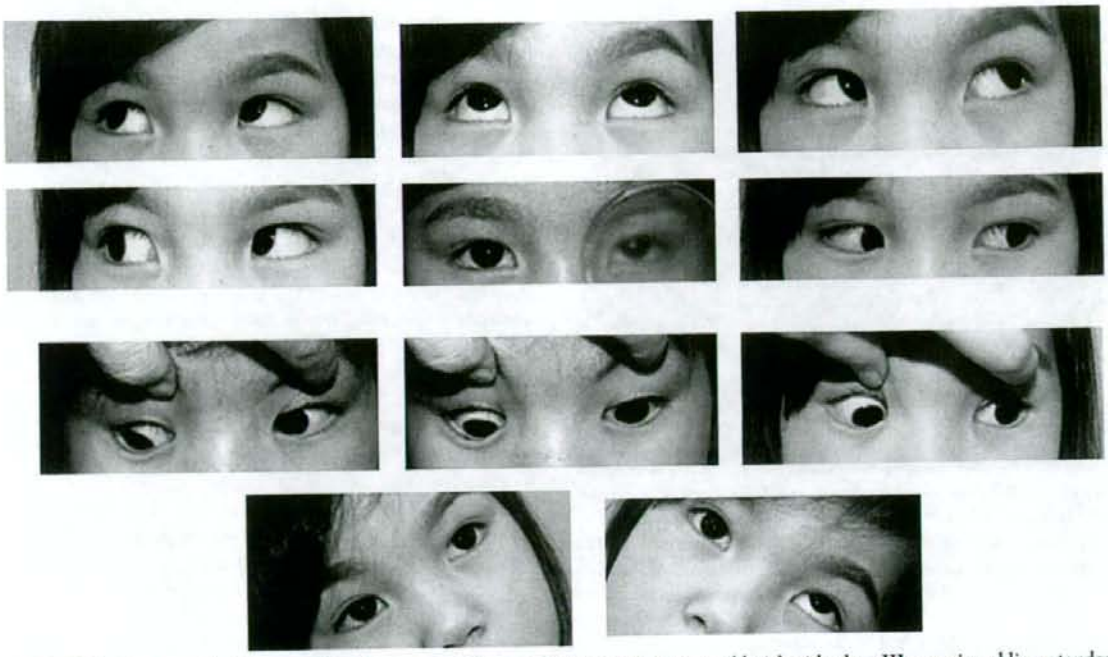

FIGURE 9. Photographs demonstrating the preoperative eye positions of a 4-year-old girl with class III superior oblique tendon anomaly (Case 5). Underaction of infraduction of the left eye (−3) and overaction of supraduction in the adduction (+2) position can be seen. The patient did not have an abnormal head tilt before surgery but showed a marked positive Bielschowsky head tilt test.

TABLE 3. Comparison of Clinical Findings of Patients with Different Types of Superior Tendon Anomaly

	No.	Vertical Deviation (PD)	Stereopsis (Seconds of Arc)	No. of Surgeries
Class I	15	20.4	418 [c]	1.27 [a]
Class II	3	19.7	1080 [b]	1.33
Class III	5	16.2 n.s.	1032 [a]	1.80
Class IV	3	31.7	5000	2.33
Total/average	26	22.0	1882	1.68

n.s. = not significant; PD = prism diopters.
[a] $P < .05$.
[b] $P < .005$.
[c] $P < .0001$.

recession with or without nasal transposition, or a combination thereof. The surgical procedures for treating superior oblique palsy with an absent tendon have not been well established, and one of the procedures[12] or combinations of the above procedures are recommended.[6,5] In our series, eight procedures were performed on five patients (Table 3). The incidence of reoperations was significantly higher in cases with class IV tendon anomaly compared with cases with class I and II anomalies. Three muscles were operated on in each patient. Although the number of our cases is limited, repositioning and strengthening of the superior oblique tendon seem to be a reasonable approach, but may be associated with postoperative limitation of upward gaze, as seen in Cases 2, 4, and 5. This iatrogenic Brown syndrome may be a result of the inferior oblique myectomy rather than the excessive tightness of the superior oblique tendon. Simultaneous superior rectus muscle recession should be reserved for cases with a large hypertropia. Alternatively, a contralateral inferior rectus muscle recession may be considered to treat a large hypertropia.

A class III tendon anomaly is not frequently diagnosed in the management of superior oblique palsy. However, when identified, a strengthening of the superior oblique tendon in the Tenon capsule can improve the eye alignment and good binocularity may be achieved.

TABLE 4. Clinical Findings of Patients with Absent Superior Oblique Tendon (Class IV Anomaly)

Case No.	Gender	Affected Side	Head Tilt	Age at Presentation (yrs)		Visual Acuity	Deviation in Primary Position (PD)	SPD in ADD	IFD in ADD	MRI Findings	TST Results (before Surgery)
1	F	L	R	2	R	1.2	45 LHT, 25 ET	0	0	Attenuated LSO	Fly (−)
					L	1.2		+2	−1		
2	M	L	R	6	R	1.0	20 LHT	0	0	Absence of LSO	Fly (−)
					L	1.0		+1	−1		
3	M	R	L	0	R	1.0	30 RHT, 25 XT	+3	−3	Absence of RSO	Fly (−)
					L	1.0		0	0		

ADD = adduction; ET = esotropia; F = female; HT = hypertropia; IFD = infraduction; L = left; LH = left hyperphoria; M = male; MRI = magnetic resonance imaging; PD = prism diopters; R = right; SO = superior oblique muscle; SPD = supraduction; TST = Titmus stereo test; XT = exotropia; yrs = years.

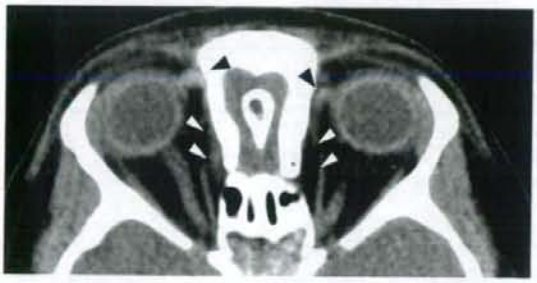

FIGURE 10. Horizontal computed tomography image from a 4-year-old girl with class III superior oblique tendon anomaly (Case 5). Black triangles show the locations of the trochlea. The left trochlea is located posterior to the right trochlea. White triangles indicate the muscle bellies. The right superior oblique muscle cannot be seen in the image.

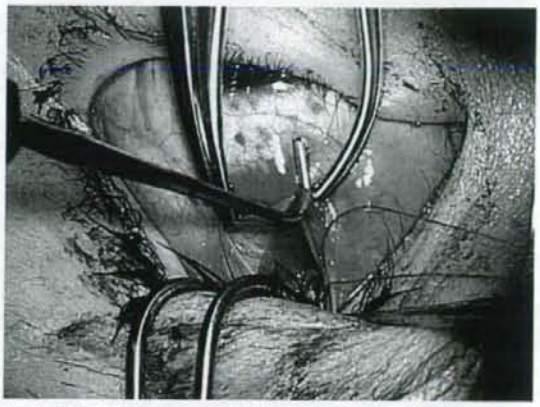

FIGURE 11. Intraoperative photograph of a 4-year-old girl with class III superior oblique tendon anomaly (Case 5). The superior rectus muscle was detached from the sclera and was grasped by two pairs of forceps. The superior oblique tendon was identified from the Tenon capsule and was separated by a small hook.

THE AUTHORS INDICATE NO FINANCIAL SUPPORT OR FINANCIAL CONFLICT OF INTEREST. INVOLVED IN DESIGN AND conduct of study (M.S.); data collection (E.A.I., Y.M.); collection and analysis (Y.T.); and preparation and review of manuscript (A.H., M.S.). The Institutional Review Board (IRB) of Nagoya University School of Medicine and the IRB of Hamamatsu University School of Medicine waived the need for approval of this retrospective study. Comprehensive written agreements for reporting the clinical data including facial photos, surgical results, and computed tomography and magnetic resonance imaging data were obtained from all the patients in this article.

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REPORTING VISUAL ACUITIES

The AJO encourages authors to report the visual acuity in the manuscript using the same nomenclature that was used in gathering the data provided they were recorded in one of the methods listed here. This table of equivalent visual acuities is provided to the readers as an aid to interpret visual acuity findings in familiar units.

