Corneal Aberrations in Former Preterm Infants: Results From The Wiesbaden Prematurity Study

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METHODS. To compare corneal aberrations in former preterm infants to that of full-term infants.

RESULTS. A total of 259 former full-term and 226 preterm infants with a mean age of 7.2 ± 2.0 years were included in this study. Statistical analysis revealed an association of extreme prematurity (GA ≤ 28 weeks) with higher-order and lower-order aberrations of the total cornea. Vertical coma was higher in extreme prematurity (P < 0.001), due to the shape of the anterior corneal surface, while there was no association with trefoil and spherical aberration. ROP was not associated with higher-order aberrations when adjusted for gestational age group.

CONCLUSIONS. This study demonstrated that specific corneal aberrations were associated with extreme prematurity rather than with ROP occurrence.

Keywords: retinopathy of prematurity, low gestational age, low birth weight, cornea, corneal aberrations

The effects of prematurity and postnatal occurrence of retinopathy of prematurity (ROP) on altered ocular organ development in infancy are well known, especially its effect on the anterior eye segment. Former preterm infants have an increased risk for steeper corneal curvature,1–3 shallower anterior chamber,4 thicker lens,4,5 and smaller axial length.3,5 New imaging modalities using Scheimpflug principles allow contactless and detailed measurements of corneal and anterior segment morphology with high reproducibility and repeatability.7,8 Additionally, this technology enables the measurement of corneal aberrations and mathematically distinguishes the different properties as described by Zernike (Z) coefficients. To date, there has only been one study reporting corneal aberrations in former preterm infants with Scheimpflug imaging,3 showing increased corneal higher-order aberrations in former preterm infants in this population at age 7 to 14 years. It is still under discussion whether corneal higher-order aberrations contribute, as one of various factors, to the increased risk of former preterm infants for deteriorated visual acuity compared to full-term infants.

Hence, the focus of this investigation was to compare corneal aberrations of former preterm infants and former full-term neonates, and to evaluate differences in the various corneal aberrations in relation to gestational age and retinopathy of prematurity occurrence.

METHODS

This study was conducted in accordance with the tenets of the Declaration of Helsinki. Study approval was obtained from the local ethics committee (Physician Chamber Hessen). Written informed consent was obtained from the parents or legal guardian of each child. The authors declare no financial or proprietary conflict of interest.

The present study analyzed infants examined within the Wiesbaden Prematurity Study (WPS) in the Dr. Horst Schmidt Klinik Wiesbaden in Germany from July 2014 to March 2015. For the WPS, all premature infants born in our hospital with a gestational age (GA) below 33 weeks and actual age between 4 to 10 years were contacted and invited for detailed ophthalmologic examination. Randomly selected full-term infants with a GA ≥ 37 weeks served as the control group. The exclusion criteria of the WPS were the presence of severe congenital anomalies since birth. Severe congenital anomalies were defined as infants with congenital chromosomal disorders or/and congenital heart diseases, or/and neural tube defects.
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WPS participants were included in this analysis if measurement of corneal parameters by Scheimpflug imaging was possible without significant movement or artefacts. In addition, the scan quality had to be sufficient for the automated assessment of corneal aberrations. Children were excluded from the analysis if corneal tomography was not possible and if the scan quality was too low due to unstable fixation or low-compliance as reported earlier. In brief, Pentacam imaging allows three-dimensional imaging of the anterior segment from the anterior corneal surface to the posterior lens surface. All measurements were standardized according to the instruction manual by an examiner masked for the study purpose. When fulfilling the requirements for optimal alignment, corneal tomography was measured within 2 seconds based on 25 Scheimpflug images. To assure high quality for all investigations, the quality description of the device was checked and only accepted if “OK” was displayed. In the case that “OK” was not displayed or if comments colored yellow or red appeared, further measurements were conducted. The following corneal aberation parameters were documented for the present analysis: oblique and vertical astigmatism ($Z_{2-}$, $Z_{3-}$); vertical and horizontal coma ($Z_{2-}$, $Z_{3-}$); vertical and oblique trefoil ($Z_{3-}$, $Z_{5-}$); spherical aberration ($Z_{4-}$); and root-mean square of higher-order aberrations (RMS HOA) and of lower-order aberrations (LOA). All parameters were assessed for total cornea, for corneal front surface and for corneal back surface. Zernike parameters were calculated on an optic zone of 6 mm diameter and with a refractive index of 1.3375.

