Myopia Progression in Children Is Linked with Reduced Foveal mfERG Response

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Purpose. To study the changes in retinal electrophysiology in children during myopia progression during a 1-year period.

Methods. Twenty-six children aged from 9 to 13 years were recruited for the global flash multifocal electroretinogram (mfERG) measured at 49% and 96% contrast, in two visits 1 year apart. The amplitudes and implicit times of both direct component (DC) and induced component (IC) measured at these two visits were analyzed and compared. Pearson's correlation was used to study the association between the changes of mfERG response and myopia progression during the test period.

Results. Myopia increased by –0.48 ± 0.32 diopter (D) ($P < 0.001$) during the year, with 24 of 26 children becoming more myopic (range = 0.00 to ~ –1.38 D); axial length increased by 0.25 ± 0.11 mm ($P < 0.001$) during the year. The increased myopia was highly correlated with increase in axial length ($r = –0.70$; $P < 0.001$). The central DC and IC amplitudes at 49% contrast reduced significantly as myopia progressed and the paracentral implicit times of these two components were reduced considerably. However, the high-contrast responses were virtually unaffected.

Conclusions. Our findings suggested that the inner retinal functions in the central retina, with some involvement of the paracentral region, were decreased as myopia progressed in children. (*Invest Ophthalmol Vis Sci.* 2012;53:5320–5325) DOI:10.1167/iovs.12-10185

Axial elongation of the eyeball is the primary anatomic change as myopia increases.[1,2] This elongated eyeball leads to irregular arrangement and morphology of photoreceptors in animal studies,[3,4] and is associated with retinal thinning in humans.[5] Because of these changes, retinal function is likely to be influenced to a certain degree in the myopic eye.

The multifocal electroretinogram (mfERG) measures retinal function of multiple loci simultaneously and can detect localized defects within the central retinal field.[6] Many authors[7–10] have also reported reduced and delayed mfERG responses in myopic adults, especially in the paracentral region. Interestingly, Luu and coworkers[11] have found that the mfERG response is affected by the magnitudes of myopia in adults but not in children, which implies that the effect of myopia on the retinal function is not the same between children and adults. Our recent study[12] using global flash mfERG stimulation also has found that myopia produces different effects on retinal function in adults and children in terms of the regions and the retinal components affected. Specifically, myopic children show reduced retinal function in the foveal region, while myopic adults have weaker retinal function in the paracentral region. Moreover, the functional changes appear to occur at the outer retinal level in myopic children but at the inner retinal level in myopic adults.

However, there are currently no longitudinal data available on changes of retinal physiology in children during myopia progression. Luu and colleagues[13] have characterized the mfERG response prospectively in children with progressing myopia; they measured both the refraction and mfERG response at the first visit and only the refraction at the follow-up visit. They found that children who have smaller foveal mfERG response at the initial visit exhibit a higher rate of myopia progression.[13] Since retinal electrophysiology was not measured at the second visit, it is not known whether there was a change in retinal function in these children. The paracentral retina has been shown to be affected in adult myopes.[9] The present study aimed to investigate the regional changes of retinal function in children during myopia progression. The global flash mfERG with different contrast stimulation was used to separate the inner and outer retinal activities to the mfERG response.

Methods

Subjects

Twenty-six subjects aged from 9 to 13 years (mean = 10.6 ± 1.2 years, median = 11.0 years) were recruited from the Optometry Clinic of The Hong Kong Polytechnic University. All subjects received eye examinations at the initial visit and again at a follow-up visit scheduled 1 year later. This eye examination included objective and subjective refraction (see below), axial length measurement, and mfERG recording. In both visits, all subjects had best corrected visual acuity of logMAR 0.00 or better in both eyes, normal color vision, and ocular health. According to the results of previous epidemiologic studies,[14,15] children who developed myopia before the age of 6 were classified as congenital myopia. Exclusion criteria were congenital myopia, any ocular disease, clinically significant retinal degeneration, systemic disease, and history of epilepsy.

All subjects were accompanied by their parents or legal guardians throughout the ophthalmic examination and experiment. Before the experiment began, the aim of the study was fully explained and written consent was obtained from the parents or legal guardians. All the experimental procedures followed the tenets of the Declaration of

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Presented in part at the 7th Asia-Pacific Conference on Vision, Hong Kong, July 2011.