Table of Equivalent Visual Acuity Measurements

Snellen Visual Acuities				
4 Meters	6 Meters	20 Feet	Decimal Fraction	LogMAR
4/40	6/60	20/200	0.10	+1.0
4/32	6/48	20/160	0.125	+0.9
4/25	6/38	20/125	0.16	+0.8
4/20	6/30	20/100	0.20	+0.7
4/16	6/24	20/80	0.25	+0.6
4/12.6	6/20	20/63	0.32	+0.5
4/10	6/15	20/50	0.40	+0.4
4/8	6/12	20/40	0.50	+0.3
4/6.3	6/10	20/32	0.63	+0.2
4/5	6/7.5	20/25	0.80	+0.1
4/4	6/6	20/20	1.00	0.0
4/3.2	6/5	20/16	1.25	−0.1
4/2.5	6/3.75	20/12.5	1.60	−0.2
4/2	6/3	20/10	2.00	−0.3

From Ferris FL III, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol 1982;94:91–96.

Jpn J Ophthalmol 2009;53:7–11
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DOI 10.1007/s10384-008-0619-6

CLINICAL INVESTIGATION

Central Corneal Thickness in Japanese Children

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Abstract

Purpose: To determine the central corneal thickness (CCT) in Japanese children and to investigate the changes in CCT with increasing age.

Methods: Pachymetry was performed on 338 eyes of 169 patients undergoing eye muscle surgery under general anesthesia, and the intraocular pressure (IOP) was measured on 312 eyes of 156 of those same patients. Patients with abnormalities other than refractive errors and strabismus were excluded. Patients were divided into four groups: group 1, ≤1 year of age; group 2, 2–4; group 3, 5–9; and group 4, 10–18 years of age. Analysis of variance (ANOVA) was performed to determine the significance of the changes in CCT.

Results: The average CCT of the right eye was 544.3 ± 36.9 μm. The CCT was thinner in group 1 than in groups 3 and 4 (ANOVA, $P = 0.02$). There was a positive but weak correlation between IOP and CCT (IOP = 6.253 + 0.014 × CCT; $r^2 = 0.047$, $P = 0.007$).

Conclusions: CCT reaches the adult thickness in Japanese children by age 5 years. The average CCT is thinner in Japanese children than in Caucasians but thicker than in African American children. **Jpn J Ophthalmol** 2009;53:7–11 © Japanese Ophthalmological Society 2009

Key Words: central corneal thickness, child, general anesthesia, intraocular pressure, ultrasound pachymeter

Introduction

Measuring central corneal thickness (CCT) has become increasingly important, particularly for the diagnosis and management of glaucoma. The Ocular Hypertension Treatment Study reported that subjects with ocular hypertension had greater CCT,[1] and subjects with smaller CCT had a higher risk of developing glaucoma.[2]

Goldmann applanation tonometer measurement is based on the assumption that CCT is 500 μm, a thickness obtained from measurements of cadaver eyes. Because a permanent thinning or flattening of the cornea induces lower intraocular pressure (IOP) after refractive surgery,[3,4] special attention has been paid to the variability of CCT in the healthy population and in patients with various eye diseases. To obtain an accurate IOP value, measurements with the Goldmann applanation tonometer should be corrected by the CCT value.[5] Thus, measuring CCT has become essential for determining true IOP for glaucoma management.

Children with congenital glaucoma also have significantly thinner CCT than healthy children.[6,7] However, aphakic[8,9] and pseudophakic[10] children with glaucoma have significantly thicker CCT than healthy children. These findings then raise the question of why up to 45% of aphakic children who have thicker than average CCT develop glaucoma.[11] Muir et al.[12] speculated that CCT increases after cataract surgery because of endothelial cell damage, or because increased IOP injures the endothelial cells. Thus, measuring CCT in children who are at high risk for glaucoma, such as children with aphakic or pseudophakic eyes, is important.

Received: January 25, 2008 / Accepted: September 26, 2008
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Jpn J Ophthalmol
Vol 53: 7–11, 2009

Another important factor that influences the CCT is race or ethnicity. The CCT of African American adults is thinner than that of Caucasian adults,[2,13] and lower IOP in African Americans may delay the diagnosis of glaucoma and determination of an appropriate treatment target.[14] CCT in the Japanese population has been found to be thinner than in Chinese and Filipino populations.[15]

These racial differences are also found in the pediatric population. African American children have thinner CCT than do Caucasian[16] or Hispanic children.[17] A literature search on PubMed did not extract any CCT data regarding healthy Japanese children. Knowing the normal range of CCT of Japanese children is important for diagnosing and treating pediatric glaucoma.

Thus, the purpose of this study was to determine the CCT in Japanese children and to investigate the changes in CCT with increasing age. To accomplish this, we measured the CCT of 338 eyes of 169 children ≤18 years of age by ultrasound pachymetry under general anesthesia.

Subjects and Methods

All patients scheduled for strabismus surgery under general anesthesia were recruited from Hamamatsu University School of Medicine and Aichi Children's Health and Medical Center from December 2005 to August 2007. Patients with corneal disease, a history of intraocular surgery, glaucoma, cataract, or eyelid abnormalities were excluded. Patients known to have abnormally thin corneas such as those with Down syndrome[18] or with Marfan syndrome,[19] or abnormally thick corneas such as those with aniridia,[20] were also excluded.

This study was approved by the Institutional Review Board of the Hamamatsu University School of Medicine and Aichi Children's Health and Medical Center. Full explanation of the research, including the measurement procedures for CCT and IOP was given, and written informed consent was obtained from a parent or legal guardian of each of the patients.

For controls, we measured the CCT of eight healthy subjects aged 26 to 52 years under topical anesthesia.

CCT was measured between 9:00 and 16:00 in the operating room with an ultrasound pachymeter (SP-100 Handy, 1640 Hz; Tomey, Nagoya, Japan). Measurements started within 5 min of endotracheal intubation. All patients were sedated by inhalation or intravenously, and a muscle relaxant was given before insertion of the airway tube. Sevoflurane and nitrous oxide were used to maintain surgical anesthesia during the surgery. The patient's eyelid was held open manually, with special care taken not to press on the eye. One drop of topical anesthesia (4% oxybuprocaine) was administered, and the central cornea was defined as the center of the pupil. The pachymeter probe was placed perpendicularly on the center of the cornea, and the average of eight measurements was recorded as the CCT. Next, the IOP was measured with a Tono-Pen XL (Reichert, Depew, NY, USA). All measurements were performed first on the right eye and then on the left eye.

For statistical purposes, only the data from the right eye were used. The patients were divided into four groups: group 1, ≤1 year of age; group 2, 2–4; group 3, 5–9; and group 4, 10–18 years of age. Statistical analysis was performed using StatView version J-5.0 for Windows (SAS Institute, Cary, NC, USA). Analysis of variance (ANOVA) with a Bonferroni post hoc test was used to determine the significance of any differences among the age groups. Paired t tests were used for comparisons between eyes. Linear regression was used to determine the correlation between CCT and IOP. A P value of <0.05 was considered to be statistically significant.

Results

We measured the CCT of 338 eyes of 169 subjects (87 boys, 82 girls) with a mean age of 6.01 ± 3.87 years and an age range of 8 months to 18 years. The patient age distribution and the IOP and CCT measurements are summarized in Table 1.

The average CCT of the right eye was 544.3 ± 36.9 μm (range, 429–648 μm). The CCT distribution is shown in Fig. 1. The CCT was significantly different between age groups (ANOVA $P = 0.0198$); it was significantly thinner in group 1 than in groups 3 or 4 ($P = 0.0071$ and 0.0157, respectively, Bonferroni; Table 1). The average CCT in group 4 was 550.6 μm, which was not significantly different from the mean CCT of the eight healthy adult subjects (525–586 μm).

Table 1. Subjects' characteristics and measurement of CCT and IOP

	n (%)	CCT (μm)	IOP (mmHg)
All patients	169 (100)		
Age distribution (years)		(right eye)	(right eye)
0–1	14 (8)	522 ± 26.7	14.07 ± 2.89
2–4	50 (30)	538 ± 36.6 *	14.14 ± 2.55
5–9	77 (45)	550 ± 36.7 **	14.13 ± 2.13
10–18	28 (17)	550 ± 37.5	12.88 ± 2.45

Values are means ± SD.
CCT, central corneal thickness; IOP, intraocular pressure.
*$P = 0.0071$.
**$P = 0.0157$.

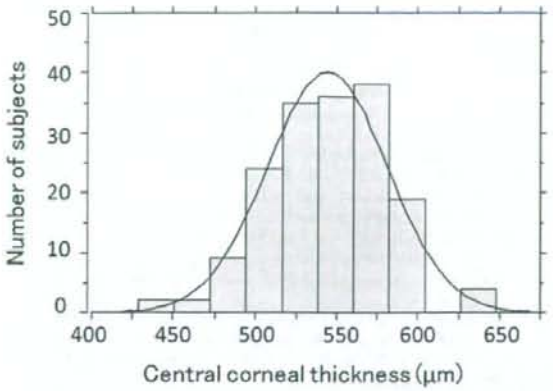

Figure 1. Distribution of central corneal thickness (CCT) in the right eye of children aged 0 to 18 years. CCT is normally distributed. The average CCT was 544.3 ± 36.9 μm.