Medical records were used to assess the peri- and postnatal history of each study participant. All parents of WPS infants completed a detailed questionnaire. Only data of the right eye were included in the statistical analysis.

### Statistical Analyses

For descriptive analysis, infants were grouped into full-term infants with GA ≥37 weeks (group 1); preterm infants of GA between 29 and 32 weeks without ROP (group 2); preterm infants of GA ≤28 weeks without ROP (group 3); and preterm infants with GA ≤32 weeks and presence of ROP (group 4). Continuous variables were expressed as means ± SD or as median values when appropriate. Categorical variables were expressed as proportions. A $\chi^2$ test was used to analyze differences between groups for categoric variables. The normal distribution of data was tested using the Kolmogorov-Smirnov test. The Kruskal-Wallis test was used to compare independent continuous parameters between several groups. Corneal aberration values were compared in a multivariable linear regression model per corneal aberation type, including this as a depending variable and gestational age in the groups (full term infants [GA ≥37 weeks]; GA 29–32 weeks; GA ≤28 weeks); and ROP occurrence (yes/no) as independent variables, adjusted for sex and age at examination. This enabled the effect of gestation age and ROP to be reported independently from each other. The nonstandardized coefficient B and 95% confidence interval (CI) were calculated. As this is an explorative study, $P$ values should be regarded as a continuous parameter reflecting the level of evidence; therefore, they are reported exactly. Furthermore, to adjust for multiple testing according to Bonferroni’s correction, a $P$ value ≤0.0025 (having performed 20 tests for analysis of total corneal aberrations) was considered as statistically significant. Calculations were performed using commercial software (IBM SPSS 20.0; SPSS, Inc., Chicago, IL, USA).

### Results

#### Participants’ Characteristics

Overall, successful Pentacam imaging was recorded for 485 of 503 children. Of these, 259 of 264 were born full term (group 1); 124 of 125 were born with a GA between 29 and 32 weeks without ROP (group 2); 51 of 59 were born with GA ≤28 weeks without ROP (group 3); and 51 of 55 were formerly preterm infants with postnatal ROP occurrence (group 4). In groups 1 to 4, 123/259 (47.5%); 71/124 (57.3%); 26/51 (51%); and 26/51 (51%) of children were male ($P = 0.37$) and mean age was 7.2 ± 2.0 in group 1; 7.0 ± 1.8 in group 2; 6.9 ± 2.1 in group 3; 7.6 ± 2.2 in group 4, ($P = 0.18$), respectively.

#### Corneal Aberrations

Descriptively, total corneal aberrations, lower-order aberrations and higher-order aberrations increased when GA was lower (Table 1). This was mainly seen on the corneal front surface (Supplementary Tables S1, S2). All total corneal aberrations are described in Table 1 and for gestational age groups without ROP occurrence in the Figure. In multivariable analysis, extreme prematurity (GA ≤28 weeks) was associated with higher vertical coma ($Z_{3-}$), and higher total aberrations and increased higher-order and lower-order aberrations (Table 2), which was mainly due to the corneal front surface. Associations with aberrations of corneal front and corneal back surface are described in Supplementary Table S1 and S2.