Supported by the associated fund (Research Postgraduate), the Niche Areas–Myopia Research (J-BB7P), and Glaucoma Research (J-BB76) from The Hong Kong Polytechnic University.

Submitted for publication May 12, 2012; revised June 23, 2012; accepted June 26, 2012.

Disclosure: **W.-C. Ho**, None; **C.-S. Kee**, None; **H.H.-L. Chan**, None

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Investigative Ophthalmology & Visual Science, August 2012, Vol. 53, No. 9

Helsinki. This study was reviewed and approved by the Human Ethics Committee of The Hong Kong Polytechnic University.

Refraction and Axial Length Measurement

Before the ophthalmic examination, one drop of 0.4% oxybuprocaine (Agepha Pharmaceuticals, Vienna, Austria) was instilled followed by 2 drops of 1% tropicamide (Alcon Laboratories, Inc., Fort Worth, TX) (5 minutes apart) to dilate the pupils of both eyes and paralyze accommodation temporarily. Cycloplegic refraction was measured objectively with an autorefractor (model KR 8800; Itabashi-ku, Tokyo, Japan) at least 30 minutes after the instillation of eyedrops; this was followed by subjective refraction and measurement of visual acuity. The objective refraction was measured three times to obtain a mean value. The reading was regarded as valid if the range of the three readings, for either spherical or cylindrical component, was $\leq$0.25 diopter (D). Axial length was measured with a noncontact optical biometer (IOL Master, v.4.08; Carl Zeiss Meditec, Inc., Dublin, CA). The axial length was measured five times to obtain a mean value. The readings of axial length were valid if the range of the five readings was $\leq$0.10 mm and the signal score of each reading was $\geq$2.0, as stated in the IOL Master user's manual.

Multifocal ERG Stimulation

The mfERG stimulus pattern was presented on a 22-inch liquid crystal display (LCD) (response time: 2 ms [grey-to-grey]) (model 2232GW+; SAMSUNG, Tianjin, China) controlled by the Visual Evoked Responses Imaging System (VERIS) (version 6.0.09d19; Electro-Diagnostic Imaging, Redwood City, CA). The stimulus consisted of a 61-hexagon array, scaled with eccentricity (stretch factor = 12.18). The hexagonal array subtended 39° horizontally and 37° vertically at a working distance of 40 cm.

The video frame sequence of the global flash mfERG stimulation began with a multifocal flash frame, followed by a dark frame, a global flash, and a second dark frame for each m-sequence stimulation, at a video frame rate of 75 Hz (Fig. 1a).[9,16,17] For the multifocal flash frame, each hexagon was flickered between bright and dark stimulation, according to the chosen pseudorandom binary m-sequence.

The global flash mfERG was measured at 49% and 96% contrast. These contrast levels were produced by the luminance differences of the bright and dark hexagons of the multifocal flash, set at 60 cd/m^2 and 96 cd/m^2, while the mean luminance of the multifocal flash was set at 50 cd/m^2. For each condition, the recording time was 3 minutes and 40 seconds with a 2^{12} binary m-sequence; the whole process was divided into 16 slightly overlapping segments for recording. The order of presentation of the two contrast conditions was randomized.

Multifocal ERG Recording

For each subject, the eye with the lower magnitude of astigmatism was chosen for recording and the other eye was occluded during measurement. If the magnitude of astigmatism was equal between the two eyes, one eye was randomly chosen for recording.

The procedure of mfERG recording was conducted according to the guideline of International Society for Clinical Electrophysiology of Vision.[18] The mfERG examination began when the pupil was dilated to at least 7 mm. A Dawson-Trick-Litzkow thread electrode was placed in the inferior fornix of the tested eye to contact with the inferior cornea as the active electrode. Gold cup electrodes were placed 10 mm lateral to the outer canthus of the tested eye and at the central forehead, to serve as reference and ground electrodes, respectively. Spectacle trial lens(es) of 35-mm diameter, which was (were) placed at the anterior

