for the study eye.

6.Ultrasound biometry. By using A-mode ultrasound(E-Z Scan A/B 5500+, Sonomed, Inc., Lake Success, NY), anterior chamber depth (ACD), axi-

al length (AL), lens thickness (LT) and vitreous length (VL) were measured with a probe slightly touching the center of the cornea. Central corneal thickness (CCT) was also measured by ultrasound pachymetry. This test was performed for the study eye.

7. Visual field (VF) testing. The Humphrey Field Analyzer (HFA2, Carl Zeiss Meditec, Dublin, CA, USA) was used for perimetry. The 24-2 SITA standard (Swedish Interactive Threshold Algorithm) test was used. A reliable result was defined as having a false positive rate <33%, false negative rate <50%, and fixation loss rate <20%. If the first perimetry was unreliable or abnormal from the glaucoma hemifield test (GHT), a second test was conducted. This test is performed for both eyes.

8. HRT (Heidelberg retinal tomography) images were taken before any contact exams. Individual refractive error data were entered according to the program. Optic nerve head (ONH) mode was used for image acquisition. Disk area, cup disc area ratio, cup and rim area/volume, and mean and maximum cup depth were calculated by the built-in algorithm after the disc margin was defined manually. This test was performed for both eyes.

9. OCT (optical coherence tomography) of the posterior segment. Macular thickness and peripapillary RNFL were scanned by their corresponding modes with Fourier domain OCT (Optovue, Inc., Fremont, CA). The average RNFL thickness in four quadrants and average macular thickness of the inner and outer sectors were selected as main outcome for inter-ethnic comparison. This test was performed for both eyes.

10. Digital fundus photography. A 50 degree fundus photographs centering the optic nerve head was taken for the study eye after dilation. Customized software will be applied for quantitative retinal vessel caliber measurement.

Data quality control

Inter-and intra-observer repeatability were conducted for BP, IOP, gonioscopy, A-scan, and VF tests. For imaging exams such as ASOCT, UBM, HRT, OCT and fundus photography, detailed protocols for image acquisition, acceptable image quality, and image analysis were set prior to the study enrollment. Inter-observor agreement for image analysis was also tested for all of the software image analyses involved.

Study objectives

The major purpose of this study is to describe and compare the distribution of clinical and biometric parameters between "normal" Caucasians and Chinese. Specifically, we'll investigate:

1. Distribution of and inter-ethnic differences in anterior ocular anatomy, mainly involving drainage angle construction, static iris profile and dynamic iris behavior, lens position, ciliary body configuration and integral anterior chamber dimensions surrogated by ACD and ACW.

2. Distribution and inter-ethnic differences related to the optic nerve, mainly involving ONH architectures, RNFL and macular thickness and retinal vessel caliber.

3. Related ocular and systemic risk factors or predictors of interested outcomes.

4. To assess the possible environmental impact on ocular traits through comparing Chinese residing in different regions.

Summary

With a prospective multi-center design, this study will enhance the understanding of ethnic variation on a variety of ocular anatomic and functional parameters. Findings from this study may provide considerable insights to the etiologies of glaucoma, particularly PACG given the ethnic predisposition of this vision-threatening disease.

Conflict of Interest

The authors have no financial or other conflicts of interest concerning this study.

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