Retinopathy of prematurity was not associated with higher-order or lower-order aberrations of the total cornea when data was adjusted for gestational age groups. In former preterm infants with postnatal ROP occurrence (group 4), total corneal thickness was observed between former preterm and full-term participants at the age of 7 and 14 years assessed with
Astigmatism is thought to be mainly due to corneal astigmatism and the palpebral position might have an effect on corneal shape and the eye globe is regulated by several factors, with some authors supporting that genetic factors determine corneal topography. Valluri et al.\(^1\) observed that corneal cylinder axis correlates with birthweight. Intraocular pressure is considered as another factor affecting the development of the eye. Looking on the extremes, infants with childhood glaucoma develop long axial length, have large corneal diameter and flatter corneal curvature. Corneal astigmatism is increased in the 5 mm zone in these children and is also configured more irregularly.\(^1\) Furthermore, Yang et al.\(^1\) observed in a school-based study of 1911 children that higher intraocular pressure correlated with steeper corneal curvature and younger age. The curvature of the cornea is also thought to be linked with birthweight.\(^1\) Yimon et al.\(^1\) observed in an animal study that suturing the eyelids of kittens during eye development leads to an increase of astigmatism, both in the sutured eye and in the fellow eye, while the controls had less astigmatism. This data indicates that lid movements affect the development of astigmatism potentially affecting the development of corneal aberrations. Astigmatism is thought to be mainly due to corneal astigmatism in younger age and in with-the-rule position.\(^1\) Differences in the palpebral position might have an effect on corneal astigmatism. Indeed, Grey et al.\(^1\) found that narrowing the palpebral aperture leads to increased cylindrical error, while Read et al.\(^1\) reported that corneal cylinder axis correlates with the eyelid angle. Nevertheless, Raffa et al.\(^1\) did not find an association of palpebral fissure length with gestational age or birthweight.

### Table 1. Total Corneal Aberrations Stratified for GA and ROP

<table>
<thead>
<tr>
<th></th>
<th>Group 1, ≥37 wk, (n = 259)</th>
<th>Group 2, 29–32 wk, no ROP, (n = 124)</th>
<th>Group 3, ≤28 wk, no ROP, (n = 51)</th>
<th>Group 4, ≤32 wk, With ROP, (n = 51)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Astigmatism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oblique ((Z_2^0))</td>
<td>-0.106 ± 0.385</td>
<td>0.004 ± 0.440</td>
<td>0.011 ± 0.334</td>
<td>-0.018 ± 0.487</td>
<td>0.09</td>
</tr>
<tr>
<td>Vertical ((Z_2^1))</td>
<td>-0.600 ± 0.456</td>
<td>-0.617 ± 0.612</td>
<td>-0.745 ± 0.603</td>
<td>-0.513 ± 0.761</td>
<td>0.25</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>1.264 ± 0.443</td>
<td>1.392 ± 0.590</td>
<td>1.488 ± 0.541</td>
<td>1.543 ± 0.680</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>HOA</strong></td>
<td>0.404 ± 0.174</td>
<td>0.429 ± 0.176</td>
<td>0.473 ± 0.218</td>
<td>0.517 ± 0.273</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>LOA</strong></td>
<td>1.188 ± 0.433</td>
<td>1.319 ± 0.578</td>
<td>1.399 ± 0.525</td>
<td>1.434 ± 0.670</td>
<td>0.002</td>
</tr>
</tbody>
</table>

All aberrations are reported in \(\mu m\). Only data of the right eye were included in the analysis, and the Kruskal-Wallis test was used to compare data between the different groups. \(n\), number of children.

* Group 1 (full-term born infants with a GA ≥37 weeks); group 2 (preterm infants with a GA between 29 and 32 weeks without ROP); group 3 (preterm infants with a GA ≤28 weeks without ROP); group 4 (preterm infants with GA ≤32 weeks with ROP).
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**Table 2.** Linear Regression Model Analyzing the Association of Total Corneal Aberrations of the Different GA Groups and ROP Adjusted for Age at Examination and Sex

