Cortical Visual Function in Preterm Infants in the First Year

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Objective To assess visual function in low-risk preterm infants at 3, 5, and 12 months corrected age to determine whether the maturation of visual function in the first year is similar to that reported in term-born infants.

Study design Seventy-five low-risk infants (25.0-30.9 weeks gestation) underwent ophthalmological examinations and a battery of tests (fix and follow, visual fields, acuity, attention at distance, and fixation shift) designed to assess various aspects of visual function at 3, 5, and 12 months corrected age.

Results The results were comparable with normative data from term-born infants in all tests but fixation shift, suggesting that maturation of most aspects of visual function is not significantly affected by preterm birth. In contrast, >25% of preterm infants failed the fixation shift test at 3 months, with a higher percentage of failing at 5 and 12 months.

Conclusions There is a specific profile of early visual behavior in low-risk preterm infants, with a high percentage of infants failing a test that specifically assesses visual attention and provides a measure of cortical processing. *(J Pediatr 2010;156:550-5)*.

There have been recent advances in the understanding of the development of vision in preterm infants with age-specific tests for evaluating different aspects of visual function.[1-5] Studies with preterm infants have mainly focused on ophthalmological findings and on retinopathy of prematurity (ROP).[3,6] Cortical aspects of visual function in preterm infants mainly have been assessed in infants with lesions, such as periventricular leukomalacia or intraventricular and parenchymal hemorrhage. Visual abnormalities are more frequent in infants with more severe lesions affecting the optic radiations and thalami.[1,7-9] A few studies have reported the development of visual function in low-risk preterm infants without major brain lesions.[10-12] We recently measured visual function at 35 and 40 weeks postmenstrual age in low-risk preterm infants.[10] Our results suggest that early extrauterine experience may accelerate the maturation of some aspects of visual function, such as ocular movements and vertical and arc tracking, because these responses were more mature in preterm infants at both 35 and 40 weeks than in term infants. Some aspects of visual development in the first year may be different in preterm infants than in term infants. Although cortical visual evoked potentials (VEPs) are similar in preterm and term infants,[13,14] visual attention as assessed with fixation shift appears to be less mature in preterm than in term infants.[14] Longitudinal data on development of the visual system are not available.

We performed a detailed longitudinal assessment of visual function, including assessment of visual attention in a cohort of low-risk preterm infants at 3, 5, and 12 months corrected age. We wanted to establish whether the maturation of more cortical aspects of visual function in the first post-natal year is similar to that reported in term-born infants. We also wanted to explain the correlation between visual attention and other aspects of visual and neurodevelopmental outcome.

Methods

Infants were recruited from the neonatal intensive care unit at Gemelli Hospital in Rome, Italy, from June 2004 to June 2006. Informed parental consent for the study was obtained for all infants.

Infants were consecutively enrolled when they were born between 25.0 and 30.9 (<31) weeks gestational age (GA) as determined from the results of first

DQ	Developmental quotient
GA	Gestational age
ROP	Retinopathy of prematurity
VEP	Visual evoked potential

From the Paediatric Neurology Unit (D.R., L.C., D.L., G.B., M.P., C.B., P.D.R., G.V., P.A., S.S., D.M.R., M.T., E.M.) and Neonatal Unit (F.G., F.S., F.C., C.R.), Catholic University, Rome, Italy; Division of Child Neurology and Psychiatry, Department of Paediatrics, University of Catania, Catania, Italy (D.M.R.); Department of Developmental Neuroscience, Stella Maris Scientific Institute, Pisa, Italy (F.T., G.C.); Ophthalmologic Unit, Catholic University, Rome, Italy (F.M., D.L., A.B.); Neonatal Unit, Ospedale Maggiore Policlinico, Mangiagalli, Fondazione IRCCS, Milan, Italy (L.R.); Department of Paediatrics and Imaging Sciences, Hammersmith Hospital, Imperial College, London, UK (F.C., E.M.); Visual Development Unit, University College, London, UK (J.A.); and Division of Child Neurology and Psychiatry, University of Pisa, Pisa, Italy (G.C.); Pediatric Neurology and Child Psychiatric Unit, Bambino Gesù Hospitale, Rome, Italy (P.A.)

