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Delayed visual maturation in infancy

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SUMMARY We describe the clinical and electrodiagnostic features of 8 infants who showed no visual responsiveness and were thought to be severely visually impaired on initial examination. Subsequently all children developed normal visual capabilities and the previously abnormal visually evoked potentials became normal. The clinical and electrodiagnostic features of these infants suggest that they suffered from a widespread cortical maturation delay.

In the past, the assessment of visual acuity in infants and preverbal children has been largely ignored owing to the difficulties of obtaining an objective, reproducible response that was quantitative as well as qualitative in nature. Data are now beginning to accumulate from the use of several different techniques that suggest that visual acuity can be assessed and quantitated objectively even in the neonatal period.[1–4] These techniques have been utilised to study the maturation of visual acuity in infants, and the results suggest that this process is much more rapid than was once thought.[2 4 5] It seems likely that a normal infant's visual system is capable of resolving a 20/20 (6/6) target by at least 18 months of age.

There is a group of normal infants who fail to show normal maturation of visual function in early infancy but who subsequently develop normal visual capabilities.[6 7] These children may present as a diagnostic dilemma, since they appear to be severely visually impaired, with no apparent ocular abnormality. We report herein the clinical and electrodiagnostic features of 8 infants who appeared to be blind in early infancy but subsequently developed normal visual capacity. We discuss the factors that contribute to the normal delay in visual maturation in infants as well as those most likely to be important in infants with pathologically delayed visual maturation.

Subjects and methods

Eight infants have been seen at the University of California Medical Center from July 1979 to September 1981 who initially appeared to have poor visual function but subsequently showed normal visual capacity. During that same period 67 infants with severe visual loss were examined and studied electrodiagnostically. Clinical examination of these infants included assessment of fixation and following reflexes, presence or absence of nystagmus, pupillary light reflex, vestibulo-ocular response, external examination of the eyes, and ocular fundus examination by direct ophthalmoscopy following cycloplegics and refraction.

Electrodiagnostic studies were performed in all infants. Electroretinograms (ERG) were performed with Burian-Allen contact lens electrodes and a Grass Model P.S. 22 Photostimulator. Photopic examinations were performed with White 1 and White 8 single-flash stimuli each lasting 20 ms and separated by at least one-minute intervals. Scotopic examinations were obtained with the White 1 stimulus after 20 minutes of dark adaptation.

Visually evoked potentials were elicited with a pattern onset-offset presentation. Two carousel projectors were focused on a retroilluminated screen subtending 20° at 1·14 m. One projector had a neutral density (ND) filter of 50% transmittance (Wratten filter 96, 0·3 ND) and provided a diffuse, non-patterned field for 710 ms. The second projected a checkerboard for 40 ms to provide the onset-offset pattern of the same average luminance as the diffuse field did without the pattern. Presentation of the pattern initiated averaging for 64 iterances. The active electrode was at the occiput (OZ) referenced to the right mastoid area, with the left mastoid area serving as ground. Signals were amplified by 2 preamplifers (Grass P-15) in cascade, with the high- and low-frequency half-amplitude cut-off at 30 and 1 Hz, respectively. Total preamplification was typically 10^5.

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Table 1 *Clinical history of infants with delayed visual function*

Patient	*Sex*	*Age at first exam.*	*Age at which normal vision apparent*	*Gestational history*	*Motor development*
1	Male	7 weeks	37 weeks	Premature	Delayed
2	Male	5 weeks	26 weeks	Small for gestational age	Delayed
3	Female	8 weeks	41 weeks	Normal	Normal
4	Male	6 weeks	29 weeks	Small for gestational age	Delayed
5	Female	11 weeks	31 weeks	Normal	Delayed
6	Female	6 weeks	39 weeks	Small for gestational age	Delayed
7	Male	7 weeks	44 weeks	Small for gestational age	Delayed
8	Male	9 weeks	28 weeks	Small for gestational age	Delayed

Electroencephalograms were monitored on a cathode-ray oscilloscope, and the visually evoked potential (VEP) was averaged with a special purpose digital computer (Nicolet 527).

