

ORIGINAL ARTICLES

Visual function and perinatal focal cerebral infarction

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Abstract

Aims—To evaluate the visual function of infants with perinatal cerebral infarction in whom the site and size of the lesion has been determined using magnetic resonance imaging (MRI).

Methods—Twelve infants with cerebral infarction on MRI were studied with a battery of tests specifically designed to evaluate visual function in infancy. This included tests: for visual attention (fixation shifts); of cerebral asymmetry (optokinetic nystagmus, visual fields); for assessment of acuity (forced choice preferential looking); and neurophysiological measures of vision (phase reversal and orientation reversal visual evoked potential).

Results—A considerable incidence of abnormalities on at least one of the tests for visual function used was observed. The presence or severity of visual abnormalities could not always be predicted by the site and extent of the lesion seen on imaging.

Conclusions—Early focal lesions affecting the visual pathway can, to some extent, be compensated for by the immature developing brain. These data suggest that all the infants presenting with focal lesions need to be investigated with a detailed assessment of various aspects of vision.

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Cerebral infarction in neonates is typically described as a focal lesion involving both grey and white matter caused by ischaemic or haemorrhagic events.¹ The advent of brain imaging has dramatically increased the identification of these lesions in vivo, providing better information about their aetiology, incidence, and extent. Haemorrhagic strokes in neonates are extremely rare and the commonest finding is that of ischaemic infarction sometimes occurring with haemorrhage within the infarcted tissue. The incidence of all infarctions in term newborns has been estimated to be around 1 in 10 000 children,² while their detection in preterm infants is rare.³ The left hemisphere is three times more likely

to be affected than the right, and the middle cerebral artery is the most common site.⁴

Several studies have reported the effects of cerebral infarction on visual function in adults. Acquired lesions involving the striate cortex in the occipital lobe usually result in hemianopsia, with loss of the visual field contralateral to the lesion. In contrast, adult patients with more anterior lesions involving the parietal lobe show neglect syndrome. These patients are not blind but have difficulties in shifting attention to objects presented in the contralateral field and, in the most severe situations, ignore the contralateral part of their body.⁵⁻⁷ No systematic study has been done to evaluate the effect of a neonatal cerebral infarction on the development of visual function in the developing brain.

The aim of this study was to investigate a cohort of infants with neonatal cerebral infarction by using a combined magnetic resonance imaging (MRI) and behavioural approach, including a battery of tests specifically designed for evaluating visual function in infants. More specifically, we wished to evaluate: (1) the incidence of visual abnormalities including neglect; and (2) the correlation between behavioural data and site and size of lesions on MRI.

Methods

This study is part of an ongoing longitudinal study aimed at evaluating the development of visual function in infants with focal perinatal infarction on neonatal MRI. The children recruited in this study were born at, or referred soon after birth, to the Hammersmith Hospital, London, between October 1991 and July 1995. All were born at term of an uncomplicated pregnancy, had normal Apgar scores, and were thought to be neurologically normal. Most infants were initially on the postnatal ward with their mothers. In all these infants the infarction was detected on imaging following the onset of convulsions in the first days of life.

CLINICAL ASSESSMENT

Details of prenatal and perinatal history were obtained from the obstetric and paediatric records for each patient. Assessment of outcome included serial neurological examination recorded on standardised proforma, and the use of the Griffiths developmental scales.⁸

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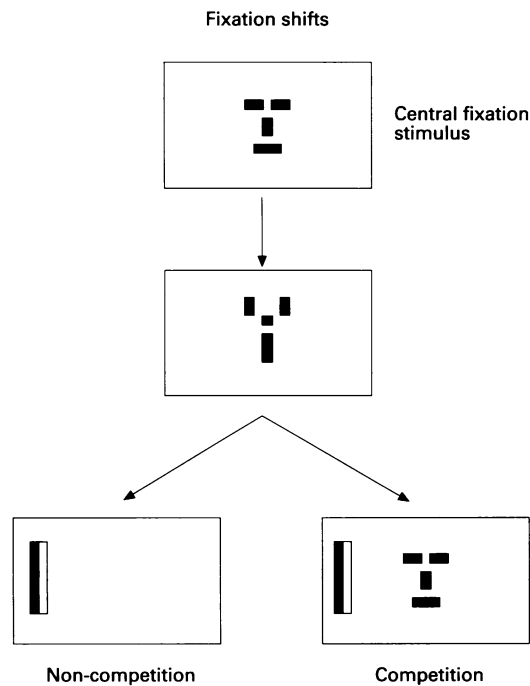


Figure 1 Fixation shift test: representation of central stimulus and peripheral target in non-competition and competition situations.

ASSESSMENT OF VISUAL FUNCTION

This was evaluated by using the Atkinson Battery of Child Development for Examining Functional Vision (ABCDEFV).^{9, 10} This includes assessment of orthoptic status (ocular movements, pupil response), refractive errors, and the following tests:

Acuity—This was tested by using forced choice preferential looking. This method is based on the inborn preference to look at a patterned field rather than a homogeneous field. Stimuli consist of square wave gratings (black and white stripes) of varying spatial frequencies, displayed at two locations at the eye level of the infant on either side of the midline. The infant, seated on the holder's knee, is presented with

one patterned stimulus and one unpatterned stimulus, matched for luminance. The observer, who is unaware of which side the patterned stimulus has been presented, views the infant's face through a peephole, making a forced judgment on the side preferentially fixated by the infant. Acuity is measured as the finest grating for which the infant show a consistent preference.