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trimester ultrasound scans or when their cranial ultrasound scanning results were normal or only showed transient flares or germinal layer hemorrhages during the first 2 postnatal weeks and at term equivalent age had no parenchymal abnormality or evidence of atrophy (defined as ventricular dilatation with a ventricular index of >14 mm, irregular ventricular margins, widened interhemispheric fissure, or enlarged extracerebral space).[15]

Infants were not included when they were still oxygen-dependent at term-equivalent age, had major congenital malformations, had genetic or chromosomal abnormalities, had known metabolic disorders, had congenital infection or any sign of encephalopathy or seizures during the neonatal course, or were greater than stage 2 ROP at the time of the assessment.

Ophthalmological Examination

A complete ophthalmological examination was performed, consisting of a slit lamp examination of the anterior segment, cycloplegic refraction with an autorefractometer, dilated fundus examination, and an orthoptic evaluation that included a cover/uncover test and extraocular movement assessment in the 9 gaze positions. Presence or absence of horizontal deviations, vertical deviations, or both was noted, as was anomalous head posture.

Behavioural Assessment of Visual Function

We assessed aspects of visual function including acuity, visual fields, attention at distance, and fixation shift that are known to mature in the first post-natal year and are at least partially cortically mediated.

Ability to fix and follow was tested by observing the ability of the infant to fix on a colored target and to follow it horizontally, vertically, and in a full circle.

Binocular acuity was assessed by means of the Teller acuity card procedure.[16-18] This method is based on an inborn preference for a pattern (black and white gratings of decreasing stripe widths depicted on cards) over a uniform field. The location of the left/right position of the test stimulus varies randomly. An observer judges the infant's reaction to the location of the test stimulus on the basis of eye and head movement. The threshold of acuity is taken as the minimum stripe width to which the subject consistently responds. Acuity values were expressed in minutes of arc (or cycles per degree) and were compared with age-specific normative data.[19]

Attention at distance was tested by moving a colored toy (approximately 8-10 cm x 8-10 cm) backward in a small arc away from the child. The maximum distance at which the child kept attention on the toy was recorded. At 3 months post-term age, a child should keep attention on the toy at 3 meters.[20]

Binocular visual fields were assessed by using kinetic perimetry, as described by van Hof-van Duin.[19] The test apparatus consists of 2 4-cm-wide black metal strips, mounted perpendicularly to each other and bent to form 2 arcs, each with a radius of 40 cm. The perimeter is placed in front of a black curtain, concealing the observer, who can watch the infant's eye and head movements through a peephole. The child is held sitting or lying in the center of the arc perimeter, with the chin supported. During central fixation of a 6-degree diameter white ball, an identical target is moved from the periphery toward the fixation point, along 1 of the arcs of the perimeter, at a velocity of about 3 degrees. Eye and head movements toward the peripheral ball are used to estimate the outline of the visual fields. Age-specific normative data for full-term and preterm infants are available.[19]

Fixation shift test assesses visual attention by evaluating the direction and the latency of saccadic eye movements in response to a peripheral target (alternating black and white stripes) in the lateral field. With a 28-inch (70-cm) monitor, a central target was used as a fixation stimulus before the appearance of the peripheral target. In some trials, the central target disappeared simultaneously with the appearance of the peripheral target (non-competition); in other trails, the central target remained visible and created a situation of competition between the 2 stimuli.[21,22] Typically, term children can reliably shift their attention in a situation of non-competition during the first weeks after birth, but brisk re-fixations in a situation of competition is only reliably found after 12 to 18 post-term weeks. Normative data indicate that when providing 5 stimuli sequentially on each side for both non-competition and competition situations, by 3 months a normal response consists of at least 4/5 re-fixations in a non-competition situation. By 5 months, a normal response should consist of at least 4/5 re-fixations in both non-competition and competition situations. Fewer than 4/5 or delayed (a latency >1.2 seconds) re-fixation after 3 months (for non-competition) and after 5 months (for competition) are considered abnormal.[2,23, 24] Infants who did not complete the assessment were also scored as abnormal, because a negligible proportion of normal infants do not complete the assessment. However, these cases were classified separately from the infants who completed the assessment but had abnormal results.

