Visual Development in Preterm and Full-Term Infants: A Prospective Masked Study

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Purpose. To compare development of visual acuity and binocular vision in preterm and full-term infants in a prospective study that used testers masked to subject's gestational age.

Methods. Seventy-three healthy full-term infants, mean gestational age 40 weeks, and 18 low-birth weight preterm infants, mean gestational age 35 weeks, were examined bimonthly between the 4th and 51st weeks of postnatal age. Ocular alignment, convergence, fusion, visual acuity, and onset of optokinetic nystagmus (OKN) were assessed at each examination.

Results. The mean postnatal ages of onset of ocular alignment, convergence, fusion, visual acuity, and onset of OKN from temporal to nasal were, respectively, 5, 7, 7, 11, 6, and 9 weeks for the full-term and 12, 14, 18, 13, and 16 weeks for the preterm infants. The mean postnatal ages of onset for the corresponding parameters were 46, 48, 46, 51, 46, and 50 weeks for full-term and 47, 48, 52, 47, and 49 weeks for preterm infants. The onset of all parameters was earlier in full-term infants than in preterm infants of the same postnatal age (P ≤ 0.0001). However, no differences were found when the parameters were compared at postnatal ages.

Conclusions. Additional visual experience of preterm infants does not influence development of visual acuity or binocular vision during the first months of life as measured from the time of conception (Journal of Pediatrics, 1992; 120:346–353).

Investigations of the effects of prematurity on human development have yielded conflicting results. On the one hand, delays in the development of neurologic functions are potentially attributed to the increased vulnerability and incomplete maturation of the premature brain.1–6 On the other hand, the fact that some functions develop somewhat earlier with age corrected for prematurity in preterm infants has been attributed to the advantage of early additional extraterrestrial experience during which infants have more environmental stimuli and more differentiated movement.7–9 The aim of our study was to compare the time frame of development of visual acuity and binocular vision in preterm and full-term infants in a masked study design using the evaluation of kinematographic responses (visual pursuit and optokinetic nystagmus [OKN]) and orthoptic parameters (ocular alignment, convergence, and fusion).

In healthy infants, visual acuity increases rapidly within the first 3 months of life, as measured by different methods (preferential looking, visual evoked potentials, and OKN).10–14 There is general agreement that the acuity of 3-month-old infants is approximately 3 cycles per degree (cpd), but cut-off values vary as much as two octaves for 3-month-old infants. Three parameters influence the improvement of visual acuity: the differentiation of the fovea, the myelination of the visual pathways, and the increase in the number of synapses.7

In healthy preterm infants, visual acuity measured in behavioral and electrophysiological studies is consistently discussed in the literature. Some investigators8–13 reported a similar maturation pattern compared with full-term infants of the same postnatal age. Others11–13 showed accelerated visual development in preterm infants, which was attributed to additional visual experience in the premature period. The reported differences between the preterm and full-term infants were small. Van Hon-Kot et al.11 observed a mean difference of only 0.3 octave across the corrected age range of 1 to 49 weeks. Most reports suggested that after 1 year of age the difference is negligible, although there are two reports of acuity at the lower end of the normal range in preterm infants at 3 to 4 years.12,14

Normal binocular vision requires orthoptic alignment of the eyes and binocular mechanisms for convergence and fusion. Many sources of healthy full-term infants indicate that these different aspects of binocularity approach adult level by 3 to 6 months of age.15–18

In most studies that have used corneal reflections from a fixation light to evaluate alignment, infants achieved orthoptia within the first few weeks after birth.19–21 However, in two other studies, both of which used the examiner's face as the fixation target, infants became orthoptic during the third and fourth months of life.19,22

The development of convergence is more complex because convergence is driven by at least two cues: disparity detecting and accommodation mechanisms.23–25
by" and Ashin and Jackson" found partial convergence during the 6th month of life in 0.5% of infants examined; the convergence was assessed by photography. Convergence spasm is often seen in infants younger than 2 months of age, and by 3 to 4 months of age convergence is accurate and consistent in healthy infants."

