

Research Article

Arrested Corneal Flattening and Low Astigmatism as Stable Trends Over Decades in Danish Ex-preterms

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Abstract

Background: Based on Danish cohort studies over half a century, to look for changes over time of corneal shape in childhood (curvature and astigmatism) in surviving Preterms (PT).

Methods: In the most recent study 178 PT and 56 Full-Term (FT) children underwent cycloplegic Retinomax autokerato-refractometry at age 4-5 years. PT was subdivided according to the presence and severity of Retinopathy of Prematurity (ROP)

Results: The PT children had either no ROP (n = 99), reversible ROP (n = 47) or laser treated ROP (n = 32) and presented median refractive values of 1.5 D, 1.8 D and 1.1 D, respectively, versus 1.3 D in controls (P<0.05). The corresponding mean values for corneal Curvature Radius (CR) were 7.59±0.27 mm, 7.60±0.28 mm and 7.46±0.28 mm, compared with 7.79 ± 0.23 mm for FT (P<0.0001). As added analyses, CR was significantly correlated to birth weight (P<0.001) but not to gestational age (P=0.14). CR and astigmatism did not correlate with refraction. Corneal Astigmatism (CA) was of normal low order (cylinder mainly < 1 D) and with no difference between the two main groups. Within the PT group, treated ROP had a higher median cylinder and a top-value of -2.25 D.

Conclusion: The stable anterior segment features over time contributed optically to occasional myopia of prematurity but did not explain it. Comparing with previous Danish PT investigations over 5 decades, a steeper cornea and low degree astigmatism remained hallmarks of PT, although with a slight impact suggested for the most advanced ROP.

Keywords: Corneal Curvature Radius; Corneal Astigmatism; Extremely Low Birth Weight; Retinopathy of Prematurity; Myopia of Prematurity; Intrauterine Growth Retardation

Introduction

Despite careful monitoring of neonatally added oxygen, from the mid-1960'es a second wave of prematurity blindness occurred which eventually occasioned the international classification of Retinopathy of Prematurity (ROP) of 1984 [1]. It denoted a shift in underlying concept from primarily 'oxygen beyond needs' to 'multifunctional immaturity' Reversibility was found in most ROP cases and anterior segment changes could be added to the basic retinal vasculopathy [2-4].

A uniformity of corneal findings eventually became evident from Danish investigations over half a century [2,3,5-9]. Our most recent study in children born 2004-2006 comprised a national cohort of extremely low Birth Weight (BW) infants, who obviously had benefitted from current improvements in neonatal care and therapy and eventually presented favourable visual outcomes [8,9]. Axial eye dimensions and keratometry were the primary focus in previous oculometric studies on Danish preterms. As partly due to its minimum impact on visual development, corneal astigmatism had low priority. The ultimate aim of the present study was to establish to what degree progress within neonatology and ophthalmology over half a century might also be reflected in corneal outcome in a western population.

Materials and Methods

Ethical Statement

This study was conducted in accordance with the ethical standards of the Institutional Ethics Committee.

Study Design and Participants

As part of a retrospective PhD study, a national cohort of extremely PT survivors were examined in 2009-2010 in the Rigshospitalet Departments of Ophthalmology. Inclusion criteria were Gestational Age [GA] <28 weeks at birth and BW ≤1500 g and with ROP, if present, given as maximum stage as recorded on a regular basis during the neonatal period [8,9]. The FT controls were randomly selected and matched to the PT population according to age and residential postal codes. Birth characteristics and perinatal data were obtained from the National Patient Register. In respect of the Helsinki declaration informed consent was signed either by both parents or by one parent with a warrant from the other and data was anonymized. The study was approved by The Danish Data Protection Agency (2007-58-0015) and by the central committees on Health Research Ethics (H-D-2008-003). Visual acuity findings and Retinomax auto-refractometry data have been discussed in previous papers [8,9]. A best corrected median visual acuity denoted an overall fair clinical outcome. For the present comparative focus over decades supplementary analyses on CR and CA were based on the already available Retinomax biometry data from the cohort.