Two pediatric neurologists (D.R. and L.C.) performed the visual assessments. The duration of the assessment was approximately 15 to 20 minutes. Both neurologists had experience in observing visual responses and had previously used the same tests in other cohorts. The senior examiner (D.R.) held training sessions with the other examiner to be sure that the assessment was performed similarly. There was >95% concordance between the senior examiner and the other observer.

The visual function assessments were performed at 3, 5, and 12 months in all infants, and the data were compared with age-specific norms collected from typically developing term-born infants that were previously used by our group and others[1,7-9,19-22,25] in studies on preterm and term-born infants with brain lesions.

Neurodevelopmental Assessment

All the infants were assessed at 12 months corrected age with the Griffith Mental Development Scales.[26] Developmental outcome was classified as normal when the developmental quotient (DQ) ≥85. All infants also were examined

neurologically with a structured assessment to evaluate cranial nerve function, posture, movements, tone, reflexes/saving reactions, and visual behavior.[27]

Statistical Analysis

Descriptive statistics were computed for variables of interest and included mean values and SDs of continuous variables and absolute and relative frequencies of categorical variables. Association between each visual item and age at assessment, GA, and stage of ROP were analyzed with the Fisher exact test. The level of significance was set at P value <.05. Data were analyzed with Stata software version 10 statistical package (StataCorp LP, College Station, Texas).

Results

Eighty-two infants fulfilled the inclusion criteria; 75 infants with a mean GA of 28.8 ± 1.2 weeks (range, 25-30 weeks), with a mean birth weight of 1174 ± 246 g (range, 490-1700 g) were assessed at 3 (median, 3.1 ± 0.2), 5 (median, 5.2 ± 0.3), and 12 (median, 12.2 ± 0.6) months corrected age. The infants had a normal results on a neurodevelopmental assessment at 12 months. The remaining 7 infants missed 1 of the 3 assessments and were not be included in the study. The infants were subdivided according to their GA at birth: 7 were born at 25 to 26 weeks, 10 were born at 27 weeks, 9 were born at 28 weeks, 26 were born at 29 weeks, and 23 were born at 30 weeks.

Ophthalmological Examination

Bilateral ROP was diagnosed in 29 of the 75 infants; 8 infants had stage 1 ROP in zone II, and 21 infants had stage 2 ROP in zone II. All cases had regression of the ROP with complete retinal vascularization. No eye had evidence of macular ectopia, disc dragging, or any macular pigmentary disturbance. Although the distribution of stage 1 ROP was equal in the different GA subgroups, stage 2 ROP occurred more commonly in the lower GA groups (Figure 1). Eye motility was normal for all GA groups; 5 infants had a mild strabismus, and only 1 of the 5 infants had ROP. There were no refractive errors.

Visual Function Assessment (Figure 2)

Fix and follow. At 3 months, 69 of the 75 infants (92%) were able to fix and follow the visual target in a complete horizontal and vertical arc and in a full circle. Another 3 infants (4%) could follow horizontally and vertically, but not in a circle, and the remaining 3 infants (4%) were able to follow only horizontally. At 5 and 12 months, all infants except 1 were able to fix and follow (>98%) in a complete horizontal and vertical arc and a circle.

Visual acuity. At 3 months, 73 infants (97%) had normal and 2 (3%) had abnormal visual acuity. At 5 and 12 months, the assessment of acuity could be completed in 74 and 71 infants, respectively, with >90% of infants achieving results within the reference range for age.