Previous studies showed that young infants prefer viewing binocularly. The retinal movements were found to be asynchronous, showing a higher frequency of beats to strips moving from temporally to nasally than in the opposite direction. This asymmetry persists in humans with impaired binocular vision. In full-term infants, OKN becomes symmetrical to strips moving in both directions by 3 to 6 months of life. The concurrent onset of binocularity and symmetrical OKN has led to the speculation that the developmental changes in monocular OKN are linked to the development of binocularly driven cells in the visual cortex.

Little information is available about the development of binocular vision in premature infants. Results of one study indicate that live preterm infants are tested to suggest that the early period of visual experience appeared to accelerate the maturation of the OKN compared to that of full-term infants. However, the incidence of strabismus in healthy preterm infants is five times higher than in the general population. The concurrent onset of binocularity and symmetrical OKN has led to the speculation that the developmental changes in monocular OKN are linked to the development of binocularly driven cells in the visual cortex.

METHODS

This research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from parents after the nature and possible consequences of the study were explained. The research was approved by the Institutional Human Experimentation Committee of Kanosphu University.

Patients

Two groups of newborn infants were recruited for the study. The first group consisted of healthy full-term infants (n = 87) with a gestational age ranging from 38 to 42 weeks (mean, 40.1 weeks) and a mean birth weight of 3385 g. The second group consisted of preterm infants of low risk (n = 19) without neurologic or ocular disorders, with a gestational age ranging from 21 to 36 weeks (mean, 31.5 weeks) and a birth weight greater than 1250 g (mean, 2058 g). All infants were born reared. They were tested biseptically between 14 and 54 weeks of postmenstrual age until the infant showed the presence of each of the examined visual functions. At each examination children were only tested for capabilities that they had not shown at earlier examinations. Postmenstrual age represents the infant’s age calculated from the date of the first day of the mother’s last menstrual period. Examiners were unaware whether the infants were born at term or were premature because premature infants were all born after the 31st postmenstrual week and were at low risk, they were not screened systematically for retinopathy of prematurity. However, the fundus of all infants was examined during the study, usually at the time of the last examination at the postmenstrual age of 54 weeks. At this time, none of the infants showed fundus abnormalities. Simultaneously with fundus examinations, 50 minutes after administration of 0.5% tropicamide and 2.5% phenylephrine (each drop was applied twice, 5 minutes apart) retinoscopy was performed in all infants. We decided prospectively to exclude infants with cycloplegic refractions outside a window of 0 and +5 diopters. This resulted in the exclusion of one full-term infant who had hyperopia of 8 diopters. The mean refraction of full-term infants was +0.6 diopters (SD 0.5 diopters), and the mean refraction of preterm infants was +1.5 diopters (SD 0.8 diopters). In addition, we decided prospectively to exclude parents demonstrating any ocular pathology. Seven additional full-term infants and one preterm infant were excluded from the study. Two full-term infants had ocular pathology: one had congenital nystagmus and the other strabismus. The other six children (five full-term and one preterm) were excluded due to noncompliance (they missed three or more sessions).

OKN responses involve both subcortical and cortical components and are affected by attention. To control for attention we used scales developed by Precht and Zeiper to grade the state of the infant’s behavior. The infants were examined in Precht’s state III, calm “awake” with opened eyes, absence of large body movements, and regular respirations. Infants’ mothers were asked to choose at a time when their children appeared most relaxed to begin Precht’s state III and the examiner had to spend sufficient time with each infant so that a complete examination in Precht’s state III was possible. Therefore, 98% of the orthoptic examinations and 94% of the visual pursuit examinations were completed. However, with OKN testing cooperation was poorer. Here only 67% of the examinations were completed.