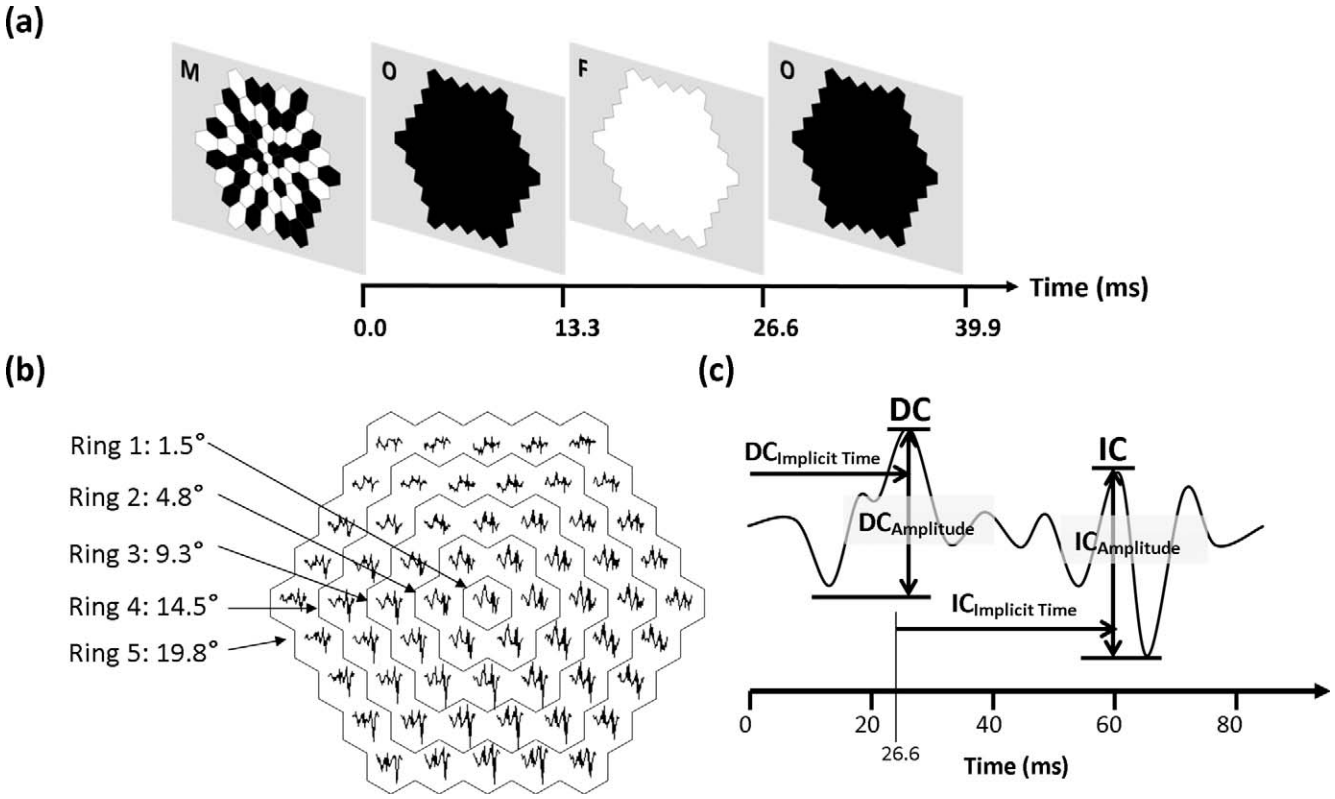

Figure 1. (**a**) A schematic diagram showing the video frame of the global flash mfERG in each m-sequence stimulation, which consisted of a multifocal flash frame (*M*), a dark frame (*O*), a global flash frame (*F*), and a second dark frame (*O*). (**b**) The 61 local responses were pooled into 5 concentric rings for analysis. The value indicated the eccentricity boundary (in visual angles) of each region. (**c**) A schematic diagram showing the typical global flash mfERG response (see text for details).

focal plane of the tested eye, was (were) used to correct for the refractive error at the viewing distance of the mfERG stimulator. The mfERG signal was amplified 100,000 times and the band pass was set at 10 to 200 Hz (model 15A54, Physiodata Amplifier System; Grass Technologies, Astro-Med, Inc., West Warwick, RI). The signal was monitored by the examiner using the real-time response provided by the VERIS program; any segment contaminated by blinks or loss of fixation was immediately rerecorded.

Analysis

The 61 local mfERG responses were pooled into 5 concentric rings for analysis (Fig. 1b). The amplitudes of direct component (DC) and induced component (IC) responses were analyzed by using peak-to-peak measurement (Fig. 1c). The implicit times of DC and IC responses were measured from the onset of multifocal flash and global flash, respectively, to their response peaks. The changes in mfERG response (including both amplitude and implicit time domains) were obtained by subtracting the mfERG responses in the follow-up visit from those in the initial visit.