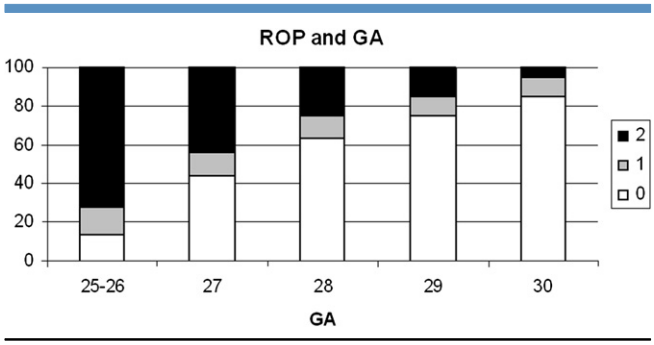

Figure 1. Distribution of ROP according to GA. GA given in weeks. ROP: 0 = no ROP; 1 = stage 1 ROP; 2 = stage 2 ROP.

Attention at distance. At 3 months, 65 infants (87%) showed normal attention at distance, and 10 infants (13%) showed abnormal attention at distance. At 5 and 12 months, all the infants had normal attention at distance.

Visual fields. At 3 months, 69 infants (92%) had normal symmetrical responses, and the other 6 infants (8%) had asymmetrical or abnormal results. Similar findings were observed at 5 and 12 months.

Fixation shift. Non-competition: At 3 months, 54 infants (72%) had normal results, and 21 infants (28%) had abnormal results. At 5 months, 43 infants (57%) had normal results, and 32 infants (43%) had abnormal results; at 12 months, 39 infants (52%) had normal results, and 36 infants (48%) had abnormal results. Competition: At 5 months, 17 infants (23%) had normal results, and 58 infants (77%) had abnormal results; and at 12 months, 23 infants (31%) had normal results, and 52 infants (69%) had abnormal results. The graphs in Figure 2 show details of the results, including the percentages of infants who were unable to complete the assessment and infants who completed the assessment but had abnormal results.

Neurodevelopmental Outcome

At 12 months corrected age, all the infants had normal developmental outcome and a normal neurological examination results.

Correlation with ROP

There was no significant association with the individual items at 3, 5, or 12 months to the presence or the stage of ROP. Both normal and abnormal results were found in all age groups with and without ROP.

Influence of GA

When we compared the results of the individual items at 3, 5, or 12 months to the GA, we did not find a significant influence of GA on the results of the visual assessment at the different ages.

