Correlation Between Refractive Amblyopic Eye Recovery Speed and High-Order Aberration: A High-Order Aberration Amblyopia Recovery Deviation (HARD) pilot study

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Research Article

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Abstract

Background: High-order aberration (HOA) may influence visual quality, therefore, we conduced a study to determine the correlation between best-corrected visual acuity (BCVA) recovery speed and high-order aberration (HOA) parameters measured using a new-generation aberrometer.

Methods: This is a prospective case series. Children aged 3–7 years with refractive amblyopic eyes (Snellen equivalent < 0.8) were recruited. All participants were followed for at least 6 months after full correction of the refraction error. By using iDesign, the BCVA and the HOA were measured before cycloplegia and after cycloplegia (baseline) and at 3-month intervals. Next, the correlation between BCVA recovery speed after 6 months and mean HOA parameters was determined. The participants were divided into two groups according to BCVA recovery speed to compare the HOA parameters.

Results: We analyzed 24 eyes of 12 children [mean age, 4.46 years (range, 3–6)]. Baseline mean BCVA was logarithm of minimal angle of resolution (logMAR) 0.335 (Snellen equivalent 0.46), which improved to logMAR 0.193 (Snellen equivalent 0.64) after treatment with full-correction spectacles for 6 months. The amblyopic eye recovery speed was significantly correlated with the tetrafoil value before cycloplegia ($p = 0.045$). The fast recovery group also showed significantly lower tetrafoil values before cycloplegia.

Conclusion: Some HOA parameters measured using the new-generation high-order aberrometer could predict the recovery speed of refractive amblyopic eyes. The current study results may aid in designing customizable HOA-corrected contact lens for refractory refractive amblyopic eyes.

Background

Amblyopia, a common ophthalmologic disease with a prevalence of 1.6%–3.6%, is considered insufficient foveal stimulation during a critical period. It has three main types: refractive, strabismus, and deprivation amblyopia [(1-4)], among them, refractive amblyopia accounts for the most amblyopia cases [(5, 6)].

High-order aberration (HOA) is a critical cause of monocular idiopathic amblyopia [(7, 8)]. Vincent et al. also indicated the HOA is significantly different between amblyopic eye and normal fellow eye [(9)]. However, most of such studies have used a small sample size and measured the HOA by using machines with older technology, and their results have varied highly [(1, 7-13)]. A recent novel study using HOA-correcting, real-time, closed-loop adaptive optics perceptual learning system demonstrated BCVA and contrast sensitivity significantly improved in refractive amblyopic eyes in adolescents (mean age, 16 years) [(14)]. Thus, the HOA potentially influences the speed of refractive amblyopic eye recovery.

A high-order aberrometer can be used in refractive surgery to improve patient's postoperative visual quality [(15, 16)]. iDesign (Abbott Medical Optics Manufacturing, Milpitas, CA, USA) is a new-generation aberrometer designed on the basis of Hartmann–Shack theory to eliminate the HOA after refractive surgery and improve final visual quality; the surgery using iDesign is called wavefront-guided refractive surgery. Wavefront-guided refractive surgery has provided satisfactory results in many patients. Therefore, some HOA parameters measured using iDesign may be critical in determining visual quality [(15-21)]. Moreover, iDesign may improve the accuracy and resolution of HOA measurements because it has relatively high number of detection points and increased resolution [(16)].

To our knowledge, no cohort study thus far has measured the HOA by using iDesign in amblyopic eyes of children. We hypothesized that the HOA measured using iDesign predicts the speed of amblyopic eye recovery. Therefore, in this prospective study, we determined the correlation between BCVA recovery speed and HOA parameters measured using iDesign in refractive amblyopic eyes after full low order aberration correction by spectacles during the critical period.

Methods

Patients

This prospective, single-center, longitudinal study was conducted from August 2015 to December 2017 at Chang Gung Memorial Hospital, Taipei, Taiwan. Children, aged 3–7 years, with refractive amblyopic eyes (Snellen equivalent < 0.8) were recruited.

This study was approved by the ethical and scientific committee of institution (IRB no.: 103-4554B) and was performed in accordance with the tenets of the Declaration of Helsinki. We received the formal consent to participate and consent for publication from the parents or legal guardians of all participants in the study after thorough explanation of the study protocol.