Eye Examinations

A Retinomax K-plus 3 autorefractometer (Nikon, Tokyo, Japan) had recorded main refractive meridians, with CR value in mm; CA was given as their difference, in D and cycloplegic refraction was given for each eye as spherical equivalent (sphere + half cylinder, in D). Prior to Cyclogyl 1% eye drops for cycloplegia, monocular and binocular visual acuity had been assessed using logMAR HOTV charts at 3 m distance.

Statistical Analysis

Based on the stated statistical uniformity of the two eyes, the right eye values were chosen for refraction, CR and astigmatism. For parametric data t-test was used and one-way ANOVA for comparing PT subgroups. Nonparametric data were logarithmic transformed with Mann-Whitney and Kruskal-Wallis tests applied and with Dunn's test added when significance was found. Spearman's test was used for the correlation analyses. A P-value < 0.05 was considered significant. Stata17 was used for the statistical calculations.

Results

Descriptive Data and Correlations

In the recent cohort 178 surviving PT and 56 FT children were examined at the median age of 4.9 years (range, 3.7-5.8 years). The three preterm subgroups were: PT no ROP (n=99), PT reversed ROP (n=47) and PT treated ROP (n=32; all by diode laser) and there were 56 FT controls. Among the preterm children, 59 (33%) had been of multiple birth; the overall gender distribution across the subgroups was 49% boys and 51% girls (Table 1). No significant differences were found according to gender regarding GA or BW in any group. The distribution of GA and BW was non-parametric. Both had a negative correlation with ROP stage. The birth parameters were the lowest for the subgroup with laser-treated ROP, followed by reversed ROP and no ROP (Table 1). Refractive status and corneal parameters are presented in Table 2. A parametric distribution held only for the CR recordings. Comparing the two main groups, FT and PT, they differed significantly regarding CR and CA (P-values of <0.0001 and 0.025, respectively). Despite the slight excess in myopia load among the PTs, groupwise their refraction did not differ significantly from the controls. Across the PT subgroups there was borderline trend for the CR (P=0.058) and highly significant P-values for refraction (P=0.0006) and CA (P=0.0001). Post hoc pairwise analysis by Dunn's test revealed that refraction deviated between the treated and the regression ROP subgroup (P=0.002). Regarding astigmatism, Dunn's test pairwise across subgroups revealed significant differences between all (P<0.04), however with highest significance when comparing treated ROP with the no ROP group (P<0.00001). To the left, Fig. 1 shows correlation between the full sample preterm CR values and BW (r=0.28, P<0.0014). Thus, the more preterm the infant at delivery, the more curved the eventual childhood keratometry reading though with a possible role also for small for date, as further suggested from the lack of a parallel trend for CR analyzed versus GA (P=0.14). The CA cylinder value showed no correlation with GA or with BW, despite the added load of small for gestational age as valid for the latter parameter. The refractive value also showed no correlation to GA and BW, whether estimated for the full PT group or its subgroups.

Delivery Group	Gender Male/Female	GA (Weeks), Median (Range)	BW (G), Median (Range)
FT (n=56)	22/34	40.0 (37-43)	3425 (2332-4650)
PT, all (n=178)	93/85	26.7 (22-27.9)	879 (530-1390)
PT no ROP (n=99)	48/51	27.0 (23-27.9)	901 (530-1390)
PT reversed ROP (n=47)	23/24	26.6 (22-27.9)	880 (535-1290)
PT treated ROP (n=32)	22/10	26.1 (23.6-27.7)	753 (540-1150)
P-value between PT subgroups		0.01*	0.028*

BW: Birth Weight; GA, Gestational Age; FT: Full-Term; PT: Preterm

*Kruskal-Wallis test for mean difference between PT subgroups were significant for GA and BW.

Table 1: Descriptive data as information on the most recent national cohort of extremely preterms when examined 2009-10 at age 4-5 years.