Orthoptic and Ophthalmologic Examinations

The orthoptic examination (performed by orthoptists) included ocular alignment, convergence, and vision. At each examination the two orthoptic examinations were attempted. Every child was examined at least once in Precht’s state III. If we could not examine an alert child, the mother was asked to wait or to return when the infant was again in Precht’s state III. Therefore, on each child all the examinations were performed at least once under optimal conditions. Because attention of infants may negatively influence the results, the better result of the two examinations was taken for data analysis. The better result consisted of ocular alignment as opposed to strabismus, full convergence compared with first sign of absent convergence, first sign of convergence versus absent convergence, and present fusion compared with absent fusion. Two examinations were completed for full-term infants in 75%, 82%, 84%, 80%, and 90% and for preterm infants in 72%, 74%, 80%, 100%, and 90% at the five consecutive examinations, respectively. These differences were not statistically significant for the two groups. The difference at the time of the last examination results from the small number of children (nine full-term infants and only one preterm infant), who did not complete the last examination who had not reached maturity in all orthoptic examinations (ocular alignment, full
Convergence, and presence of fusion) at an earlier examination date.

Ocular alignment was measured by the Hirschberg or cover tests, or both. We only analyzed manifest ocular deviations; phorans were not evaluated. During the Hirschberg test an illuminated toy was jigged at a distance of 1 m from the infant's face to trigger attention and fixation while the positions of the corneal light reflections were observed. A conversion for the Hirschberg test of 20 prism/mm was used. 

Because of the infant's large angle kappa (0° - 10°), we considered decentralized corneal reflections to indicate exotropia only when they were more than midway from pupillary center to nasal pupillary margin. 

Convergence was tested by attracting the infant's fixation with an illuminated toy at a distance of 0.5 m. The toy was then moved slowly toward the infant's face while the examiner observed the infant's eyes. Convergence was classified as absent, first sign of convergence (any bilateral adnation), and full convergence (bination in 12 cm from the face). 

Binocular fusion was measured by the four prism base out test. After attracting the infant's fixation with an illuminated toy, the prism was placed base out in front of each eye. Binocular vision was considered to be present when a consistent eye movement was observed with or without a preceding saccadic eye movement. Binocular vision was judged to be absent when no eye movement or only a saccadic eye movement was observed. Although the four prism base out test may show atypical responses in certain subjects, it is fast and simple and therefore was useful in this infant study.

A complete ophthalmologic examination (performed by ophthalmologists) including limits examination and retinoscopy was performed on each infant. Anterior segments and fundus were normal in all children.

Infrared Eye Movement Recordings

The eye movements were recorded by a corneal reflection tracker, which consisted of a cathode ray tube in which stimuli for visual pursuit and OKN were generated. The infant was placed 30 cm in front of the screen. While the infant was looking at different stimuli, infrared light was directed to the infant's right eye, and the eye movements were recorded by an infrared-sensitive camera. Infrared source and camera were installed over the infant's head, and infrared light was reflected by a hot mirror positioned in the center of a cathode ray tube and directed to the infant's eye. Analysis of the eye movements is based on the measurement of the relative position of the reflected image of the infrared source on the cornea and pupil center.

Grating Acuity

Grating acuity was measured by pursuit eye movement recordings. The stimulus was a square of 9° of visual angle on a gray surface of equal luminance. It consisted of gratings moving along a horizontal axis at a constant velocity of 7.5 degrees per second. We tested five different spatial frequencies: 0.1, 0.2, 0.4, 0.8, and 1.6 cpd. Pursuit eye movements were evoked binocularly and were recorded from the right eye. After attracting the infant's attention with a flashing light to the screen, a grating was presented for 30 seconds. If the initial grating elicited a pursuit response, the spatial frequency of the stimulus was increased, otherwise it was decreased. The criterion for presence of the grating acuity for a certain stimulus was if the infant followed this stimulus by saccadic or smooth pursuit at least once over the entire screen (6.2 seconds).