Examination

All children received complete, standard, scheduled ocular examinations at baseline and thereafter at regular trimonthly follow-ups. Uncorrected distance vision acuity measurement, BCVA measurement, slit-lamp anterior segment examination, and measurement of objective refractive errors before and after cycloplegia by using an autorefractometer (Auto Ref/Keratometer-1a/ARK-1; Nidek Co., Ltd., Aichi, Japan) were performed; moreover, HOA measurements before and after cycloplegia were performed using iDesign (Abbott Medical Optics Manufacturing, Milpitas, CA, USA) at the same time. All these measurements were performed at baseline and every 3 months. Moreover, fundus photography and axial length measurement were performed at baseline and every 6 months, and macular optical coherence tomography (Optovue RTVue XR Avanti; Optovue Inc., Fremont, CA, USA) was performed at baseline and thereafter annually.

For cycloplegia induction, phenylephrine (10%) and tropicamide (1%) was instilled three times every 10 min in each eye; after waiting at least 1 hour of the first instillation, enlargement of the pupil without any light reflex was confirmed using a penlight.

HOA parameters

HOA parameters acquired using a 4-mm diameter on iDesign were statistically analyzed (Figure 1). The patients were asked to blink once just before the scan and focus on the fixation target. The measurements were repeated five times for each eye. The appropriate values from the acquired data were selected by an experienced refractive ophthalmologist (C-F Liu), according to the manufacturer's suggestions, such as larger pupil size, better wavefront quality-check signal light, and closer refractive error to objective cycloplegic refractive error (Figure 1). The average values acquired for the subsequent 3-month measurements of the same eye were used for further analysis.

Treatment

All patients received full correction with spectacles for cycloplegic refractive errors measured using the autorefractometer as a standard treatment. We replaced the glasses when differences in the refractive errors and spectacle lens powers was >0.25 diopter of spherical (astigmatism) power. We also educated the patients' parents to ensure fulltime wearing of the spectacles and ensure compliance at every visit.

Grouping

The eyes were divided into two groups according to BCVA recovery speed: fast (BCVA improvement more than or equal to the median value of each improvement amount after treatment) and slow (BCVA improvement less than the median value of each improvement amount after treatment).

Exclusion criteria

The exclusion criteria were as follows: (1) follow-up duration of <6 months, (2) poor quality of data of HOA measurements even after repeated measurements, (3) the better eye was covered for amblyopic treatment during follow-up, (4) patient refusal to receive full correction of the spherical and astigmatism refractive error because of personal reasons, (5) lack of compliance with an average spectacle-wearing time less than 90% (information was acquired carefully from the parents' parents at every visit), (6) diagnosis of any form of strabismus.

Statistical analysis

The data were analyzed using SPSS (version 20.0; SPSS, Inc., Chicago, IL, USA). The correlation between the amount of BCVA improvement and average HOA of all successful measurements of each eye was determined using the bivariate Spearman's Rho correlation test. Regarding the two-group comparison analysis, the chi-square and independent samples *t* tests were applied to categorical and continuous data, respectively. Fisher's exact test was used when one or more of the cells in the chi-square test had expected values of <5. Statistically significant differences were defined using a two-tailed p of <0.05.

Results

In total, 56 eyes of 28 cases were recruited; of them, 16 eyes (8 cases), 4 eyes (2 cases), 6 eyes (3 cases), and 6 eyes (3 cases) were excluded because of loss to follow-up after baseline examination, strabismus, only poor quality of HOA examination data even after repeated measurements, and cover therapy during the follow-up period, respectively. Finally, 24 eyes of 12 cases [mean ± standard deviation (SD) age, 4.46 ± 0.17 years (range, 3–6); 12 boys and 12 girls] were enrolled. Table 1 summarizes the demographic data of all these children.

The correlation analysis indicated that the speed of amblyopic eye recovery significantly negatively correlated with the average tetrafoil value before cycloplegia and the values tended to remain negative after cycloplegia ($p = 0.045$ and 0.077, respectively; Table 2).

Compared with the slow recovery group, the fast recovery group demonstrated significantly lower tetrafoil values ($p = 0.032$) before cycloplegia; even after cycloplegia, the values tended to remain lower ($p = 0.057$), along with lower total effective blur power ($p = 0.084$) and total root mean square (RMS) error ($p = 0.061$; Table 3).