<table>
<thead>
<tr>
<th>Linear Regression Model</th>
<th>GA ≥37 wks</th>
<th>GA 29–32 wks</th>
<th>GA ≤28 wks</th>
<th>ROP (yes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 485</td>
<td>B (95% CI)</td>
<td>P Value</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>Astigmatism</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oblique (Z2 3)</td>
<td>Ref.</td>
<td>0.11 (0.02; 0.19)</td>
<td>0.013</td>
<td>0.11 (−0.01; 0.23)</td>
</tr>
<tr>
<td>Vertical (Z2 0)</td>
<td>Ref.</td>
<td>−0.02 (−0.14; 0.10)</td>
<td>0.74</td>
<td>−0.15 (−0.30; 0.01)</td>
</tr>
<tr>
<td>Coma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Horizontal (Z4 1)</td>
<td>Ref.</td>
<td>0.01 (−0.04; 0.05)</td>
<td>0.79</td>
<td>−0.01 (−0.07; 0.05)</td>
</tr>
<tr>
<td>Vertical (Z4 0)</td>
<td>Ref.</td>
<td>0.003 (−0.01; 0.07)</td>
<td>0.07</td>
<td>0.12 (0.07; 0.17)</td>
</tr>
<tr>
<td>Trefoil</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oblique (Z2 0)</td>
<td>Ref.</td>
<td>0.03 (−0.01; 0.06)</td>
<td>0.14</td>
<td>0.001 (−0.05; 0.05)</td>
</tr>
<tr>
<td>Vertical (Z2 0–3)</td>
<td>Ref.</td>
<td>0.01 (−0.03; 0.05)</td>
<td>0.61</td>
<td>−0.04 (−0.09; 0.01)</td>
</tr>
<tr>
<td>Spherical aberration (Z2 0)</td>
<td>Ref.</td>
<td>0.01 (−0.01; 0.03)</td>
<td>0.29</td>
<td>−0.002 (−0.02; 0.02)</td>
</tr>
<tr>
<td>Corneal aberrations (RMS)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Ref.</td>
<td>0.10 (−0.01; 0.21)</td>
<td>0.06</td>
<td>0.28 (0.13; 0.42)</td>
</tr>
<tr>
<td>HOA</td>
<td>Ref.</td>
<td>0.02 (−0.02; 0.06)</td>
<td>0.43</td>
<td>0.09 (0.03; 0.14)</td>
</tr>
<tr>
<td>LOA</td>
<td>Ref.</td>
<td>0.11 (0.001; 0.22)</td>
<td>0.048</td>
<td>0.26 (0.12; 0.40)</td>
</tr>
</tbody>
</table>

Corneal aberration values were compared in a multivariable linear regression model per corneal aberration type, including this as a depending variable and GA in the groups (full-term infants [GA ≥ 37 weeks]; GA 29–32 weeks; GA ≤ 28 weeks) and ROP occurrence (yes/no) as independent variables, adjusted for sex and age at examination. The nonstandardized coefficient B and 95% CI were calculated. Only data of the right eye were included in the analysis. Ref., reference.

Overall, prematurity leads to altered ocular growth and morphologic alterations like a steeper cornea, smaller anterior chamber depth, thicker lens, and smaller axial length in childhood, which contributes to refractive error development and probably to altered corneal HOA and LOA.

To date, it is unclear whether these associations and/or environmental changes after preterm delivery may affect corneal aberrations. However, it is well known that preterm birth completely changes the newborns’ environment; therefore, it is likely that different factors associated with prematurity contribute to the altered corneal aberrations in preterm infants. Optical aberrations lead to visual disturbance, degraded retinal image quality, and play a role in the emmetropization processes potentially influencing refractive error development. Prematurity and ROP are well-known risk factors for myopic refractive error, which is also applicable in total cornea when the data was adjusted for gestational age. These results demonstrated that specific corneal aberrations associated with extreme prematurity potentially contributing as another factor to myopic refractive error, and visual dysfunction in extreme preterm infants.

### Study Limitations

The strengths of our study are the large sample size with preterm infants with and without ROP as well as the large control group. Limitations are the single center study design and that some parents declined to participate in the study. Although Scheimpflug examination was quality controlled, poorer fixation control in the extremely preterm infants may have had an influence on corneal aberration measurements particularly in extreme preterm infants. In addition, we were not able to evaluate the impact of corneal aberrations on the optical quality of the eye in prematurity as ocular wavefront measurements were not performed.

### Conclusions

In conclusion, this study has for the first time revealed an association of extreme prematurity (GA ≤28) with higher-order and lower-order aberrations as well as with higher vertical coma, independently of ROP status. In contrast, ROP was not associated with total higher-order aberrations of the total cornea when the data was adjusted for gestational age. These results demonstrated that specific corneal aberrations were associated with extreme prematurity potentially contributing as another factor to myopic refractive error, and visual dysfunction in extreme preterm infants.

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APPENDIX

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