Optokinetic Nystagmus

The stimulus was a vertical grating of 0.5 cpd covering a visual field of 56 × 43° and moving along a horizontal axis at a constant velocity of 30 degrees per second. OKN was evoked monocularly from the right eye by covering the left eye with an orthoptic patch and was recorded during the presentation of stripes moving temporally nasally and in the opposite direction. OKN was considered present if the typical pattern of slow and fast phase nystagmus was shown in correlation with the displacement of the stimulus. OKN examinations were completed in full-term infants in 48%, 50%, 67%, 77%, and 82% and in preterm infants in 25%, 54%, 56%, 63%, and 87% at the five examination times, respectively.

Statistical Evaluation

Data were analyzed by survival analysis using the time of onset for each parameter and for each infant as variables. Thus, only the plotted curves on the figures represent the percentage of subjects showing onset of each visual function at each age. Two estimators for the percentage of infants showing the onset of the parameter of interest up to a certain time were used. They were the nonparametric Kaplan-Meier estimator and the logistic fitting. The logistic function was preferred for other link functions because it fits the Kaplan-Meier curves best. To compare the parameters of the two groups of infants we used the log rank test.

Results

Between the 4th and 6th weeks of postmenstrual age, 66% of the infants were orthotropic, 56% were exotropic, and 8% were esotropic. The mean postnatal age (SD) of onset of ocular convergence was 5.0 (0.2) weeks for full-term and 12.0 (0.6) weeks for preterm infants. The mean postmenstrual age of onset of ocular convergence was 45.0 (0.2) weeks for full-term and 45.0 (0.4) weeks for preterm infants. The percentage of infants showing orthophoria at different ages is plotted in Figure 1A for postmenstrual ages and Figure 1B for postmenstrual ages. The onset of ocular alignment was significantly earlier (P = 0.0001) in full-term infants compared with preterm infants of the same postnatal ages. However, no statistically significant difference was found when postmenstrual ages were compared (P = 0.69).

The mean (SD) postnatal age of onset of the first signs of convergence was 5.0 (0.2) weeks for full-term and 11.0 (0.5) weeks for preterm infants. Full convergence occurred at 7.0 (0.5) weeks postnatally for full-term infants and at 13.0 (0.4) weeks postnatally for preterm infants. The mean (SD) postmenstrual age of onset of first signs of convergence was 45.0 (0.2) weeks for full-term and 45.0 (0.4) weeks for preterm infants. Full convergence occurred at 48.0 (0.3) weeks postmenstrually for full-term infants and at 47.0 (0.4) weeks postmenstrually for preterm infants. The percentages of infants showing first signs and full convergence at different ages are shown in Figure 2. The onset of convergence (first signs and full convergence) was significantly earlier (P < 0.0001) in full-term infants compared with preterm infants of the same postmenstrual ages. How-
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Figure 1. Kaplan-Meier curves and log-logistic fitting of percentages of preterm and fullterm infants showing orthophoria at different postnatal (A) and postmenstrual (B) ages.

However, no statistically significant differences were found when postmenstrual ages were considered ($P = 0.76$), first signs and $P = 0.12$ for full convergence.

The mean (SD) postnatal age of onset of fusion was 7 (0.3) weeks for fullterm infants and 14 (0.4) weeks for preterm infants. The mean (SD) postmenstrual age of onset of fusion was 48 (0.3) weeks for fullterm infants and 48 (0.4) weeks for preterm infants. We plotted the percentage of infants showing fusion at different ages in Figure 3. The onset of fusion was significantly earlier ($P = 0.0001$) in fullterm infants compared with preterm infants based on postnatal ages. However, based on postmenstrual ages no statistically significant difference was found ($P = 0.88$).