Discussion

To our knowledge, this is the first study determining the correlation between BCVA recovery speed and iDesign-measured HOA parameters in refractive amblyopic eyes after treatment with spectacles for 6 months during a critical period. This is also first study using iDesign data of preschool-aged (3–7-year-old) children. We found that the recovery speed of amblyopic eyes after spectacle treatment was significantly negatively correlated with tetrafoil values before and tended to remain negative after cycloplegia. Furthermore, the fast recovery group demonstrated significantly lower tetrafoil values before cycloplegia, and even after cycloplegia, this trend continued along with lower total RMS error and total effective blur power. Thus, the HOA may be a crucial determinant of the recovery speed of refractive amblyopic eyes.

Tetrafoil values seemed to play the most important role in the current study. Studies have shown that image quality disturbance by the HOA may lead to idiopathic amblyopia [(7, 8)]. For instance, Prakash et al indicated the maximum differences of R-squared variability estimation value (stepwise regression analysis model in one Zernike polynomial) in the trefoil, coma, and tetrafoil values between idiopathic amblyopic eye and normal fellow eye [(8)]. However, in some studies, the results have varied, probably because they performed measurements using equipment based on different theories, with lower resolution, or from an older generation [(1, 9, 10, 12, 13)]. Nevertheless, the HOA affects the image quality; therefore, the HOA, particularly the tetrafoil value measured using iDesign, may influence the amblyopic eye recovery speed. Additional large-scale studies confirming this observation are warranted.

In our patients, initial BCVA values were not so bad at least Snellen chart over 0.2 with obvious refractive problem (mean Snellen equivalent 0.4); thus, we prescribed full-correction spectacles as the first-line treatment and then followed the patient at 3-month intervals, wherein we determined HOA values by using iDesign and selected the mean value at each visit for analysis to make the HOA measurements more reliable. We also excluded patients receiving cover therapy to prevent its influence. Therefore, patients with low-order aberration fully corrected by spectacles with only HOA left in daily life were included properly to suit our study purpose.

The total RMS error and total effective blur power tended to be correlated with amblyopic eye recovery speed, rather than with the total HOA RMS error and effective blur power. Moreover, HOA (%) was high in the fast recovery group after cycloplegia, suggesting lower rati of low-order aberration in the fast recovery group (Table 3), potentially indicating that low-order aberration remained a crucial determinant of the speed of amblyopic eye recovery. It could be further explained by BCVA recovery after eliminating low-order aberrations by spectacles. Additional larger-scale studies may confirm this observation.

Most studies have used diagnosis-based machines, such as Complete Ophthalmic Analysis System (COAS Wavefront Sciences Inc, Albuquerque, NM, USA), KR-1w (Topcon Co., Tokyo, Japan), and iTrace Visual Function Analyzer (Tracey Technologies, Houston, TX, USA); some have used treatment functions of previous low-resolution models, all which are no longer available due to various reasons [e.g., WaveScan Wavefront System (AMO, Santa Ana, CA, USA) and Zywave II (Bausch & Lomb, Rochester, NY, USA)] [(1, 7-10, 12, 13)]. The new-generation machines, such as iDesign, not only have high measurement resolution but also require shorter examination time; thus, they can provide reliable data in younger unsteady children. Furthermore, iDesign can be used for HOA correction in combination with an excimer laser (VISX STAR S4; AMO, Santa Ana, CA, USA). Thus, this combination can aid in constructing software for customizing HOA-corrected contact lens to treat refractory refractive or idiopathic amblyopia.

In children, HOA should be evaluated after cycloplegia to prevent the effects of accommodation [(22)]; however, manufacturers suggest measuring without cycloplegia for refractive surgery. Therefore, we performed measurements under both conditions for the analysis. We selected a 4-mm area of visual-axis HOA analysis, regardless of cycloplegia, because it played the most important role for image quality [(1, 7, 9, 10, 12, 13, 22-25)].

Because parents become highly concerned when their children are diagnosed as having amblyopia, a safe and reliable tool that predicts the speed of amblyopic eye recovery is required. In the current study, iDesign appeared to be a useful tool that provides clinicians with holistic information regarding the recovery speed during the follow-up period.

This study has some limitations: noncompliance of the children during the examination and small sample size. To counter the first issue, we repeated the examination several times and tried to convince the children to cooperate as much as possible. Nevertheless, this was a pilot study that provided information regarding the influence of HOA on amblyopic eye recovery. It also provided information useful for large-scale prospective study design and customizable HOA-corrected contact lens for amblyopia treatment in the future.