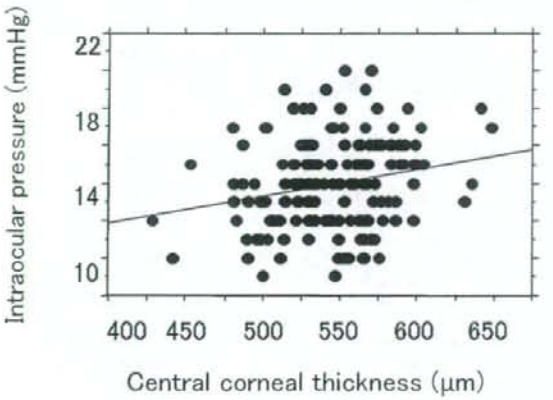

Figure 2. Relationship between CCT and intraocular pressure (IOP). There is a positive but weak correlation between CCT and IOP.

The mean CCT in our adults was comparable to the published average range for the adult Japanese population.[21,22]

The average IOP in the right eye was 13.9 ± 2.4 mmHg (range, 9.0–10.0 mmHg). The IOP did not differ significantly among the different age groups. IOP (y) and CCT (x) were positively correlated, but the correlation coefficient was low ($y = 6.253 + 0.014x$, $r^2 = 0.047$; $P = 0.007$; Fig. 2).

Discussion

Differences in CCT values measured with different instruments have been reported,[23–25] but the values obtained by ultrasound pachymetry and by noncontact optical low-coherence reflectometry are reported to be highly correlated.[26] Bovelle et al.[27] reported that the Topcon specular microscope gives significantly lower values than the ultrasound pachymeter. Suzuki et al.[21] compared CCT values obtained using Orbscan scanning-slit corneal topography/pachymetry, the Topcon SP-2000P, noncontact specular microscopy, and Tomey ultrasonic pachymetry in a Japanese population. The mean CCT was not significantly different between scanning-slit topography (546.9 ± 35.4 μm) and ultrasonic pachymetry (548.1 ± 33.0 μm). However, contact specular microscopy gave a significantly smaller mean (525.3 ± 31.4 μm) than did the other two instruments.[21] Therefore, it is advisable not to compare CCT values obtained using different instruments.

Table 2. Comparison of CCT values of children by race

Race	Hussein[29] (μm)	Dai[17] (μm)	This study (μm)
Caucasians	551	563	
Hispanic	550	568	
Japanese			544
African Americans	532	523	

The SP100 ultrasonic pachymeter is compact and easy to use in the operating room. The measurements are accurate if the instrument is used appropriately. We took special care to place the probe on the center of the cornea because the cornea is thinnest at the center.[28,29]

In adults, CCT is negatively correlated with age in men,[30] or in both sexes.[31] In children, CCT is reported to decrease rapidly during the neonatal period,[32,33] and then to increase slowly and reach the adult level at 3[34] or 5 years of age.[29] Sawa[35] studied the Japanese population and found that the mean CCT of 1-month-old infants (534 ± 36 μm) is thicker than that of 3-month-old infants (508 ± 22 μm), but they found no difference between the 3-month-old infants and the 20- to 29-year-old adults (516 ± 17 μm). Muir et al.[36] suggested that CCT slowly increases in children up to the age of 5 and then decreases at around age 10–14 years. Hussein et al.[29] reported that CCT increases in children until age 9 years and then decreases between ages 10 and 14.[29] In our study, CCT was significantly less in group 1 than in groups 3 or 4, suggesting that adult CCT values are reached by 5 years of age.

Earlier studies have reported racial differences in CCT, not only in adults but also in children. Table 2 summarizes results from other countries for CCTs in pediatric populations from 0 to 18 years of age, measured with ultrasound pachymetry. We understand that it is not ideal to compare our data directly with those of previous reports, but as long as all the measurements were obtained with ultrasound pachymetry, it is reasonable to do so. Compared with the readings obtained from two different institutions,[17,29] the CCT of Japanese children still appears to be thicker than that of African American children and thinner than that of Caucasian or Hispanic children.

Studies focusing on the relationship between CCT and IOP have reported a significant correlation between IOP and CCT in children,[36] as in adults. Suzuki et al.[31] studied Japanese adults and found that IOP measured with the

Goldmann applanation tonometer was positively correlated with CCT. We found a positive correlation between CCT and IOP measured by Tono-Pen in children, but the correlation coefficient was low.

The Tono-Pen is generally used in children whose IOP is neither very high (>21 mmHg) nor very low (<9 mmHg).[37] IOPs obtained with Tono-Pen are significantly correlated with those obtained using the Goldmann tonotmeter.[38,39] IOPs measured with the Goldmann tonometer, the noncontact tonometer, and the Tono-Pen are known to be influenced by CCT, but IOPs measured by Tono-Pen are less affected by CCT than the other tonometers.[40,41]

We are aware that measured IOP differs significantly with the type and state of anesthesia; for example, succinylcholine can increase IOP, whereas halothane can reduce it.[42] In addition, IOP in the human infant depends strongly on the level of relaxation.[42]

In conclusion, the CCT of Japanese children increases up to age 5 years, when it does not differ significantly from that of adults. The CCT of Japanese children is thinner than that of Caucasian children but thicker than that of African American children. Knowing the average CCT value in the Japanese pediatric population will be useful when caring for not only congenital anomalies involving the cornea but also pediatric glaucoma.

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Jpn J Ophthalmol 2009;53:12–17
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DOI 10.1007/s10384-008-0602-2

CLINICAL INVESTIGATION

Age-Related Changes of Phoria Myopia in Patients with Intermittent Exotropia

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Abstract

Purpose: To investigate the age-related changes in a myopic shift under binocular conditions (phoria myopia) in patients with intermittent exotropia (IXT).

Methods: Forty-five patients with IXT were studied: 21 were ≤9 years old (children), 11 were between 10 and 19 years (adolescents), and 13 were between 20 and 43 years (adults). The angle of strabismus was determined by the alternating prism cover test. The spherical refractive error was measured at 1 m using infrared video retinoscopy under monocular and binocular viewing conditions.

Results: The change in the spherical refractive error (ΔR) between binocular and monocular conditions was significantly larger in adults (ΔR = –1.11 ± 1.01 diopters (D), average ± standard deviation) than in children (ΔR = –0.34 ± 0.34 D; $P < 0.05$, analysis of variance). ΔR was significantly correlated with the angle of exotropia only in adults ($r = 0.55$, $P = 0.04$). After strabismus surgery, ΔR decreased in adults ($n = 3$).

Conclusions: Because a significant myopic shift under binocular conditions was detected in IXT patients older than 20 years, phoria myopia can occur after age 20 even if functional disturbances are not observed in children or adolescent IXT patients, a fact that specialists need to bear in mind when treating younger patients. **Jpn J Ophthalmol** 2009;53:12–17 © Japanese Ophthalmological Society 2009

Key Words: aging, intermittent exotropia, myopic shift, phoria myopia, pupil constriction

Introduction

In adults with intermittent exotropia (IXT), a myopic shift and miosis are observed when the visual system switches from monocular to binocular viewing conditions.[1–5] A significant myopic shift under binocular conditions in IXT with a relatively large angle is called "phoria myopia" in Japan. Phoria myopia was first named by K. Yuge in Japanese and by K. Adachi in English.[4,5]

Received: March 5, 2008 / Accepted: July 31, 2008
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The miosis in the near reflex is reported to be larger in normal subjects >20 years old than in those ≤20 years.[6] However, the relationship between age and the myopic shift or pupillary constriction in patients with IXT has not been well investigated.

The relationship between convergence (C) and accommodation (A) is principally linear (AC/A or CA/C ratio) under open-loop conditions, in which either a convergence or an accommodation cue is present. However, it is not linear under closed-loop conditions, in which both cues are present. In patients with IXT, a greater effort to converge is required to fixate a near target binocularly compared with patients with orthophoria. Therefore, a greater myopic shift and miosis can be expected under exophoric (binocular) than under exotropic (monocular) conditions, especially if the angle of strabismus is large and the connection between convergence and accommodation in the central nervous system is rigid.