The mean (SD) postnatal ages of onset of visual pursuit to stimuli of 0.1, 0.2, 0.4, 0.8, and 1.6 cpd were, respectively, 5 (0.2), 5 (0.2), 8 (0.2), and 11 (0.3) weeks for fullterm infants and 11 (0.5), 12 (0.4), 12 (0.4), 15 (0.6), and 18 (0.8) weeks for preterm infants. The mean (SD) postmenstrual ages of onset of visual pursuit to the above stimuli were, respectively, 46 (0.2), 45 (0.2), 45 (0.2), 48 (0.2), and 51 (0.3) weeks for fullterm infants, and 45 (0.5), 45 (0.5), 46 (0.3), 49 (0.5), and 52 (0.7) weeks for preterm infants. The percentages of infants showing visual pursuit to the various stimuli at different ages are represented in Figure 4. The times of onset of visual pursuit for all stimuli between 0.1 and 1.6 cpd were significantly earlier for all stimuli ($P \leq 0.0001$) in fullterm infants than in preterm infants based on postnatal ages. However, no differences were found when postmenstrual ages were compared ($P = 0.56$, 0.93, 0.99, 0.65, and 0.90 for stimuli in increasing cpd as above).

The mean (SD) postnatal ages of onset of OKN were 6 (0.3) weeks for fullterm and 13 (0.6) weeks for preterm infants when stripes moved from temporal to nasal and 19 (0.5) weeks for fullterm and 16 (0.6) weeks for preterm infants when stripes moved in the opposite direction. The mean (SD) postmenstrual ages of onset of the OKN were 46 (0.4) weeks for fullterm infants and 43 (0.5) weeks for preterm infants when stripes moved from temporal to nasal and 50 (0.5) weeks for fullterm infants and 49 (0.6) weeks for preterm infants when stripes moved in the opposite direction. The percentage of infants showing OKN to stripes moving in the two directions are shown in Figure 5. The onset of OKN in either direction was significantly earlier ($P \leq 0.0001$) in fullterm infants than in preterm infants of the same postnatal age. However, no statistically significant differences were found when postmenstrual ages were compared ($P = 0.64$) for temporal to nasal and $P = 0.74$ for nasal to temporal.
DISCUSSION

The present study demonstrates that all parameters reflecting visual acuity and binocular functions that we investigated show onset at similar ages in preterm and full-term infants when the comparison is based on age from conception.

These results indicate that at least with respect to visual functions, prematurity and the associated additional visual experience do not appear to confer a developmental advantage. However, our data only apply to low-risk preterm infants. Preterm infants born at gestational ages less than 34 weeks or with perinatal complications may show a different visual development. With our methods we could not confirm other studies suggesting an accelerated development of binocular vision. We are in agreement with studies showing no differences between gestational age of low-risk preterm and full-term infants. With regard to parameters of binocular vision, little was known about the influence of prematurity. To our knowledge, our present study is the first one to analyze parameters reflecting binocular vision in preterm infants compared with full-term infants. We could not document an acceleration of the development of ocular alignment, fusion, and convergence in premature infants. In contrast to Roy et al. who analyzed the gain (ratio of the velocity of the fast phase of the OKN and of the stimulus) of the OKN (another indicator of binocularity), we could not find differences in the OKN development between preterm and full-term infants. However, our evaluation was based on the onset of OKN and not on the gain.

Our results indicate that at least in the first 3 months of life, clinical examinations of premature born infants should be adjusted for the date of conception. Investigations of several developmental milestones showed that correction for prematurity should be applied during the first year of life. However, at 2 years of age the developmental milestones of the premature children were equal to or better than those of children born at term. With regard to visual function, the results of comparisons between premature and full-term children during the first year of life are inconclusive. Further studies investigating visual function at later ages than in our study would be interesting.

The large number of full-term infants we evaluated offered the opportunity to investigate the normal visual development in the first 3 months of life and to compare them to the results of other studies. Because mean refractive values of normal neonates were found to be hyperopic, we decided prospectively to exclude infants with cycloplegic refractive outside of a window of 0 ± 5 diopters. In this study we used tropicamide for cycloplegia. The cycloplegic effect of this drug is known to be only minimally less than cyclopentolate.