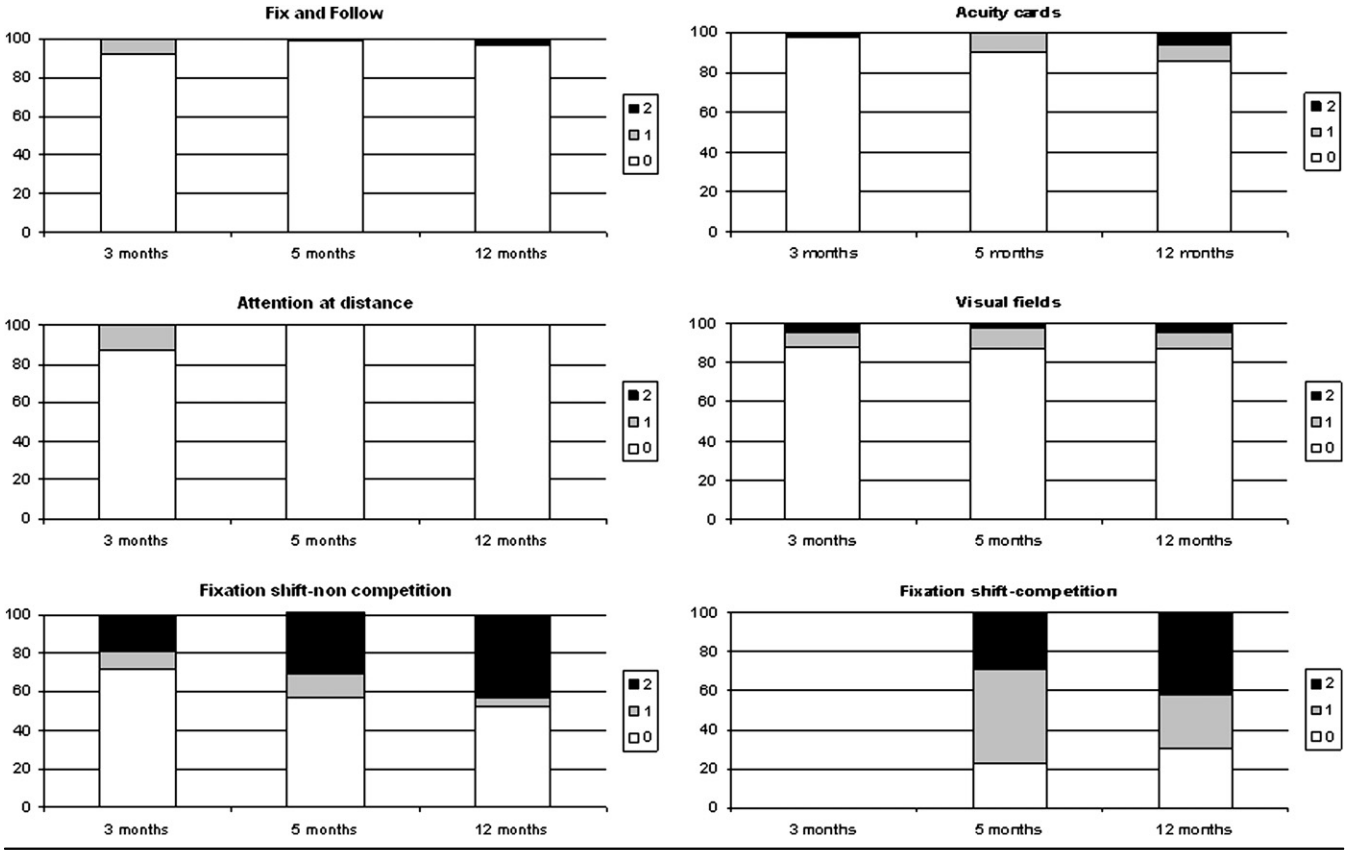

Figure 2. Details of visual function assessment at 3, 5, and 12 months. 0 = normal results; 1 = results outside the reference range; 2 = poor collaboration.

Discussion

In our preterm cohort, nearly all the aspects of vision that we assessed at 3, 5, and 12 months corrected age were within the normal reference range for term-born infants assessed at the same post-term age. More specifically, the ability to fix and follow, acuity, visual fields, and attention at distance had consistently normal results (>85%), suggesting that the maturation of these aspects of vision was not affected by preterm birth. These results are in agreement with earlier studies also showing that when adjusting for prematurity, acuity and visual fields in infants born preterm in their first post-natal year are similar to those obtained in full-term infants.[11,19,28]

The only test in which preterm infants showed different results compared with age-matched term-born normative data was fixation shift. By 3 months, low-risk term-born infants have achieved the ability to shift attention in a simple situation of non-competition, and by 5 months, 85%[23] of infants are able to shift the gaze even in a situation of competition. By performing serial assessments, we were able to demonstrate that the early abnormalities of fixation shift measured at 3 months were not caused by delayed visual maturation, because the number of infants with abnormal results further increased at 5 and at 12 months. However, in the children who did not pass the fixation shift test, a considerable number did not complete the assessment because they found it difficult to sit throughout the session or would not focus their attention on the screen for the duration of this part of the study. This was surprising because these children had been cooperative when examined for ocular movements and the ability to fix and follow, routinely performed before the assessment of the fixation shift, and were, immediately after, able to complete all the other assessments in the protocol, including the Griffith neurodevelopmental scales. The lack of attention was not related to the time when the assessment was performed because, when not completed, it was repeated at the end of the protocol with similar results.

This behavior is at variance with what has been reported when collecting normative data and from what we have observed in other infants examined at the same age, even in infants with other risk factors such as brain lesions[9,20-24] or craniosynostosis,[25] who generally complete the number of trials for both competition and non-competition, even when their results are not within the reference range.