The averaged value of the three objective refraction findings provided by the autorefractor was converted into spherical-equivalent (SE) value (SE = spherical component + 0.5 × cylindrical component). Myopia progression was calculated as the difference in cycloplegic objective refraction (in SE value) between two visits, that is, subtracting the refractive error in the follow-up visit from the refractive error in the initial visit. Pearson's correlation was used to investigate any association between myopia progression and changes in mfERG response. Bonferroni adjustment was applied to correct for multiple comparisons of different retinal regions, that is, the level of significance was set at 0.01. Statistical Package for Social Sciences (SPSS 15.0; SPSS Inc., Chicago, IL) was used to carry out the statistical analysis.

Results

Twenty-three of the 26 subjects were myopic at the initial visit. One more child became myopic at the follow-up visit. Twenty-four children showed a myopic shift during the study. Table 1 summarizes the refractive error and axial length findings, as well as the changes in these ocular parameters between the two visits. There was a statistically significant increment in myopic refractive error of 0.48 D (paired *t*-test, $t = 7.58$, $P < 0.001$) and an increase of axial length of 0.25 mm (paired *t*-test, $t = -11.57$, $P < 0.001$) during the study. The increase in myopia was correlated with the increase in axial length (Pearson's correlation, $r = -0.70$, $P < 0.001$) (Fig. 2).

Table 1. Refractive Error and Axial Length of the Subjects at the Initial and Follow-Up Visits

	Range				
	Minimum	Maximum	Mean	SD	Median
Refractive error (in SE, D)					
Initial	+0.50	−6.25	−2.14	1.62	−2.00
Follow-up	+0.25	−7.00	−2.62	1.72	−2.38
Changes in refractive error (= follow up – initial)	0.00	−1.38	−0.48	0.32	−0.50
Axial length (mm)					
Initial	22.94	26.07	24.36	0.80	24.41
Follow-up	23.19	26.31	24.61	0.84	24.62
Changes in axial length (= follow up – initial)	0.05	0.47	0.25	0.11	0.25

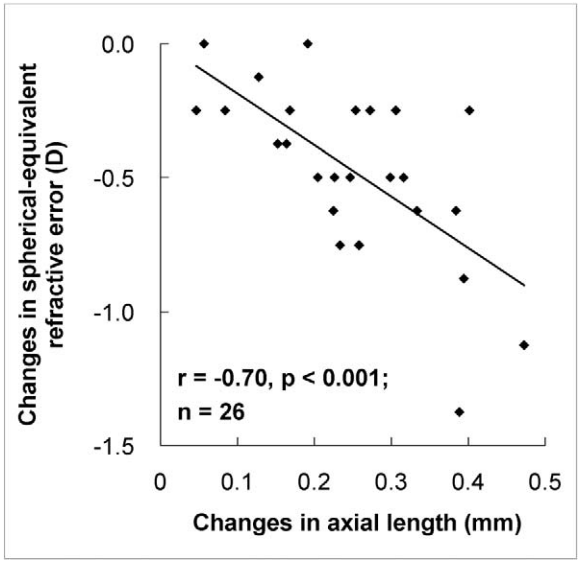

Figure 2. The correlation between changes in axial length and myopia progression ($n = 26$).

Figure 3 illustrates the typical global flash mfERG waveforms recorded at 49% and 96% contrast for a subject at the initial visit. As shown, the waveforms consisted of both DC and IC responses for all regions examined. For both contrasts, both DC and IC responses had reduced amplitudes and mildly reduced implicit times with increasing eccentricity.

Table 2 shows the changes of mfERG response at 49% and 96% contrast for different regions during myopia progression during the 1-year period of this study. As myopia increased, the DC amplitudes at 96% contrast, and both the DC and IC amplitudes at 49% contrast, of all regions examined, were reduced. The IC amplitudes at 96% contrast of central rings 1 and 2 were reduced, but the amplitudes of rings 3 and 4 were slightly increased (Table 2). For the time domain (Table 2), the IC implicit times at both contrasts tended to be reduced. In contrast, the DC implicit times at 49% contrast of rings 1 and 2 were increased and those of paracentral region from rings 3 to 5 were decreased. The DC implicit times at 96% contrast were slightly increased for all regions examined, except ring 1.