In conclusion, the current study in which HOA was measured using iDesign demonstrated that after spectacle treatment, the recovery of refractive amblyopic eyes was fast with low tetrafoil values before and after cycloplegia. Thus, iDesign-based HOA measurement without cycloplegia can provide useful information regarding the recovery speed of refractive amblyopic eyes.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital, Taiwan (Reference No.103-4554B) in accordance with the Declaration of Helsinki.

We received the formal consent to participate from the parents or legal guardians of all participants in the study after thorough explanation of the study protocol.

Consent for publication

We received the formal consent for publication from the parents or legal guardians of all participants in the study after thorough explanation of the study protocol.

Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

No competing interests between authors.

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Authors' contributions

C-F-L and M-L-Y conceived of the presented idea, C-F-L, M-L-Y and C-H-T analyzed and interpreted the patient data. C-F-L, M-L-Y, H-C-Y and C-H-T performed the ocular examination and collect the data form the patients. C-C-S and L-Y helped supervise the project. C-F-L was a major contributor in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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Tables

Table 1. Patient demographic data

Parameters	Cases (n=24)
Age (year) (Mean ± SD)	4.46 ± 0.853
Gender (Male: Female)	6 : 6
BCVA baseline (LogMAR) (Mean ± SD)	0.335 ± 0.160
BCVA 6 months after treatment (LogMAR) (Mean ± SD)	0.193 ± 0.156
Follow-up times (months) (Mean ± SD)	10.25 ± 2.54
Average number of idesign/person (Mean ± SD)	4.6 ± 0.86
Before cycloplegia	
Total RMS error (μ) (Mean ± SD)	1.8567 ± 1.2354
Total high order RMS error (μ) (Mean ± SD)	0.3729 ± 0.2050
High order aberration (%) (Mean ± SD)	8.219 ± 5.072
Total Effective blur (D) (Mean ± SD)	3.208 ± 2.144
Total high order Effective blur (D) (Mean ± SD)	0.774 ± 0.511
Coma (μ) (Mean ± SD)	0.0669 ± 0.0421
Trefoil (μ) (Mean ± SD)	0.0577 ± 0.0227
Sphere aberration (μ) (Mean ± SD)	0.0026 ± 0.0248
Tetrafoil (μ) (Mean ± SD)	0.2713 ± 0.0170
After cycloplegia	
Total RMS error (μ) (Mean ± SD)	1.6129 ± 0.9975
Total high order RMS error (μ) (Mean ± SD)	0.5308 ± 0.2086
High order aberration (%) (Mean ± SD)	8.409 ± 4.038
Total Effective blur (D) (Mean ± SD)	2.925 ± 1.594
Total high order Effective blur (D) (Mean ± SD)	0.917 ± 0.358
Coma (μ) (Mean ± SD)	0.0674 ± 0.0459
Trefoil (μ) (Mean ± SD)	0.0702 ± 0.0375
Sphere aberration (μ) (Mean ± SD)	-0.0026 ± 0.0246
Tetrafoil (μ) (Mean ± SD)	0.0221 ± 0.0117

BCVA: best-corrected visual acuity. D: diopter. LogMAR: logarithm of minimal angle of resolution. RMS: root mean square. SD: standard deviation.

Table 2. Correlation analysis between amblyopic eye recovery speed and high-order aberration

	Mean ± SD	rs	*p value*
Before cycloplegia			
Total RMS error (μ) (Mean ± SD)	1.8567 ± 1.2354	-0.132	0.538
Total high order Rms error (μ) (Mean ± SD)	0.3729 ± 0.2050	-0.158	0.461
High order aberration (%) (Mean ± SD)	8.219 ± 5.072	0.242	0.255
Total effective blur (D) (Mean ± SD)	3.208 ± 2.144	-0.119	0.581
Total high order effective blur (D) (Mean ± SD)	0.774 ± 0.511	-0.007	0.973
Coma (Mean ± SD)	0.0669 ± 0.0421	-0.106	0.623
Trefoil (Mean ± SD)	0.0577 ± 0.0227	0.085	0.693
Sphere aberration (Mean ± SD)	0.0026 ± 0.0248	-0.187	0.380
Tetrafoil(Mean ± SD)	0.2713 ± 0.0170	-0.412	0.045
After cycloplegia			
Total RMS error (μ) (Mean ± SD)	1.6129 ± 0.9975	-0.217	0.309
Total high order RMS error (μ) (Mean ± SD)	0.5308 ± 0.2086	-0.053	0.805
High order aberration (%) (Mean ± SD)	8.409 ± 4.038	0.170	0.428
Total effective blur (D) (Mean ± SD)	2.925 ± 1.594	-0.185	0.386
Total high order effective blur (D) (Mean ± SD)	0.917 ± 0.358	-0.062	0.774
Coma (μ) (Mean ± SD)	0.0674 ± 0.0459	-0.089	0.679
Trefoil (μ) (Mean ± SD)	0.0702 ± 0.0375	-0.123	0.567
Sphere aberration (μ) (Mean ± SD)	-0.0026 ± 0.0246	0.063	0.770
Tetrafoil (μ) (Mean ± SD)	0.0221 ± 0.0117	-0.368	0.077