Ophthalmic Genetics, 29:29–32, 2008

ISSN: 1381-6810 (print) / 1744-5094 (online)
DOI: 10.1080/13816810701663535

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CASE REPORT

Novel *RDH5* Mutation in Family with Mother Having Fundus Albipunctatus and Three Children with Retinitis Pigmentosa

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***Purpose*: To identify mutations in the *RDH5* gene in a family with a mother having fundus albipunctatus (FA) and 3 children with retinitis pigmentosa (RP). *Methods*: Ophthalmological examinations were performed to diagnose FA and RP. Mutational analysis of *RDH5* was performed. *Results/Conclusions*: The mother was diagnosed with FA, and 3 children were diagnosed with RP. The proband's mother, brother, and sister had a novel mutation c.689_690CT>GG in *RDH5*. The proband and mother had a previously reported mutation c.928delCinsGAAG. Consequently, the mother's FA was caused by compound heterozygous mutations. Further studies will be needed to determine the gene responsible for children's RP.**

Keywords fundus albipunctatus; retinitis pigmentosa; night blindness; RDH5 gene; mutation

INTRODUCTION

Fundus albipunctatus (FA) is an autosomal recessive disease and is characterized by the presence of numerous small white dots throughout the retina and congenital stationary night blindness. FA is caused by mutations of the *RDH5* gene in most cases.[1] In Japanese cases of FA, a c.928delCinsGAAG mutation has been detected in many families suggesting a founder effect.[2–6] We describe an unusual family which included a mother with FA and three children with typical retinitis pigmentosa (RP). We examined the *RDH5* genotype of this family and found a novel mutation.

Received 13 July 2007; accepted 3 September 2007.
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MATERIALS AND METHODS

Patients

A 12-year-old young girl (proband, patient P1, Fig. 1) was referred to our hospital with a tentative diagnosis of RP. She had

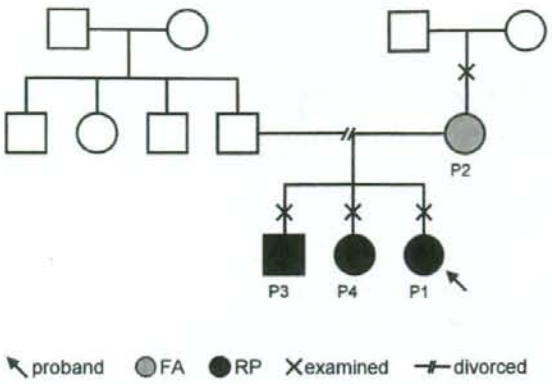

FIG. 1. Pedigree of a family with fundus albipunctatus (FA) and retinitis pigmentosa (RP). All affected patients complained of night blindness.

complained of night blindness since 7 years of age. Her best-corrected visual acuity was 1.0 in both eyes, and her peripheral visual fields were mildly constricted. Funduscopic examination revealed numerous bone-spicule pigments, a typical appearance of eyes with RP (Fig. 2A). The a- and b-waves of single flash ERGs were severely reduced (data not shown).

The proband's mother (P2, 43-year-old) also complained of night blindness. She was being treated by several medications for iron deficiency anemia and hypertension. Her best-corrected visual acuity was 0.9 OD and 1.0 OS, and her visual fields were normal. Funduscopic examination showed numerous yellow-white punctuate deposits around the vascular arcades without a central macular involvement (Fig. 2A). The scotopic, full-field ERGs were markedly reduced but recovered to normal levels after 120 minutes of dark-adaptation (Fig. 2B). The recovery of the ERG amplitudes following prolonged dark-adaptation is pathognomonic of eyes with FA.

The proband's brother (P3, 19-year-old) and sister (P4, 18-year-old) also complained about night blindness. The best-corrected visual acuity was 1.0 in both eyes of both siblings. A mild peripheral visual field constriction was detected in P3 and a ring scotoma in P4. Although funduscopic examination revealed pigment deposits in the mid-peripheral retina in P3, fluorescein angiography showed a broad window defect due to retinal pigment epithelium atrophy around the vascular arcades without central macular involvement. Numerous bone-spicule

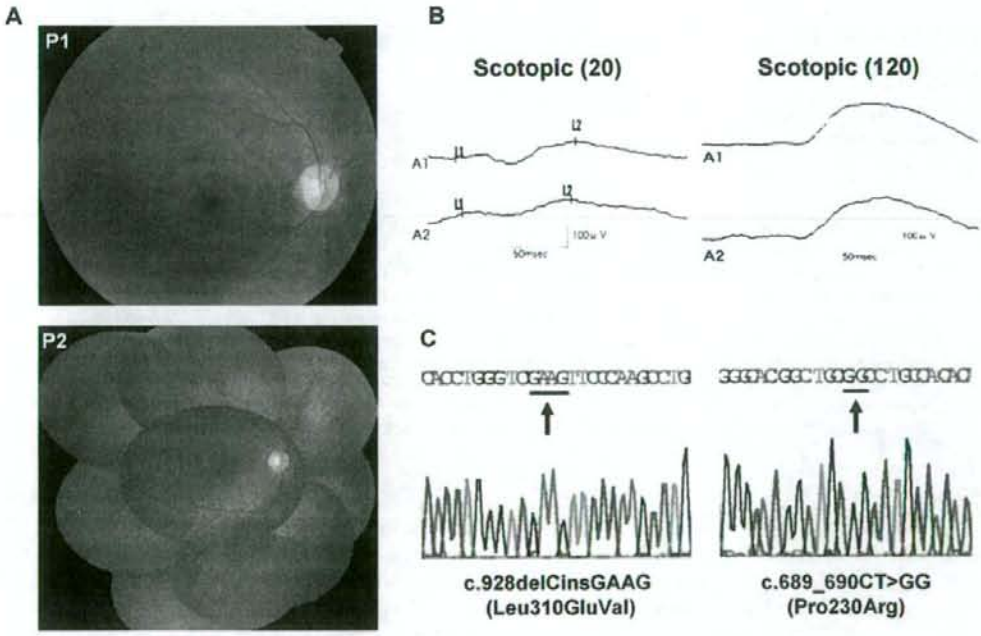

FIG. 2. Results of clinical examination and detected mutations in the family. A. Fundus photographs of P1 showing numerous bone-spicule pigments in the peripheral retina, and P2 showing numerous yellow-white punctuate deposits around the vascular arcades without central macular involvement. B. Scotopic ERGs of P2, showing markedly reduced scotopic response which recovered after 120 minutes of dark-adaptation. C. Mutations found in this family. Left, c.928delCinsGAAG in P1 and P2; right, c.689_690CT>GG in P2, P3 and P4. The other alleles of P1, P3, and P4 are normal (data not shown). Notation of mutation is done according to Nomenclature system by MDI.[12] Bars and arrows indicate the position of the mutations.

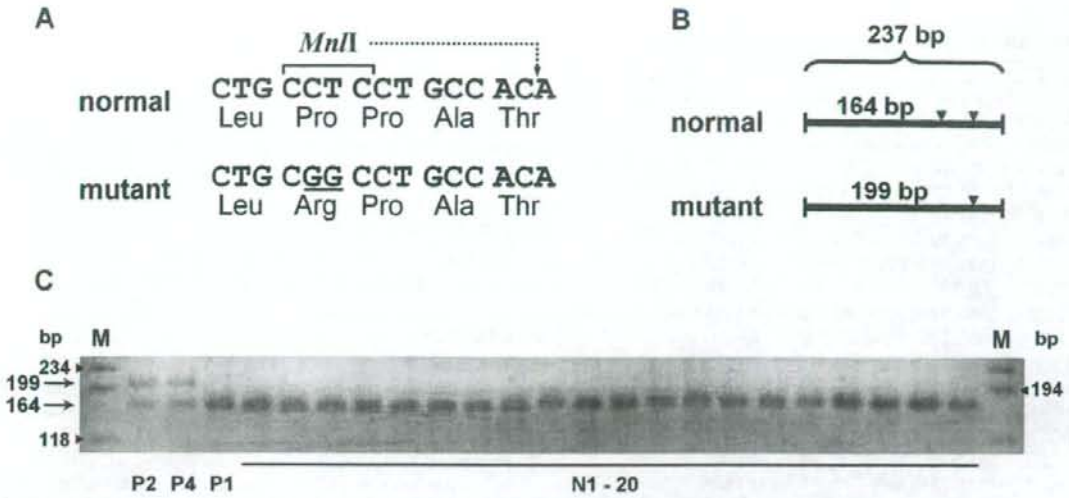

FIG. 3. Restriction endonuclease analysis for a novel mutation, c. 689_690CT>GG. A. Partial sequences of exon 4 of the normal allele and the mutant allele. The recognition site of *MnlI* (CCTC) existing in the relevant position of normal allele is not present in the mutated gene. Dotted arrow indicates the cutting site. B. *MnlI* sites (arrowheads) on the amplified DNA (237 bp) of exon 4 and its surrounding introns. The DNA derived from the mutant allele should not be cut at the mutation site, but the normal allele should be at the corresponding site to produce a 164-bp fragment. Another *MnlI* site (right) exists in both mutant and normal alleles. C. Results of restriction endonuclease analysis using PCR-amplified DNA from three patients (P1, P2, P4) and unaffected controls (N1 through 20). Only DNA from P2 and P4 produced 199-bp fragment of mutation. The 164-bp fragment was detected in P1, P2, P4 and controls. M = DNA size marker; arrowheads indicate the position of marker and arrows indicate the position of the produced DNA fragments.

pigments were observed in the retina of P4. The a- and b-waves of the single flash ERGs were severely reduced in both siblings (data not shown).