Table 3 summarizes the Pearson's correlation values between the change in refraction and those in global flash mfERG response. Myopia progression mainly influenced the global flash mfERG response at 49% contrast but not at 96% contrast. For the amplitude domain (Table 3), at 49% contrast, both the DC and IC amplitudes for ring 1 were reduced as myopia progressed (Pearson's correlation, $r = 0.50 \sim 0.53$, both $P < 0.01$). However, the amplitudes of these components for the remaining regions were not significantly correlated with the change in refraction. For the time domain (Table 3), as myopia progressed, both the DC and IC implicit times of most regions examined were unaffected, except the DC implicit time at 49% contrast for ring 3 ($r = 0.54$, $P < 0.01$) and the IC implicit time at 96% contrast for ring 5 ($r = 0.49$, $P = 0.01$).

Discussion

We found that myopia progression mainly affected retinal function at central regions (i.e., ring 1, within 1.5° eccentricity; Table 3). There is no longitudinal study in the literature

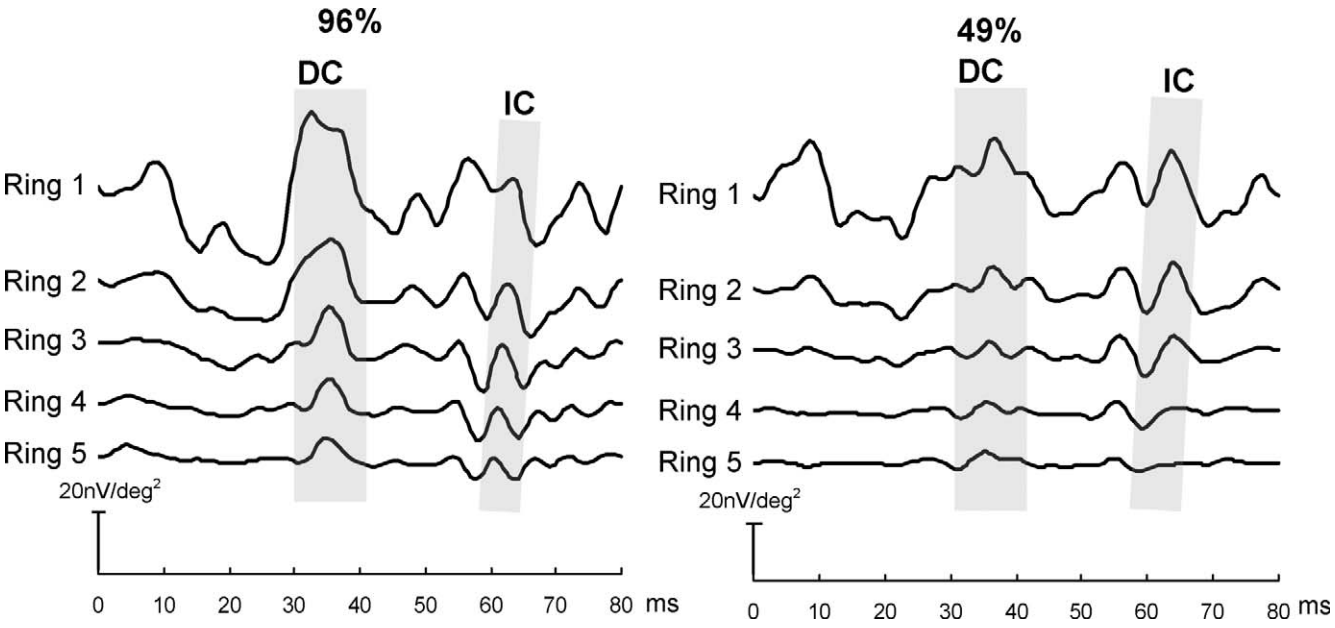

Figure 3. The global flash mfERG response recorded from a subject at 96% contrast (*left*) and 49% contrast (*right*) (refractive error = −3.75/−1.25 × 5).

investigating the change of retinal function in children during myopia progression. Luu and colleagues[13] have examined the mfERG response in children with progressing myopia. However, they only measure the mfERG response at the initial visit but not at the follow-up visit. They show that retinal function in the foveal region is substantially reduced before the subjects become more myopic. Our study demonstrated that attenuated retinal function was present mainly in the central region as myopia progressed, in agreement with the conclusion of Luu and colleagues.[13]