Group	Refraction (D), Median (Range)*	Corneal Curvature Radius (Mm), Mean (Range)**	Astigmatism (D), Median (Range)***
FT (n=56)	+1.25 (-0.6-4.8)	7.78 (7.4-8.3)	-0.25 (-1.8-0.0)
PT, all (n=178)	+1.50 (-4.0-5.1)	7.57 (6.7-8.3)	-0.25 (-2.3-0.0)
P-value between PT vs FT	0.1	<0.0001	0.025
PT no ROP (n=99)	+1.50 (-1.1-5.1)	7.59 (7.0-8.4)	-0.25 (-1.0-0.0)
PT reversed ROP (n=47)	+1.75 (-3.6-5.0)	7.61 (7.1-8.3)	-0.25 (-2.0-0.0)
PT treated ROP (n=32)	+1.12 (-4.0-3.0)	7.46 (6.7-8.0)	-0.75 (-2.3-0.0)
P-value between PT subgroups	0.006	0.058	0.0001

FT: Full-Term; PT: Preterm

*P=0.1 by Mann-Whitney test for refraction FT against PT. P=0.006 by Kruskal-Wallis between PT subgroups

**Corneal curvature radius normally distributed, t-test for FT against PT. P<0.0001. One-way ANOVA between PT subgroups, P=0.058, variances only close to significance

***P=0.025 (Mann-Whitney) for astigmatism, FT tested against PT; P<0.0001 between PT subgroups (Kruskal-Wallis)

Table 2: As a continuation of Table 1, refraction and corneal parameters in our most recent Danish cohort, right eye data.

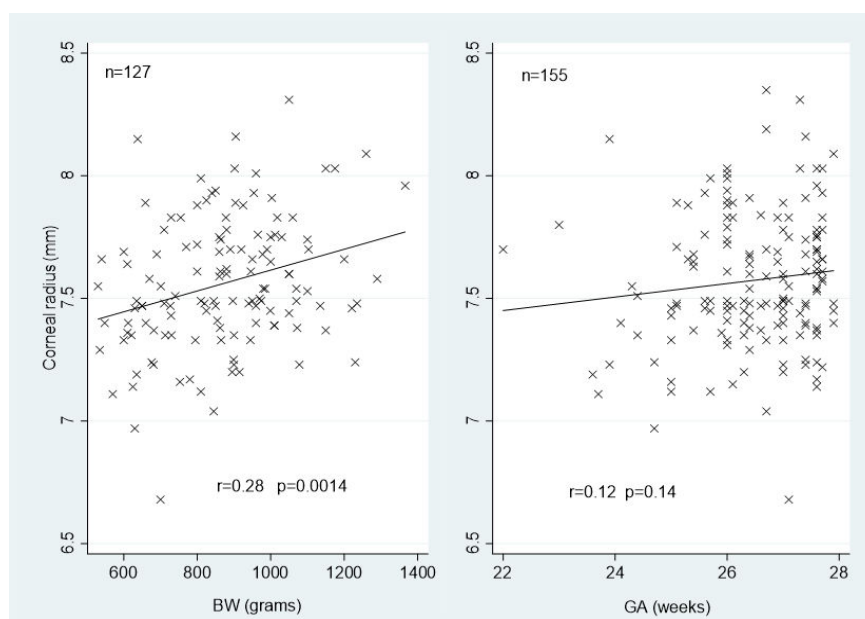


Figure 1: Scatterplots including all preterms showing significant correlation between corneal curvature radius and birth weight (left plot) unlike the condition for gestational age (right plot).

Discussion

Corneal Curvature Over Time in Danish Preterm Cohort Studies

In accord with previous Danish investigations, the recent 4-year cohort of PTs demonstrated a steeper curvature as the main corneal feature, the most peaked recordings particularly being associated with early laser treatment for advanced ROP [8,9]. In most PTs, this relative corneal myopization would be balanced inter al. by the shorter axial length and refractive distribution in PTs thus differed only marginally from FTs. Small PT outlier tails seemed to represent either restricted emmetropization (high plus) or myopia of prematurity.

A general and longstanding growth restriction in ex-PTs was first suggested after the advent of ultrasonic oculometry, as introduced in our Copenhagen PT 1959-61 cohort of 10-year-old PT survivors [2]. With relatively normal refractive and visual acuity findings, the eventual effects on axial length and corneal curvature radius as main findings came unexpected. The restrictions further seemed to hold more generally and not merely based on a small section of those considered the most preterm and vulnerable. Follow-up at age 18-19 years indicated that the growth-related restrictions were permanent. Longitudinally, as a group the preterm infants in our initial cohort thus never caught up [5,6].