Mutation Analyses

This study was approved by the Institutional Review Board for Human Genetic and Genomic Research of Hamamatsu University School of Medicine, and the procedures used conformed to the tenets of the Declaration of Helsinki. Informed consent was obtained from the patients and unrelated normal controls. Genomic DNA was isolated from peripheral blood leukocytes. The regions corresponding to the protein-coding exons, exon 2–5, of the *RDH5* gene were amplified by PCR using primers previously described.[1] The PCR products were sequenced on an Applied Biosystems model 3100 automated sequencer (Perkin-Elmer, Foster City, CA, USA) with primers that were used for the PCR amplification. For the cases which had some sequence abnormality, both alleles were cloned using pBLUESCRIPT II SK(+) vector (Stratagene, La Jolla, CA) to examine their sequences separately.

RESULTS AND DISCUSSION

A novel 2-base missense mutation c.689_690CT>GG (Pro230Arg) in exon 4 (Fig. 2C) was found in P2, P3, and P4, and was not detected in the normal controls using restriction endonuclease *MnlI* digestion of PCR-amplified DNAs (Fig. 3). This confirmed that c.689_690CT>GG is a pathogenic mutation and not a polymorphism. This type of mutation (missense by 2 consecutive base change) is very rare. Until this article, we were able to find 25 kinds of this type of mutation in 15 genes in all of the 1,700 disease-causing genes (see mutation databases *MutationView*[7] and HGMD[8]).

All of this type of mutation are listed in the Table 1 including our case. Of these, the change from CT to GG of the *RDH5* gene in our patient is the first case. The complementary change (AG to CC) was not found. This mutation of *RDH5* is the first one in all known missense mutations in human disease-causing genes. Mutations of 2 base or more are considered to be caused by the failure in the repair of DNA lesion or replication errors, in which various mechanisms should work, such as nucleotide excision repair, mismatch repair or homologous recombination mediated repair.[9]

However, it is not known if a particular mechanism exists for 2 consecutive base pair changes. In this table, transversions are found more frequently than transitions, 32 *vs.* 20 (Table 1). This is interesting because transition mutations are found more than transversions in cases of single base change mutations, suggesting that something related to the generation mechanism of this type of mutation. Further studies are necessary to analyze this type of mutation.

TABLE 1
Summary of reported 2 consecutive base mutations

# Gene	Gene symbol	Mutation	Type*	Amino acid change
1	ARSA	286_287TC>CT	SS	S96L
2	ATM	7875_7876TG>GC	VV	D2625_A2626indelEP
	ATM	8565_8566TG>AA	VS	S2855_V2856indelRI
3	CFTR	1294_1295AC>TA	VV	T388X
	CFTR	2916_2917TC>AT	VS	L973F
4	CNGB3	1573_1574TT>AA	VV	F525N
5	DYSF	200_201TG>AT	VV	V67D
	DYSF	3444_3445TG>AA	VS	Y1148X
6	F9	1092_1093TA>CG	SS	S365G
7	GJB1	64_65CG>TA	SS	R22X
8	IL2RG	536_537TG>AA	VS	L179X
9	KCNE1	152_153TG>AT	VV	L51H
	KCNE1	176_177TG>CT	SV	L59P
10	MLH1	531_532GG>AT	SV	E178X
	MLH1	1852_1853AA>GC	SV	K618A
	MLH1	1852_1853AA>CG	VS	K618R
11	NF1	945_946GC>AA	SV	L316M
	NF1	4861_4862GT>AG	SV	V1621R
	NF1	7424_7425CT>AG	VV	S2475X
12	NPHP4	1334_1335TC>AA	VV	F445X
13	NR5A1	104_105GC>AA	SV	G35E
14	PAH	470_471GA>AC	SV	R157N
	PAH	796_797AC>GA	SV	T266E
15	PAX6	363_364AT>CA	VV	M1Q
	PAX6	862_863CG>GA	VS	S167X
16	RDH5	689_690CT>GG	VV	P230R

*Types of 2 consecutive mutations are shown in S (transition) or V (transversion). Total S and V are 20 and 32, respectively.

Another mutation found in P1 and P2 was c.928delCins GAAG (Leu310GluVal) in exon 5 (Fig. 2C), which has been reported in many cases of FA.[2–6] Consequently, the FA of P2 was most likely caused by compound heterozygous mutations of *RDH5*, viz., c.689_690CT>GG and c.928delCinsGAAG.

Only two reports have been published on families with both FA and RP. Kuroiwa *et al* reported a family which included a FA patient with compound heterozygous *RDH5* mutations (Val177Gly and Arg280His) and a family member with RP without a mutation in the gene.[10] Sato and colleagues described a case of FA associated with sectorial RP in the inferonasal retinal quadrants of both eyes, in which a homozygous RDH5 mutation (Gly107Arg) was found.[11] To the best of our knowledge, our family is the first with a mother with FA and 3 children with typical RP. Further studies will be needed to determine the responsible genetic defects for the RP of the 3 children of this family.

ACKNOWLEDGMENTS

This work was supported in part by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) and a Grant-in-Aid for Scientific Research from the Japan Society for the Promotion of Science (JSPS).

Chunxia Wang is a scholarship student of the Japanese Government (Monbukagakusho:MEXT) (2003–2007).

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顕微鏡下における立体視機能の検討

Evaluation of stereopsis under the microscope

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【要約】 目的：顕微鏡下で奥行き感を測定できる三杆法(M三杆法)装置を試作し，顕微鏡下で立体感が得られにくいケースの要因を検討した．

対象および方法：Titmus Stereo Test(TST)で40秒の立体視を有する33例に対して，M三杆法でのズレ量(片眼視下および両眼視下)を測定した．また，顕微鏡下でのTST，非顕微鏡下のTNO Stereo Test(TNO)，調節幅，融像幅，AC/A比を測定し，M三杆法の結果と比較検討した．

結果：M三杆法でのズレ量は，片眼視下と比較して両眼視下で有意に少なかった．また，TNOの成績が不良のケースでは，M三杆法でのズレ量も大きく，両者は有意な相関を示したが，他の検査結果との比較では有意な関係はみられなかった．M三杆法でのズレ量が非常に大きいケースでは，感覚性および運動性の融像が低値を示していた．

結論：顕微鏡下での奥行き感の精度には，両眼視機能が影響することが示唆された．今回試作したM三杆法は，まだ開発段階ではあるが，顕微鏡下作業の適正判定の一助となる可能性が示された．

【キーワード】 顕微鏡，両眼視機能，三杆法，融像，立体視

緒言

眼科領域では細隙灯顕微鏡や手術用顕微鏡などの光学顕微鏡が汎用されている[1]．また，精密器械の技術者や，生命科学の研究者も双眼顕微鏡を使用する機会が多い．その中には，日常視下では立体視が良好であるにもかかわらず，顕微鏡下では立体視ができずに複視を感じる者や，奥行きの判断が困難な者がいる．

今回我々は，M三杆法装置を試作し，顕微鏡下で立体感を得られにくいケースの要因を検討する目的で，顕微鏡下と非顕微鏡下での両眼視機能につき比較検討を行ったので報告する．

対象および方法

1．対象

眼疾患がなく，正常な視力とTSTのcirclesで40秒の立体視が認められた33例(男性11例，女性22例)で，年齢は22～44(平均29.6±4.9)歳であった．屈折異常が大きいほうの眼の屈折は等価球面値で＋0.75～－8.5(平均－1.2±1.7) D，乱視が1.5D以上あったのは4眼2例(－2.25D，－3.25D)，不同視差が2.0D以上あったのは2例(1.5D，2.5D)であった．眼位は正位または外斜位で，交