Eye position of patients was monitored directly by the experimenter. If patients turned their eyes away from the screen, became fussy, cried, or fell asleep, averaging was stopped and resumed only when the patient was looking in the direction of the screen.

Results

This study included 5 males and 3 females who were first examined between 5 to 11 weeks of life (Table 1). Although all of these infants failed to demonstrate visual responsiveness initially, normal function was noted by 26 to 44 weeks of age. General delays in motor development were observed in 7 of the 8 patients, and 6 had been premature or small for gestational age at birth.

The clinical and electrodiagnostic features of these children are summarised in Table 2. Only one patient showed nystagmus and the same patient had sluggish pupillary reflexes. Abnormal vestibulo-ocular reflexes were seen in 6 of the 8 patients. Although the ERG was normal in all patients the visually evoked response (VER) was not. The VER was absent in one patient and significantly attenuated in all others. The latency measurement ranged from 100 to 200 ms and the amplitude from 3 to 10 μV.

Discussion

The absence of visual responsiveness in a baby of more than 4 weeks old has to be taken seriously and warrants careful investigation. The importance of early identification of serious visual disability is important for both rehabilitation reasons and genetic counselling.[8] However, an incorrect diagnosis of visual impairment in an infant can be devastating to the family. The 8 infants described in this report all appeared to be visually unresponsive on initial examination but subsequently developed normal visual capabilities. They appear to be a group of normal infants in whom an abnormal delay in visual maturation mimics serious visual impairment.

Several different subsystems within the visual system account for the normal delay in visual function in infancy. These include portions of both the sensory and motor systems.

The retina undergoes considerable structural and functional change postnatally. Rods and cones are distinguishable 15 weeks prior to birth, but cones within the central retina do not attain adult-like

Table 2 *Findings of infants with delayed visual maturation*

Patient	*Nystagmus*	*Pupils*	*Vestibulo-ocular response*	*VER*		*ERG*
				Latency	*Amplitude*	
1	No	Reactive	No fast phase	100 ms	5 μV	Normal
2	No	Reactive	Normal	160 ms	3 μV	Normal
3	No	Reactive	No fast phase	175 ms	5 μV	Normal
4	No	Reactive	No fast phase	175 ms	4 μV	Normal
5	No	Reactive	No fast phase	160 ms	10 μV	Normal
6	Intermittent	Sluggish	Normal	Absent	Absent	Normal
7	No	Reactive	No fast phase	200 ms	3 μV	Normal
8	No	Reactive	No fast phase	150 ms	5 μV	Normal

dimensions until at least 4 months after birth.[9] On the other hand there is considerable evidence from electroretinographic[10–12] and psychophysical studies[13 14] to show that the central cones are functionally quite competent, if not fully mature, at birth. A longer than normal delay in foveal development could play a role in the apparently 'blind' infants reported on here, since a normal electroretinogram does not rule out selective foveal underdevelopment. However, these infants appear to be much more handicapped than can be accounted for by isolated foveal dysfunction.

Although it has been stated that the anterior visual pathway is completely myelinated within the first month of life,[15 16] more recent studies contradict this view.[17] By term some fibres in the optic nerve near the globe are beginning to become myelinated, but the amount of myelin surrounding individual nerves increases dramatically during the ensuing months and may continue to increase up to the age of 2 years.[17] There can be no question that this extended period of myelination must be reflected in the normal delay of visual maturation. It is noteworthy that the latency of the first wave of visually evoked potentials is not adult-like until 3 years of age when tested with small pattern elements.[18] Beauvieux reported 3 cases of apparent blindness in infancy with a peculiar black colouration of the optic discs.[19] These infants subsequently developed normal visual function and normal appearing optic nerves. Beauvieux postulated that these observations were compatible with an exaggerated delay in myelination of the anterior visual pathway. We have not noted similar ophthalmoscopic changes in any of our patients. Furthermore it would seem unlikely that the appearance of the optic nerve head would change with additional myelination.