We first tested the new ROP classification in a regional sample born between 1982 and 1984, a period where retinal cryo-ablation therapy for advanced ROP had not yet been introduced in Denmark. Four of the 28 with observed ROP had an irreversible course and acquired bilateral blindness [7]. In the remaining 24, reversible ROP stage 2 was the most advanced finding and new trends were not disclosed at the follow-up at age 7-10 years. Only the marginal subgroup with myopia of prematurity stood out, supporting the previous observations of shorter axial length and steeper cornea. In addition to a slightly lower best corrected visual acuity, they also presented a significantly thicker lens and a shallower anterior chamber [2,3,10]. In the literature, the likewise environmental foetal alcohol syndrome has presented with a less flattened cornea, although of no obvious relevance for our data [11].

Astigmatism In the Danish Preterm Cohort Series

Besides the steeper cornea, the Danish cohort studies emphasized that astigmatism remained of low order. The childhood CA distribution thus appeared close to normal and with only a minimum contribution to the predominance of ametropia that is usually recorded in preterm follow-up series. In about 85%-cylinder values did not exceed 1 D.

Summarizing the cohort-based Danish results over time, both corneal parameters appeared uniform, so far from the variability shown in posterior segment findings. A general growth restriction was suggested, primarily manifesting as a reduced early postnatal physiological flattening of the central cornea. Allover refractive distributions came close to those of normal childhood, although with small tails of disturbed development as just mentioned. As added to the eventual astigmatism of low order, only regressed ROP after treatment of advanced disease had cases of significantly higher astigmatism and only here to suggest an impact on the apparent robustness of the cornea due to increased vulnerability in a sensitive perinatal phase of development.

Studies From Elsewhere

Swedish PT population studies over 3 decades are in keeping with the Danish childhood levels of predominantly quite low astigmatism and benign visual outcomes were also similar [12]. Further, studies from Israel, Ireland, the United Kingdom and recently also from Germany, have reported similar findings. Corneal astigmatism has generally been recorded below a cylinder value of -1 D [13-15].

In marked contrast, advanced early ROP cases from elsewhere have been reported as having high cylinder values in various childhood PT series. In particular, this held for the US cryoROP multicenter studies from 1988 and onwards, which prospectively followed threshold ROP cases (BW <1251 g), with or without cryotherapy performed neonatally [16,17]. Irrespective of intervention, a high prevalence of significant permanent astigmatism was recorded and often on line with myopia of prematurity and macular scarring. High astigmatism was also reported in Chinese studies [18,19]. Except for ethnicity (Caucasian versus Asian or mixed in the US) and the vague socio-economic concept of general health (Scandinavian welfare models), we have no valid suggestions for the differences in response as here quoted.

As indicated already, the overall corneal trends under study cannot alone be explained by elective PT minorities. This would have set other marks on the descriptive statistics. In lack of a more specific pathogenesis, the results are best explained as broadly pertaining to the PT state as such, more than to its degree. Similar suggestions found support from Fiess and coworkers based on Caucasian ex-PT adults in Germany, regarding eventual thickness of central cornea and peripapillary nerve fiber layer [20].

Conclusion

In summary, whereas corneal steepening is commonplace, corneal astigmatism has only a small place in most western PT follow-up studies. Stable corneal trends have been suggested and significant astigmatism seems to occur mainly in relation to exceptional ROP (stage 3+). As further inversely deduced from the predominating mild courses mainly encountered, corneal responses have overruled only in tougher cases. Overall, the increased eye morbidity so convincingly documented among surviving small premature individuals includes ametropias in general and still warrants ophthalmic attention during at least the preschool years.

Conflict of Interests

The authors declare that they have no conflicts of interest.

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Patient Consent

Informed consent for examination and for publishing anonymized data were obtained from the parents to the participating children.

Data Availability

Delivery and perinatal data were from the National Patient Register, after approval by the Danish Data Protection Agency and the Central Committees on Health Research Ethics. The study respected the World Association Declaration of Helsinki.

Author's Contribution

All authors took part in data acquisition, study design and final accept of the manuscript. HAA and HCF were further responsible for the analyses added to those previously published and to writing the article, the latter to include professional UK language revision.

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