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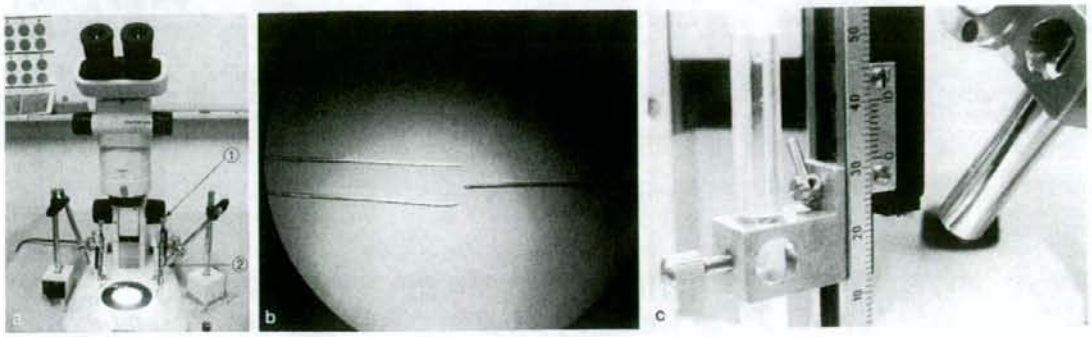

図1　M三杆法について
a：全景写真．①つまみ（被検者自身で回してもらうと三杆部分の一本の棒が上下する），②マイクロメーター．b：三杆部分の実際の見え方．c：マイクロメーター部の拡大．

代プリズム遮閉試験による遠見斜視角は，＋2～－14（平均－3.7±3.3）⊿であった．

2．検査装置

（1）M三杆法

ガリレオ式平行光学系の顕微鏡（OLYMPUS社）の対物レンズの下方に，マニピュレータ（Narishige，BE-806009）に針金（直径0.5mm，長さ50mm）を取り付けたものを設置し，M三杆法装置を作成した（図1a）．顕微鏡を覗くと，視野には左側に2本の棒，右側に1本の棒が見える（図1b）．左側の2本の棒は定位置で固定しており，右側の1本の棒をつまみ操作により下から上へと被検者自身で動かしてもらい，3本の棒が同じ高さになったと自覚した時点でつまみ操作を終了させ，左側の2本の棒とのズレ量を測定する．ズレ量は，マイクロメーターにより0.1mmの精度での評価が可能である（図1c）．顕微鏡の倍率は2倍で行い，5回測定の平均値（絶対値）を算出した．測定に先立って，被検者には検査に慣れてもらう目的で，十分に視度と瞳孔間距離を調整した上で何度か練習してもらい，測定時には，反復せずに下から上への一方向のみに動かしてもらった．

（2）細隙灯顕微鏡（スリットランプ）

用いたスリットランプ（カールツァイスメディテック社製）は，平行光学系の器械であり，5倍の拡大下で測定を行った[2]．

3．方法

顕微鏡下での検査として，M三杆法を両眼視下と片眼視下で測定し，加えてスリットランプ下でTSTのcirclesを施行した．

非顕微鏡下での検査として，TNO，ワック社製のD'ACOMOにより調節幅を，さらに大型弱視鏡による融像幅とAC/A比を測定した．以上の検査はすべて完全矯正下で施行し，それぞれの検査結果の比較検討を行った．

4．統計処理

paired t-test，およびSpearman rank order correlationで統計学的検討を行い，$p \leqq 0.05$を有意とみなした．

結果

最初に，M三杆法における両眼視下と片眼視下でのズレ量の比較を行った（図2）．ズレ量は，両眼視下で0.9±0.99mm，片眼視下で4.42±4.23mmであり，M三杆法におけるズレ量は，片眼視下と比較して両眼視下で有意に少なかった（$p < 0.001$，paired t-test）．

次に，スリットランプ下でのTSTとM三杆法の比較を示す（図3）．M三杆法でのズレ量が小さい場合，スリットランプ下でのTSTも小さな視差まで正答可能な人が多く，またM三杆法でのズレ量が大きい場合，スリットランプ下でのTSTでも大きな視差でしか正答できない人が存在したが両者に有意な関係はみられなかった（$r = -0.205$，$p = 0.249$，Spearman）．

TNOとM三杆法の比較においては（図4），M三杆法でのズレ量が小さいケースではTNOの成績も良好であり，ズレ量が大きいケースではTNOの成績が低値を示し，両者は有意に相関した（$r = -0.390$，$p = 0.0253$，Spearman rank order correlation）．

調節幅とM三杆法の比較では（図5），M三杆法のズレ量が小さいケースでも調節幅にバラつきがあり，有意ではなかったが融像幅が狭いとM三杆法の値は大きくなる傾向があった（$r = -0.313$，$p = 0.0762$，Spearman rank order correlation）．

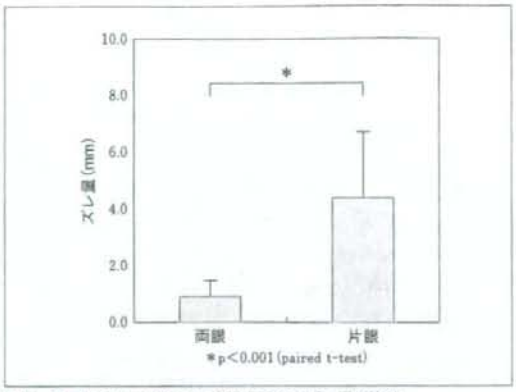

図2　M三杆法の両眼視下と片眼視下でのズレ量の比較
M三杆法におけるズレ量は，片眼視下と比較して両眼視下で有意に少なかった．

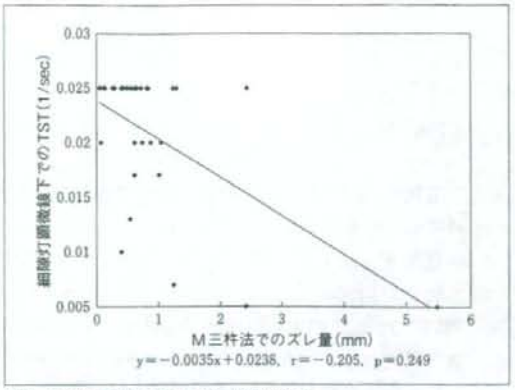

図3　顕微鏡下でのTSTとM三杆法の比較
縦軸の視差の目盛りは，秒の逆数で表しており，目盛りの数値が大きいほど視差は小さくなる．M三杆法とスリットランプ下でのTSTに有意な関係はみられなかった．

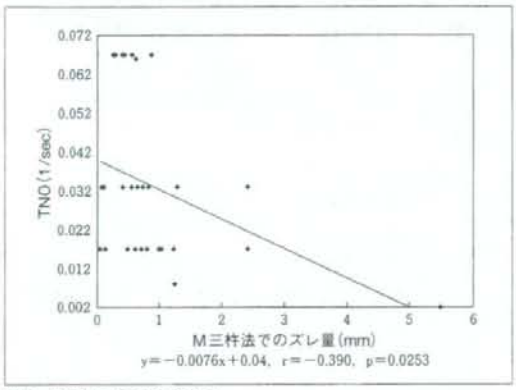

図4　TNOとM三杆法の比較
TNOとM三杆法の結果は有意に相関した．

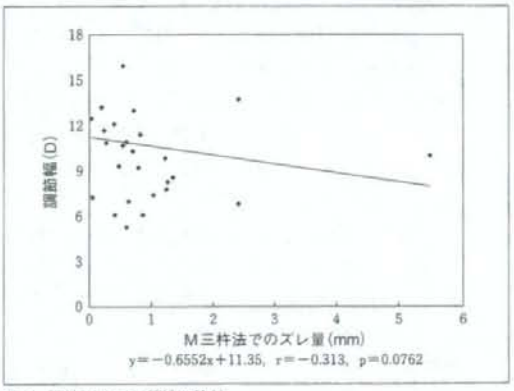

図5　調節幅とM三杆法の比較
調節幅にバラつきはあるが，統計的には有意ではなかった．

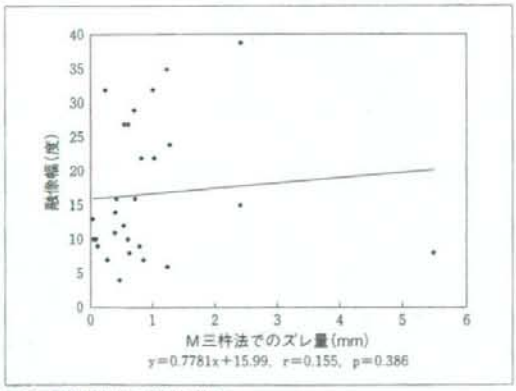

図6　融像幅とM三杆法の比較
広い範囲にバラつきがみられたが，有意な相関は認められなかった．

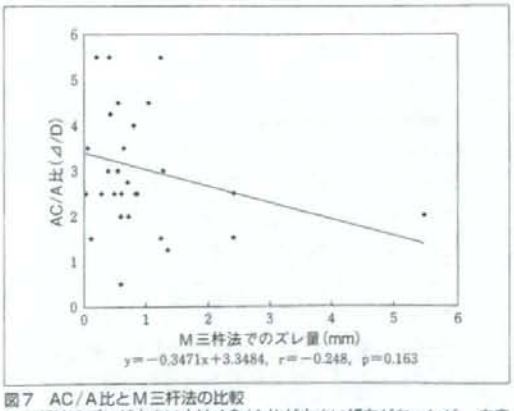

図7　AC/A比とM三杆法の比較
M三杆法のズレが大きい人はAC/A比が小さい傾向があったが，有意な相関は認められなかった．

融像幅とM三杆法の比較(図6)，AC/A比とM三杆法の比較(図7)においては，M三杆法のズレ量が小さい人でも，融像幅やAC/A比に広い範囲でバラつきがみられ，有意な相関は認められなかった($r=0.155$, $p=0.386$, $r=-0.248$, $p=0.163$, Spearman)．