The latency of the first wave of the visually evoked potentials was mildly prolonged in some of the infants reported here. Yet the delays were not so large as to imply that delayed myelination is the major factor responsible for the delay in acquisition of visual responsiveness. Moreover, the pupillary responses were brisk in all but one of the infants when first examined. It is also important to stress that the rate of myelination appears to be hastened by several factors, including exposure to light.[7] Thus a preterm baby on reaching his expected date of delivery will have more advanced myelination than a newly born term infant. This may account for the relatively short latency of the visually evoked potential of patient number one.

Cortical neuronal dendritic growth and synaptic formation begins at 25 weeks of gestational age, is very active around the time of birth, and continues into the first two postnatal years.[7] There are conflicting reports of the proportion of visual cortical cells in experimental animals that have normal functional properties at birth. The presence of cells with adult types of functions have been found in neonatal kittens[20 21] and monkeys.[22] In human infants the maturity of the visually evoked potential has been correlated with the degree of dendritic formation, as shown by post-mortem golgi preparations in preterm infants of 25 to 33 weeks of gestational age.[23] Delayed dendritic and synaptic formation in the visual cortex could explain both the clinical and electrophysiological findings in the infants we describe here.

The ability to fixate and 'follow' a target is one of the principal tests employed to assess central visual function in infants. Despite many misconceptions that state the contrary one can demonstrate visual fixation in most newborn infants if appropriate targets are used.[24 25] If the infant does not 'follow' a visual target it must be ascertained whether the infant has the ability to generate the appropriate eye movements necessary. One should not expect a young infant to follow a target with smooth pursuit eye movements but rather with coarse, jerky, hypometric saccades.[26] Saccadic eye movements can be generated in all normal full-term infants of 7 days or older as a result of vestibular stimulation.[27] If the infant fails to develop nystagmus with a fast phase in response to perotatory stimulation, it must be concluded that the infant is incapable of generating saccadic eye movements. In this situation the patient may appear to be blind owing to the inability to develop normal oculomotor reflexes. It is noteworthy that 6 of the 8 infants studied by us failed to develop nystagmus with a fast phase when rotated at the time of the initial examination. Subsequently all infants showed normal vestibulo-ocular reflexes.

We believe that the clinical and electrophysiological features of the 8 infants described here can be explained as a result of widespread maturational delay of cortical function. Six of the 8 infants were either small for their gestational age at birth or premature. Seven of the 8 had obvious delays in general motor development at presentation. Six of the 8 could not generate saccadic eye movements initially. In all of the patients a normal ERG was recorded and an attenuated VER with only mild abnormalities in latency measurements. One should be cautious when evaluating young infants with poor visual function who were premature or small for gestational age, show generalised delays in motor function, and fail to develop nystagmus with a fast phase in response to perotation. Although it may require electrodiagnostic studies to be certain, one should suspect that a maturational delay is responsible, and the long-term prognosis for development of good visual function is excellent.

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References

1 Atkinson J, Braddick O, Moar K. Development of contrast sensitivity over the first three months of life in the human infant. *Vision Res* 1977; **17:** 1037–44.

2 Dobson V, Teller DY. Visual acuity in human infants: a review and comparison of behavioral and electrophysiological studies. *Vision Res* 1978; **18:** 1469–83.

3 Dobson V. Behavioral tests of visual acuity in infants. *Int Ophthalmol Clin* 1980; **20:** 233–50.

4 Fulton AB, Hansen RM, Manning KA. Measuring visual acuity in infants. *Surv Ophthalmol* 1981; **25:** 325–32.

5 Marg E, Freeman, DN, Peltzman P, Goldstein PJ. Visual acuity development in human infants: evoked potential measurements. *Invest Ophthalmol Visual Sci* 1976; **15:** 150–3.