We demonstrated that ocular alignment based on observations of corneal reflections of a fixation light occurred in full-term infants at a mean age of 5 to 6 weeks after birth. Our results are in agreement with several other studies in which the same examination technique was used. Archer et al. investigated a large group of infants with the Hirschberg test and found the occurrence of orthophoria later than in our study. They found that approximately 50% of the infants were orthotropic at 2 months of age, whereas in our study at 2 months of age almost 100% were orthotropic. Differences may be explained by the difficulty in measuring ocular alignment with the Hirschberg test in children. In addition, we examined most children twice, and the "better result" (consisting of ocular alignment as opposed to strabismus) of the two examinations was taken for data analysis. This could also explain the earlier development of orthophoria in our study. In agreement with results of Archer et al., we found that most of the children were exotropic or orthotropic at 4 weeks of age. Therefore, a convergent squint at this age should raise a high suspicion of pathology and prompt close follow-up examinations.

We showed the first signs of convergence at a mean postnatal age of 4.8 weeks and of full convergence at a mean postnatal age of 7.4 weeks in full-term infants. These findings are in agreement with previous studies, which found systematic and reliable changes in convergence and accommodation to be present after 6 to 8 weeks postnatally. Thoen et al. on the other hand, found the onset of full convergence at a later age (13.7 weeks). Because Aslin showed that stimulus velocity influences convergence capability, differences in the velocity of the target approaching the infant's face may explain the different results.

Although the four prism base out test can be difficult to perform in infants, in our experience it was shown to have a good re-test reliability and reproducibility when performed by experienced examiners. We found a mean age of onset of fusion to be at 7.5 weeks after birth in full-term infants.
agreement with previous studies, we found the onset of fusion at an age similar to that of full convergence. However, we found the onset of convergence and fusion at an earlier age than the above-mentioned studies, in which investigators found a mean age of onset of fusion at 13.7 weeks of age. These differences may be explained by methodological differences. Fusion was investigated in those studies by preferentially looking at fixable versus movable gratings and in our study by the four prism base-out test. In addition, in our study we evaluated data that were the better result of two orthoptic examinations.

We demonstrated that visual acuity of 1.0 cnd measured by pursuit eye movement recordings is reached at a mean postnatal age of 11.2 weeks in full-term infants. Based on pursuit eye movement recordings, our results show a lower visual acuity than the average age-matched values measured with the preferential looking technique. This may be because of methodological differences. Visual pursuit was only considered present if the infant followed the stimulus for at least 6.2 seconds. However, no defined fixation time is required in the preferential looking technique. In addition, pursuit eye movements involve an oculomotor response that may be controlled at a different cortical level than preferential looking. Another method used to assess visual acuity in infants involving the oculomotor system is the determination of OKN eye movements. Although with this method stimulus-related variations are found, results are in a comparable range to those found in our study with pursuit eye movements.

The examination of the OKN confirmed the known asymmetry of monocular elicited OKN in infants younger than 3 months of age, appearing earlier in the temporoparietal direction. Most studies showed the OKN to become symmetrical at approximately 3 months of age. We found the mean onset of OKN if stimuli moved from nasal to temporal only at the beginning of the third month of age (mean postnatal age in full-term infants: 9.3 weeks). In the infants tested with OKN until 14 weeks of age, we observed still an obvious difference between the OKN response to stimuli from nasal to temporal direction and response to stimuli from temporal to nasal direction. With our method, the appearance of OKN of OKN asymmetry seems to be later than reported in the literature. This may be because of the fact that we used a smaller stimulation field, whereas full field stimulation was used in the studies above.

In conclusion, our results indicate that the development of parameters reflecting visual acuity and binocular vision is similar in healthy preterm and full-term infants, when infants of the same postnatal age are compared. Normative data obtained for full-term infants are an appropriate standard also
for preterm infants as long as the preterm infant's corrected age is used for comparison in the first months of life. Our results contradict the hypothesis that early visual experience gained by preterm infants positively influences the development of visual acuity or binocular functions.

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References


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