最後に，M三杆法のズレ量が最も大きかった1例の各検査における成績を検討する．各グラフでM三杆法のズレ量が5.6mmの症例であるが，25歳の男性で屈折が−0.88D，眼位は−2⊿であった．スリットランプ下のTST，TNO，融像幅がすべて低値を示していた．被検者にM三杆法の感想を聞くと，両眼視下ではあったが，三杆の中央の棒が上下しているのがわからなかったと述べている．

考按

一般的に，両眼を分離して立体的にものを見る装置では眼精疲労をきたしやすく，その原因として，機器の幾何学的な特性や輻湊と調節の矛盾等が挙げられている[3]．また，画質や奥行きの調整など機器側の光学系の設定の問題や，調節や使用環境など被検者側の条件に原因があるともいわれている[4]．

今回我々が試作した三杆法装置は，眼科で普及している細隙灯顕微鏡に類似した低倍率の実体顕微鏡（ガリレオ式の平行光学系のもの）下で，三杆法を行うものであり（図1），測定は十分に視度と瞳孔間距離を調整した上で行った．その結果，片眼視時と比較して両眼視時のほうが有意にズレ量が少なかった（図2）．このことから，顕微鏡下で奥行き感の同定をするには両眼視が必要であり，両眼視機能が奥行き感の精度に影響することが示唆された．また同時に，開発したM三杆法装置の有用性を確認することができた．

今回の対象者は全員非顕微鏡下ではTSTで40秒の立体視機能が認められていたが，スリットランプ下でTSTを行った結果は，ばらつきがみられ，両眼分離が強い条件では，TSTが正常範囲にあっても，立体視が低下することが確認された（図3）．M三杆法とスリットランプ下でのTSTの結果には有意な相関はみられなかったが，M三杆法と，非顕微鏡下のTNOの結果には有意な相関がみられた．

M三杆法は，両眼分離下で主として調節および視差の手がかりを基に立体視を調べる検査といえる．TNOは赤緑眼鏡を用いて，比較的強い両眼分離下で精密な立体視を調べる検査である．両者は，強い両眼分離下での精密な両眼視機能が必要な検査という点が共通しているため，有意な相関がみられたのではないかと考えられた．また，TNOの方がTSTより小さい視差まで測定可能であることも，有意な相関が得られた一因と考えられた．

M三杆法の成績が悪かった被検者では，顕微鏡下でのTSTや非顕微鏡下でのTNO，融像幅といった感覚性および運動性の融像が不良であった．実際その被検者は顕微鏡を使用し始めた当初は，顕微鏡下での両眼視に違和感があり1ヵ月の間は立体視ができなかったと述べている．手術用顕微鏡下では非顕微鏡下と比較して立体視能力が低下するという報告がある[5]．一方，顕微鏡では左右の像が分離しており，像がとまっている場合には精密な立体視が必要と考えられるが，実際の顕微鏡下の操作は器具を動かして行うため，影や輪郭の重なりなどが奥行き感覚の手掛かりとなり，経験を積めば視差に依存した立体視が弱くとも十分作業が行える[6]，という報告もある．今回のM三杆法の成績が悪かったケースはこれに該当しており，実際に，1ヵ月後は顕微鏡下での作業に支障がなくなっている．経験を積むことにより顕微鏡下での作業が可能になった一例であると考えられた．

今回試作したM三杆法は，まだ開発段階ではあるが，顕微鏡下作業の適正判定の一助となる可能性が示された．今後は，融像能力が弱い斜視や弱視の症例を対象に，さらに検討を行う予定である．

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Jpn J Ophthalmol 2008;52:380–385
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DOI 10.1007/s10384-008-0575-1

CLINICAL INVESTIGATION

Photoreceptor Images of Normal Eyes and of Eyes with Macular Dystrophy Obtained In Vivo with an Adaptive Optics Fundus Camera

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Abstract

Purpose: To report on images of the human photoreceptor mosaic acquired in vivo with a newly developed, compact adaptive optics (AO) fundus camera.

Methods: The photoreceptors of two normal subjects and a patient with macular dystrophy were examined by using an AO fundus camera equipped with a liquid crystal phase modulator. In the eye with macular dystrophy, the fixation point in the AO images was identified using scanning laser ophthalmoscope (SLO) microperimetric image superimposed on a color fundus photograph.

Results: Photoreceptor cells were detected as bright dots approximately 4 μm in diameter in normal subjects. In the eye with macular dystrophy, the fixation point was located within the bull's eye lesion and uniform small whitish spots with irregular patchiness were observed in the AO images of this area. The distance between the small spots was 3–4 μm. In other parts of the bull's eye retinal lesion, the whitish spots were larger and of different sizes.

Conclusions: The photoreceptor mosaic could be identified in photographs of eyes of normal subjects and an eye with macular dystrophy in vivo by an AO fundus camera. In the eye with macular dystrophy, a relatively uniform photoreceptor mosaic was observed around the fixation point, whereas presumed debris of photoreceptor degradation was observed in the other bull's eye retinal lesion. **Jpn J Ophthalmol** 2008;52:380–385 © Japanese Ophthalmological Society 2008

Key Words: adaptive optics, cone mosaic, macular dystrophy, retinal imaging

Introduction

Adaptive optics (AO) technology, originally developed by astronomers to use with ground telescopes to compensate for atmospheric turbulence, has now been applied to fundus imaging. AO increases the resolution limits of retinal images by compensating for ocular wavefront aberrations.[1,2] Using an AO device, several studies have reported in vivo imaging of normal retinas[2–6] and the two-dimensional configuration of cone mosaic images. Recently, photoreceptor images from eyes with macular dystrophy have been obtained,[7,8] and a decrease of cone density was observed, which was correlated with a decrease in the amplitude of multifocal electroretinograms (ERGs). However, none of these reports referred to the fixation area in relation to the cone mosaic images.

The AO system consists of a wavefront sensor and a wavefront corrector, which form a closed loop of real-time wavefront compensation. The optical image with a reduced wavefront error is transferred to an imaging device such as a confocal scanning laser ophthalmoscope (SLO),[3] an optical coherence tomograph,[4] or a conventional fundus

Received: November 5, 2007 / Accepted: June 3, 2008
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camera.[1,2,5] The combination of a Hartmann-Shack wavefront sensor and a mechanical deformable mirror wavefront corrector seems to be the most widely used current AO system.

We developed a compact AO fundus camera using a Hartmann-Shack sensor and a liquid crystal wavefront modulator. We reported previously that our system could resolve individual photoreceptors in healthy eyes, and we have now used this system to measure interphotoreceptor spacing in both normal eyes and myopic eyes.[9]

Here we report another way in which our AO system can be applied. Our aim was to compare the AO images of a normal retina with those of an eye with macular dystrophy. More specifically, we examined whether the configuration of the cone mosaic in the fixation area differed from that in other areas within a bull's eye lesion.

Methods

Adaptive Optics System

A schematic diagram of the AO system is shown in Fig. 1. The main components of the system are a nematic liquid crystal phase modulator (LCPM; X8267-12, Hamamatsu Photonics, Hamamatsu, Japan), a Hartmann-Shack wavefront sensor (HSWS; 28 × 28 lenslets, especially made by Topcon, Tokyo, Japan), and a scientific charge-coupled device (CCD) digital camera (C9100-02, Hamamatsu Photonics). The light source for the wavefront sensing path was a 690-nm super luminescence diode (FiberMax, Blue Sky Research, Milpitas, CA, USA), and that for the retinal illumination path was a 635-nm laser diode (LLS-635–50, Moritex, Tokyo, Japan).