D: diopter. LogMAR: logarithm of minimal angle of resolution. RMS: root mean square. SD: standard deviation.

$p < 0.05$, Spearman's correlation.

Table 3. Comparison of fast and slow recovery groups

Parameters	**Fast (n=15 eyes)**	**Slow (n=9 eyes)**	***P value***
Age (Mean ± SD)	4.40 ± 0.79	4.56 ± 0.98	0.666
Gender (Male : Female)	7:7	5:4	0.689[a]
Mean follow-up times (months) (Mean ± SD)	10.6 ± 2.69	9.56 ± 2.24	0.310
Average Number of iDesign exam/per case (Mean ± SD)	4.6 ± 0.90	4.6 ± 0.86	1.000
BCVA improvement after correction for 6 moths (LogMAR) (Mean ± SD)	-0.2266 ± 0.099	-0.0016 ± 0.142	<0.001
Before cycloplegia (4mm zone)			
Total RMS error (μ) **(**Mean ± SD**)**	1.5393 ± 0.8358	2.3856 ± 1.6316	0.105
Total high order RMS error (μ) **(**Mean ± SD**)**	0.3600 ± 0.1710	0.3944 ± 0.2623	0.700
High order aberration (%) **(**Mean ± SD**)**	2.651 ± 1.443	4.137 ± 2.833	0.179
Total effective blur (D) **(**Mean ± SD**)**	2.651 ± 1.443	4.137 ± 2.833	0.101
Total high order effective blur (D) **(**Mean ± SD**)**	0.724 ± 0.454	0.858 ± 0.613	0.543
Coma (μ) **(**Mean ± SD**)**	0.6401 ± 0.0411	0.0717 ± 0.0458	0.673
Trefoil (μ) **(**Mean ± SD**)**	0.0578 ± 0.0212	0.0576 ± 0.0263	0.984
Sphere aberration (μ) **(**Mean ± SD**)**	-0.0038 ± 0.0118	0.0134 ± 0.0362	0.200
Tetrafoil (μ) **(**Mean ± SD**)**	0.0214 ± 0.0124	0.0365 ± 0.0200	0.032
After cycloplegia (4mm zone)			
Total RMS error (μ) **(**Mean ± SD**)**	1.3193 ± 0.6101	1.8558 ± 1.2567	0.061
Total high order RMS error (μ) **(**Mean ± SD**)**	0.5413 ± 0.2175	0.5133 ± 0.2043	0.758
High order aberration (%) **(**Mean ± SD**)**	9.259 ± 4.291	6.993 ± 3.322	0.189
Total effective blur (D) **(**Mean ± SD**)**	2.490 ± 1.109	3.650 ± 2.051	0.084
Total high order effective blur (D) **(**Mean ± SD**)**	0.936 ± 0.375	0.887 ± 0.348	0.758
Coma (μ) **(**Mean ± SD**)**	0.0632 ± 0.0429	0.0744 ± 0.0523	0.573
Trefoil (μ) **(**Mean ± SD**)**	0.0546 ± 0.0300	0.0795 ± 0.0481	0.359
Sphere aberration (μ) **(**Mean ± SD**)**	-0.0063 ± 0.0106	0.0035 ± 0.0384	0.469
Tetrafoil (μ) **(**Mean ± SD**)**	0.0177 ± 0.0065	0.0293 ± 0.0151	0.057

BCVA: best-corrected visual acuity. D: diopter. LogMAR: logarithm of minimal angle of resolution. RMS: root mean square. SD: standard deviation.

* $p < 0.05$, independent t test.