6 Illingworth RS. Delayed visual maturation. *Arch Dis Child* 1961; **36:** 407–11

7 Mellor DH, Fielder AR. Dissociated visual development: electrodiagnostic studies in infants who are 'slow to see'. *Dev Med Child Neurol* 1980; **22:** 327–35.

8 Jan JE, Freeman RD, Scott EP *Visual impairment in children and adolescents*. New York: Grune and Stratton, 1977: 53.

9 Hollenberg MJ, Spira AW. Human retinal development: ultrastructure of the outer retina. *Am J Anat* 1973; **137:** 357–77

10 Winkleman JE, Horsten GPM. The ERG of premature and full-term born infants during the first days of life. *Ophthalmologica* 1962; **143:** 92–101.

11 Horstein GPM, Winkleman JE. Electrical activity of the retina in relation to histological differentiation in infants born prematurely and at full-term. *Vision Res* 1962; **2:** 269–76.

12 François J, DeRouck A. The electroretinogram in young children (single stimulus, twin flashes and intermittent stimulation). *Doc Ophthalmol* 1964; **18:** 330–43.

13 Lewis TL, Maurer D, Kay D. Newborns' central vision: whole or hole? *J Exp Child Psychol* 1978; **26:** 193–203.

14 Lewis TL, Maurer D. Central vision in the newborn. *J Exp Child Psychol* 1980; **29:** 475–80.

15 Sattler CH. Über die Marscneiden-entwicklung in tractus opticus: Chiasms und nervus opticus. *Albrecht von Graefes Arch Klin Ophthalmol* 1915; **90:** 271–98.

16 Cravioto H. Electron microscopic studies of the developing human nervous system. II. The optic nerves. *J Neuropathol Exp Neurol* 1965; **24:** 166–77.

17 Magoon EH, Robb RM. Development of myelin in human optic nerve and tract. A light and electron microscopic study. *Arch Ophthalmol* 1981; **99:** 655–9.

18 Harter MR, Deaton FK, Odom JV. Maturation of pattern visual evoked potentials and visual performance in 6–45 day old infants: effects of check size, visual acuity, and refractive error. *EEG Clin Neurophysiol* 1977; **42:** 595–601.

19 Beauvieux J. La pseudo-atrophie optique des nouveau-dès (dysgénésie myélinque des voies optiques). *Ann Oculist* 1926; **163:** 881–921.

20 Hubel DH, Wiesel TN. Receptive fields of cells in striate cortex of very young, visually inexperienced kittens. *J Neurophysiol* 1963; **26:** 994–1008.

21 Sherk H, Stryker MP. Quantitative study of cortical orientation selectivity in visually inexperienced kittens. *J Neurophysiol* 1976; **39:** 63–74.

22 Wiesel TN, Hubel DH. Ordered arrangement of orientation columns in monkeys lacking visual experience. *J Comp Neurol* 1974; **158:** 307–18.

23 Purpura DP. Structure-dysfunction relations in the visual cortex of preterm infants. In Brazier MAB, Coceani F, eds. *Brain dysfunction in infantile febrile convulsions*. New York: Raven Press, 1976: 223–30.

24 Ling B. Genetic study of sustained fixation and associated behavior in the human infant from birth to six months. *J Genet Psychol* 1942; **61:** 227–40.

25 Goren CC, Sarty M, Wand-Wu PYK. Visual following and pattern discrimination of face-like stimuli by newborn infants. *Pediatrics* 1975; **56:** 544–9.

26 Ablin RN, Salapatek P. Saccadic localization of peripheral targets by the very young human infant. *Percept Psychophys* 1975; **17:** 293–302.

27 Eviatar L, Miranda S, Eviatar A, Freeman K, Borkowski M. Development of nystagmus in response to vestibular stimulation in infants. *Ann Neurol* 1979; **5:** 508–14.