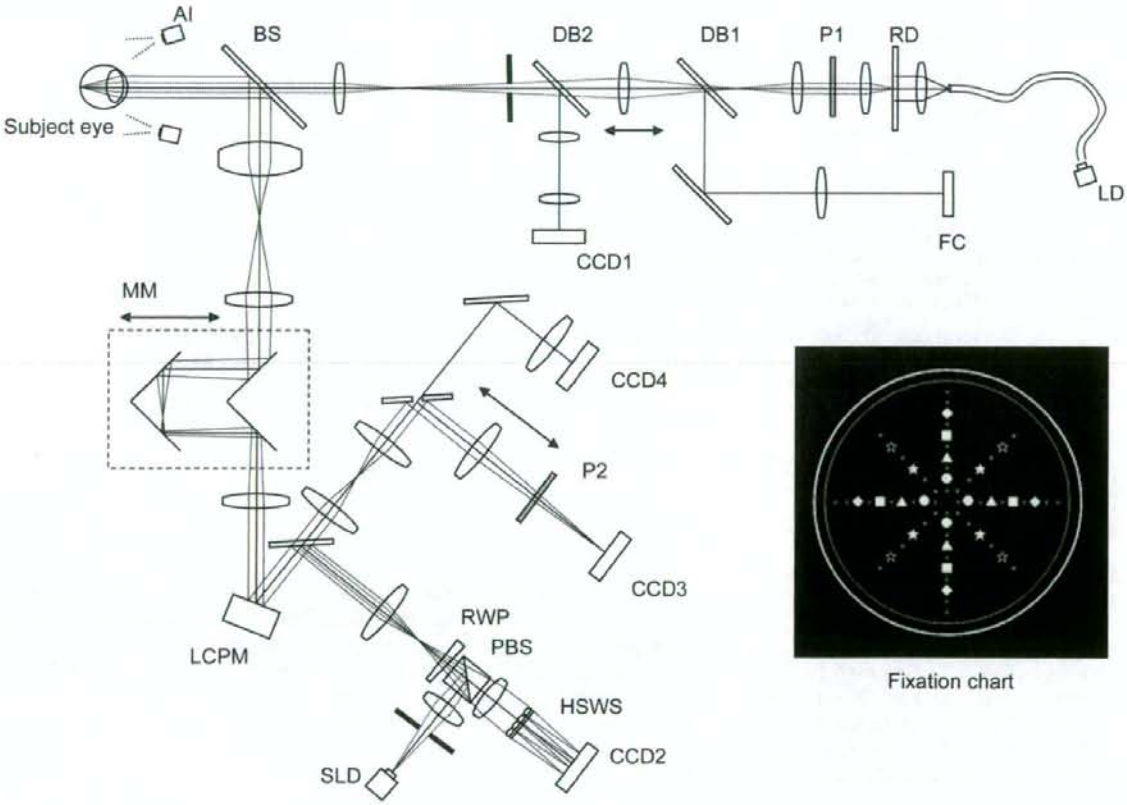

Figure 1. Schematic diagram of an adaptive optics fundus camera using a liquid crystal light modulator. AI, light source (LED 940 nm) for anterior segment illumination; *LD*, laser diode illuminator (635 nm); *SLD*, super luminescence diode illuminator (690 nm); *CCD*, charge-coupled device; *BS*, beam splitter; *DB1/DB2*, dichroic beam splitter; *FC*, fixation chart; *RD*, rotating diffuser; *P1*, *P2*, linear polarizers; *MM*, moving mirror; *RWP*, rotary wedged prism; *HSWS*, Hartmann-Shack wavefront sensor; *LCPM*, liquid crystal phase modulator (Hamamatsu PAL-SLM).

To avoid generation of speckles due to the coherence of the light sources, a rotary wedged prism was placed in the optical path of the HSWS, and a light-shaping diffuser sheet (LSD, Physical Optics, Torrance, CA, USA), which rotated at 20000 rpm in the retinal illumination path.

The HSWS measured the ocular wavefront up to the eighth Zernike order, and the LCPM compensated for the measured wavefronts. These two components formed a closed loop of continuous wavefront compensations, and operated at approximately 3 Hz, limited by the working speed of the LCPM. The system was also equipped with coaxial, 8° wide view optics to identify the location and orientation of the highly magnified retinal images observed. The area occupied by the AO system was 0.8 m × 0.8 m with a height of 25 cm, which might be compact enough to place in a clinical examination room. The entire AO system can be maneuvered by a single operator. Each series of AO images from the selected retinal locus can be captured in about 2 min, including targeting of the area, focusing, and wavefront compensation.

Subjects

A 40-year-old Japanese man presented with a progressive decrease of visual acuity over 20 years; his best-corrected visual acuity was 20/60 OU. Ophthalmoscopic examination revealed an annular zone of retinal pigment epithelial atrophy in the macula (bull's eye maculopathy) in both eyes (Fig. 2). His younger brother had a similar macular lesion. Bilateral ring scotomas were detected in both eyes of the patient by Goldmann perimetry. A moderate window defect without leakage was observed in the macular area by fluorescein angiography. The 30-Hz flicker ERGs and flash ERGs were of normal amplitude.

Two healthy volunteers (a 38-year-old man and a 31-year-old woman) were also examined.

Image Capturing

The research protocols were approved by the institutional review board of Osaka University Medical School and conformed to the tenets of the Declaration of Helsinki. After the nature and possible consequences of the study were explained, written informed consent was obtained from the two subjects and the patient.

After the pupils were dilated by topical 0.5% tropicamide and 0.5% phenylephrine, the examinee was seated in front of the AO system with a regular chin rest and asked to fixate the target. A retinal photograph was taken by the CCD as a 20-frame movie sequence with 10-bit grayscale images (1000 × 1000 pixels) and the total root mean square (RMS) error was reduced below the preset trigger value (usually 0.10 μm for a 5-mm pupil). The magnification of the image was calculated from the axial length of the eye.[10]

In the macular dystrophy patient, the retinal locus of fixation was verified by microperimetry using a confocal SLO (Rodenstock SLO ver 1.0, Rodenstock, Munich, Germany),[11] conventional color fundus photographs (Topcon TRC50LX, Topcon), and optical coherence tomography (OCT3000, Carl Zeiss Meditec, Dublin, CA, USA). The mosaic AO image was manually processed with Adobe Photoshop CS1 (Adobe, San Jose, CA, USA) image-processing software. With the same software, the color fundus image and the SLO image were superimposed on the mosaic AO image and the retinal locus of fixation in the AO image was determined.

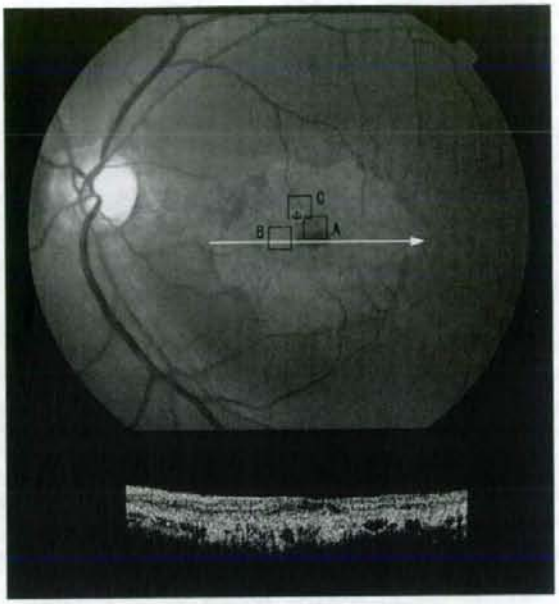

Figure 2. Fundus and optical coherence tomography (OCT) images of the left eye of a patient with macular dystrophy. The *blue cross* represents the fixation point, verified by the scanning laser ophthalmoscope microperimetry. The *white arrow* shows the position of the OCT transect. The *square boxes* represent the areas examined by adaptive optics (AO) and are labeled with *letters* corresponding to the parts of Fig. 4.

Calculation of the Cone Density

Cone density was calculated in three steps.

1. Image processing of each grabbed image before image summation using the deconvolution function, "deconvlucy," of MATLAB (Mathworks, Natick, MA, USA) was performed to get a clear separation of the cones.
2. Image summation to improve the signal-to-noise ratio was performed using our original program. The number of superimposed images ranged from 8 to 64 frames, depending on the imaging conditions.
3. The cones were marked. Retinal loci about 2° temporal of the center of the fovea were examined. Three 100 μm