[a] Fisher's exact test

Figures

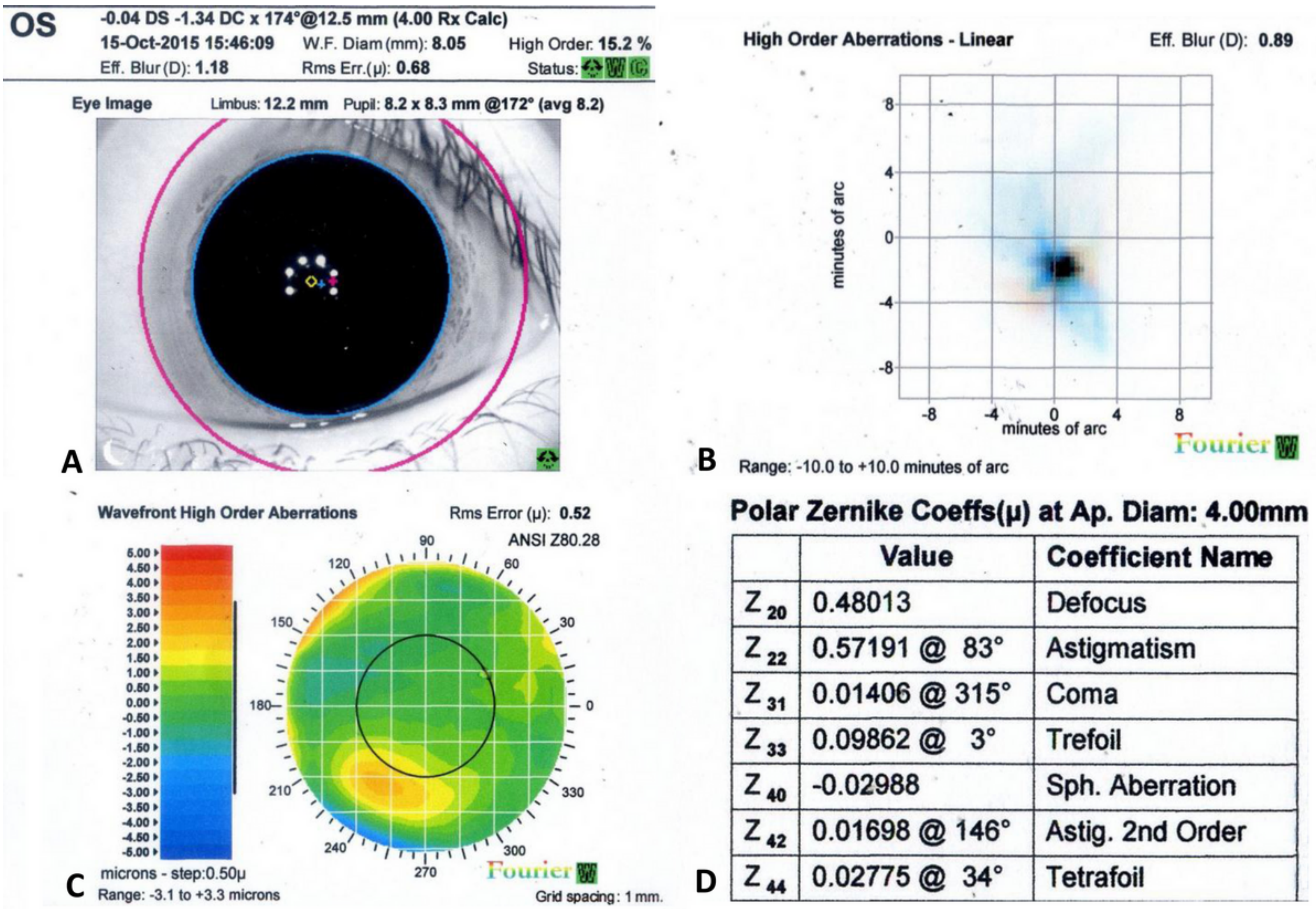

Figure 1

Example to explain data collection: Left eye of a 5-year-old girl who underwent iDesign examination at baseline after cycloplegia. (A) Refraction power (diopter), total RMS error (μ), total effective blur power (diopter), HOA (%), and status check; (B) Point spread function and HOA effective blur power (diopter); (C) Wavefront HOA 2D map showing the HOA RMS error (μ); (D) Polar Zernike coefficients (μ) at a pupil diameter of 4 mm.