We were also surprised that even in the infants who completed the fixation shift test, there was a relatively high number of infants who had abnormal results. Because nearly all the infants with abnormal results on fixation shift had

normal results on all the other visual tests and on the neurodevelopmental scales, these results suggest a specific problem with the mechanisms underlying the shift of attention. The abnormal fixation shift was also not related to GA or the presence of stages 1 and 2 ROP.

The ability to shift attention has been reported to be mediated by the superior parietal lobe and has been found to be impaired in patients who have undergone hemispherectomy for intractable epilepsy.[24] Postoperatively, these infants could shift gaze toward a target appearing in the peripheral field contralateral to the removed hemisphere when an initial central fixation target disappeared. However, they failed to disengage and fixate on the peripheral target when the central target remained visible, although they could do so toward a target in the intact visual field, reflecting the need for a cortical disengage mechanism.

The abnormal findings on the fixation shift test in our preterm cohort raises questions about early signs of attention deficits in children born preterm. Preterm infants have a higher risk of the development of attention deficits and visuo-perceptual and visuo-spatial problems at school age, and these problems can influence cognitive development independently from the presence of focal brain lesions.[29-30] Whereas at school and preschool age there are several tests assessing attention, it is much more difficult to detect early signs of attentional deficit in the first 2 years. Our results appear to suggest that fixation shift may provide early information on possible attentional deficits. But further studies with longer follow-up are needed to correlate the performance on fixation-shift test in the first year to cognitive and attentional development at preschool and school age, when more accurate and specific measures of attention can be obtained.

Our cohort underwent serial cranial ultrasound scanning examination from birth to 3 months corrected age, but this tool is not the most appropriate for detecting the wide range of less-severe lesions affecting the white matter of premature infants, such as "punctuate lesions" and DEHSI (diffuse excessive high-signal intensity).[1,31] Magnetic resonance imaging studies may have helped to establish whether some of the variability observed in our cohort may have an association with minor changes not detected on cranial ultrasound scanning. Even mild to moderate white matter injuries can be associated with increased risk of neurodevelopmental and neurosensory impairment during the first 2 years of age.[9,32] ■

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50 Years Ago in The Journal of Pediatrics

Early Recognition of Infantile Autism

Lewis SR, Van Ferney S. *J Pediatr* 1960;56:510-12

Infantile Autism

Bakwin H. *J Pediatr* 1960;56:584

As a pediatrics intern in Baltimore, I often passed by an oil painting of a dour, seemingly aloof gentleman, dressed in a dark suit. Only later as a neurologist did I learn that this lonely gentleman was Leo Kanner, who identified infantile autism in *The Journal* in 1944 as a syndrome of impaired reciprocal social interaction, abnormal communication, and restricted behaviors.

Sixteen years later in *The Journal*, Lewis and Van Ferney described a 6-month-old as "the youngest child ever reported to have infantile autism," even though "the condition is usually recognized at 3 to 4 years of age." The girl had a father characterized as "compulsive and rigid and states that all situations can be met with accurate scheduling." She exhibited a "reversal of the abnormal behavior when. . . separated from the mother and given active stimulation." Bakwin then opined, "The early recognition of infantile autism is the task of the physician who cares for children. . . . Whether a stimulating parent figure will prevent infantile autism, lighten its symptoms, defer its development, or be ineffective will be known only when physicians become alert to this unfortunate ailment and do something about it."

Was Bakwin right about early diagnosis? Yes. Identification can be made often by 15 to 18 months, not 3 to 4 years. Early recognition is essential, we believe, to provide targeted interventions and comprehensive management. Pediatricians must be vigilant to identify delayed social milestones deficits in joint attention. Even more simply, they can ask any parent, "Are you worried that your child is autistic?"

Were Kanner and then Bakwin correct that "children are genetically endowed with an inability to relate to persons in normal fashion and that this deviation is exaggerated further by the way they are handled by their parents"? Partly. We know that autism is largely genetic in origin, and not due to thimerosal, gluten, or many environmental exposures. But, as the diagnosis of autism shifts and increases in incidence, we await a more specific understanding of cause, as well as definitive data about which strategies best treat this malady. We hope to have these answers before another 50 years pass.

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