Chen and coworkers[8,19] have characterized the mfERG response of adults with progressing myopia. They group their subjects into either stable or progressing myopes by comparing the current refractive status with their previous clinical records. They show that myopia progression in adults predominantly affects paracentral to midperipheral regions with either a reduced response amplitude[8] or a shortened implicit time of mfERG response,[19] depending on the stimulation used. Similarly, our current study showed that the paracentral DC implicit time at 49% contrast (ring 3) and the

Table 2. Changes of Global Flash mfERG Response (a) Amplitude and (b) Implicit Time of the Children at 96% and 49% Contrast during the 1-Year Period

Parameter	**Changes of Amplitude (nV/deg²) (Mean ± SD)***			
Contrast	**96%**		**49%**	
Component	**DC**	**IC**	**DC**	**IC**
Region				
Ring 1	−11.69 ± 26.24	−12.27 ± 25.63	−11.42 ± 24.16	−5.32 ± 19.81
Ring 2	−6.17 ± 11.38	−0.59 ± 14.76	−3.15 ± 8.12	−1.46 ± 6.30
Ring 3	−2.37 ± 5.46	1.53 ± 10.33	−0.63 ± 4.08	−1.14 ± 4.19
Ring 4	−2.22 ± 3.54	0.52 ± 7.07	−0.15 ± 2.81	−0.70 ± 2.37
Ring 5	−1.58 ± 2.62	−0.49 ± 4.14	−0.81 ± 2.10	−0.20 ± 1.69

Parameter	**Changes of Implicit Time (ms) (Mean ± SD)†**			
Contrast	**96%**		**49%**	
Component	**DC**	**IC**	**DC**	**IC**
Region				
Ring 1	−0.46 ± 2.65	−0.23 ± 2.67	0.15 ± 4.02	0.44 ± 2.58
Ring 2	0.25 ± 2.36	−0.33 ± 2.40	0.02 ± 3.01	−0.48 ± 2.15
Ring 3	0.19 ± 1.29	−0.36 ± 3.06	−0.21 ± 3.53	−0.57 ± 2.47
Ring 4	0.38 ± 1.47	−0.64 ± 2.36	−0.16 ± 1.88	−0.02 ± 2.73
Ring 5	0.30 ± 1.65	−0.26 ± 2.00	−0.41 ± 2.68	0.30 ± 3.07

* Changes of Amplitude = Follow-Up − Initial Visit.
† Changes of Implicit Time = Follow-Up − Initial Visit.

Table 3. Pearson's Correlation (*r*) between the Change in Refraction and the Change in Global Flash mfERG Response (a) Amplitude and (b) Implicit Time for Different Regions and Their Corresponding Significance Levels (*P*) ($n = 26$)

Parameter	Amplitude							
Contrast	96%				49%			
Component	DC		IC		DC		IC	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Region								
Ring 1	0.34	0.09	−0.09	0.66	**0.50**	**<0.01***	**0.53**	**<0.01***
Ring 2	0.15	0.48	−0.08	0.69	0.45	0.02	0.26	0.21
Ring 3	0.17	0.41	0.02	0.91	−0.02	0.94	0.44	0.02
Ring 4	0.08	0.70	−0.02	0.92	0.08	0.71	0.04	0.86
Ring 5	0.15	0.46	−0.08	0.69	−0.05	0.81	0.17	0.41

Parameter	Implicit Time							
Contrast	96%				49%			
Component	DC		IC		DC		IC	
	r	*P*	*r*	*P*	*r*	*P*	*r*	*P*
Region								
Ring 1	−0.03	0.88	−0.20	0.33	−0.11	0.58	0.22	0.28
Ring 2	−0.18	0.37	−0.32	0.11	0.12	0.95	−0.19	0.37
Ring 3	−0.11	0.60	−0.24	0.25	**0.54**	**<0.01***	−0.26	0.19
Ring 4	−0.01	0.96	0.24	0.24	0.32	0.11	−0.40	0.04
Ring 5	−0.08	0.68	**0.49**	**0.01***	0.10	0.63	−0.29	0.15

* These *P* values reach the Bonferroni-corrected statistically significant level ($P \leq 0.01$).

paracentral IC implicit time at 96% (ring 5) contrast were also considerably reduced in the eyes of children showing more myopic progression (Table 3). Our results suggest that the central region is the critical area adversely affected during myopia progression in children (i.e., ring 1, within eccentricity 1.5°; Table 3), in agreement with the findings of Luu and colleagues.[13] The difference between our study and those of Chen and coworkers[8,19] might be due to the different mfERG stimulation modes used and, most likely, the age of the subjects (children versus young adults). According to our previous study, the effect of myopia on regional retinal function varies in different age groups.[12]

The paracentral DC implicit time at 49% contrast (ring 3) was reduced in children with progressing myopia (Table 3). Chen et al.[19] have used the slow flash paradigm (i.e., a multifocal flash frame followed by three dark frames for each of the m-sequence stimulation) and extracted the oscillatory potentials by filtering, restricting the signal to the high frequency range (100–300 Hz). They report that the implicit times of these oscillatory potentials are reduced in adults with progressing myopia. In contrast to their protocol, we used a global flash paradigm; it has been found that the contour of DC response in the global flash paradigm superimposes several "oscillatory potentials" in porcine eyes.[20] The reduction of DC implicit time in the paracentral region may also be related to the alteration of the activity of these oscillatory potentials, which is generally consistent with the findings of Chen and coworkers.[19]

Myopia progression predominantly affected central mfERG responses at middle contrast (i.e., 49%) stimulation but not at high contrast (i.e., 96%) (Table 3). Specifically, the central DC and IC amplitudes for middle contrast stimulation reduced as myopia progressed. In contrast, the mfERG response at high contrast was virtually unaffected during myopia progression. The IC response, representing the adaptive response to the global flash following the multifocal flash frame, originates from retinal ganglion cells and amacrine cells of the inner retina.[20] The reduced central IC response suggests that inner retinal function is reduced as myopia progresses. This idea is supported by the finding that eye disease involving inner retinal defects, for example, glaucoma, also shows significant reduction in DC amplitude at middle contrast but only mild reduction in DC amplitude at high contrast.[16,21] Taken together, our results suggest that inner retinal function from central to paracentral regions is predominantly attenuated during myopia progression.

Our results of reduced inner retinal function in children with progressing myopia are consistent with the results reported by Fujikado et al.[22] in a chicken model of myopia development. In a longitudinal study of the electrophysiologic change in chick eye during form-deprivation–induced myopia, Fujikado et al.[22] have found that the oscillatory potentials of the full-field ERG response, which predominantly represents the activity from inner plexiform cells,[23] are reduced gradually during myopia development and occur before axial elongation. In contrast, the b-wave of the full-field ERG response, representing response of outer retinal cells, such as bipolar cells and Müller cells,[24] is less affected throughout myopia development.[22] These results support the hypothesis that inner retinal function is most affected during myopia progression.

Adult myopes show impaired retinal function from paracentral to peripheral regions.[7–10] Children with progressing myopia showed retinal functional change from central to paracentral regions, especially in the central region. There is progressive change of the regional defect in retinal function

from children to adults as myopia progresses. Both adults with myopia[9] and children with progressing myopia (current study) consistently show functional change in the paracentral retina. We believe that the functional change of the paracentral retina in children during myopia progression is related to impaired retinal function of the paracentral retina in adults with myopia. On the other hand, we did not expect to find, as we did, reduced function of the central region in children with progressing myopia but no such finding in adults with myopia. We speculate that this difference in foveal function between myopic children and adults may be related to age-dependent modulation of eye growth as well as myopia progression, which requires further investigation.

As in our previous study,[12] LCD was used as a stimulator for the mfERG recording. Compared to the flash impulse generated from cathode ray tube (CRT) monitor, the stimulus from LCD monitor takes a relative longer time to reach its highest intensity and longer decay time to reach the minimal intensity. Since the mfERG response with conventional fast stimulation measures the temporal interactive response between successive stimuli,[25] the response generated from LCD is not fully compatible with the response from CRT.[26] Therefore, the overall scan delay among stimuli should be adjusted to prevent the overlapping of the stimulus. For the stimulus chosen in this study, a flash never presented twice or more within the stimulation and a dark frame was always incorporated between flashes. Unlike the conventional mfERG stimulus, the flash separation eliminates the overlapping of the stimulus between its onset and offset and so reduces malformed response, especially the higher order kernels. Thus, the adaptive response, presented as IC, can still be obtained by using LCD.

Conclusions

During myopia progression, the DC and IC responses for middle contrast stimulation were reduced in the central region of the retina and these responses were also considerably reduced in implicit time in the paracentral region. Our findings suggest that the inner retinal functions of the central and perhaps paracentral regions deteriorate during myopia progression in children.

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