Optokinetic nystagmus (OKN)—Binocular OKN was elicited using a large monitor (52 x 38 cm) displaying a computer generated random dot pattern at 20 cm from the front of the infant's eyes. This pattern could be moved laterally (velocity 10-25 degrees/second) The examiner observed the infant's eye movements, recording the presence and the symmetry in ease of generation of the OKN.

Visual fields—These were tested by gradually moving a small white ball (a Stycar ball of 40 mm in diameter) from 90 degrees laterally inwards towards the child's midline at an approximate velocity of 15 degrees/second. The observer was positioned centrally in front of the child and attracted his attention before the ball was moved. Eyes and head movements of the infant were observed to estimate the border of the visual fields and their symmetry.

Fixation shift—This was tested evaluating the direction and latency of saccadic eye movements in response to the onset of peripheral visual targets in the lateral field. The infant, seated on the holder's lap, was turned to face a large monitor at a distance of 40 cm. The stimuli used were computer generated monochrome patterns consisting of one cycle of square wave gratings (black and white stripes) that phase reversed at a rate of six reversals/second and were randomly shown in the right or left part of the screen.

A central target consisting of a high contrast schematic face, blinking also at a frequency of six reversals/second, was used as a fixation

Table 1 Visual findings in children with cerebral infarction

Case No	Age	Orthoptic status	Acuity	OKN	Fields	Fixation shift	VEP	Global outcome
1	5 m	Alternate strabismus	Normal	Normal	R field narrower	Poor competition/ non-competition R	PH 8rps normal, OR 8rps normal	12 m: normal
2	5 m	Normal	Normal	Normal	Neglect R field	Poor competition R	PH 8rps normal, OR 8rps normal	10 m: normal
3	5 m	Normal	Normal	Normal	R field narrower	Poor competition R	PH 8rps not significant, OR 8rps not significant	18 m: asymmetry of tone (reduced on the R)
4	5 m	Normal	Normal	Normal	Normal	Poor competition bilateral	PH 8rps normal, OR 8rps not significant	18 m: normal
5	7 m	Normal	Normal	Normal	Normal	Normal	PH 8rps normal, OR 8rps not significant	18 m: mild hemiplegia
6	10 m	Normal	Normal	Normal	Normal	Slower competition R	Not done	18 m: normal
7	10 m	Normal	Normal	Normal	Normal	Poor competition R	PH 8rps normal, OR 4 rps normal, 8 not significant	21 m: normal
8	14 m	Normal	Normal	Normal	Normal	Normal	Not done	2 y: normal
9	2 y, 8 m	Normal	Normal	Normal	Normal	Normal	Not done	3 y: moderate hemiplegia
10	3 y	Normal	Normal	Normal	Normal	Normal	Not done	3 y: normal
11	3 y, 8 m	Normal	Normal	Normal	R field narrower	Normal	PH 8rps normal, OR 4 rps normal, 8 not significant	4 y: mild hemiplegia
12	4 y, 2 m	Normal	Normal	Normal	Normal	Normal	Not done	4 y: moderate hemiplegia, speech delay

(m = months; y = years; OKN = optokinetic nystagmus; R = right; L = left; PH = phase reversal; OR = orientation reversal; rps = reversals per second).

Table 2 MRI findings in children with cerebral infarction

Case No	Age at MRI	Side	Cortex	Primary visual cortex	Optic radiations	Basal ganglia	Brainstem
1	5 m	L	P	Normal	L +	Lcyst	Normal
2	4 m	L	FP/PO	L + +	L + +	Normal	Normal
3	5 m	R	FPO	Normal	R + +	R: lentiform, L: PLIC	Normal
4	8 m	L	P	Normal	Normal	Normal	Normal
5	10 m	L	P	Normal	L +	Normal	Normal
6	10 m	L	PO	L + +	L + +	Normal	Normal
7	1 y	L	PO	Normal	L +	Normal	Normal
8	14 m	L	P	Normal	Normal	Normal	Normal
9	2 y, 6 m	Bilateral L > R	R: P, L: PO	Normal	L +	L: thalamus, L: PLIC	Normal
10	2 y	R	FP	Normal	Normal	Normal	Normal
11	3 y	L	TFPO	L +	L + +	Lentiform thalamus	Abnormal
12	2 y	Bilateral L > R	R: P, L: TFPO	Normal	Normal	Lentiform	Abnormal

(m = months; y = years; L = left; R = right; P = parietal; N = normal; F = frontal; O = occipital; T = temporal; PLIC = posterior limb internal capsule).

stimulus before the onset of the peripheral target, and as a competition stimulus in addition to it. The stimulus sequence was determined by the computer. In some trials the central target disappeared simultaneously with the appearance of the peripheral target (non-competition) while in others the face target remained visible when the peripheral target appeared on the monitor (competition) (fig 1). A total of 20 stimuli (five on the right and five on the left for both competition and non-competition) were provided in a random sequence for each infant. The examiner, unaware of the site of the presentation of the peripheral pattern, observed on a monitor the face of the infant, recording the direction and the time of onset of the ocular movements using a hand operated switch. The results were evaluated looking for the number of correct refixations, and the mean latency for each of the four series of five responses was recorded. According to the distribution of the results obtained in a normal population in the Visual Development Unit, by 12 and 15 weeks of age, all normal children show brisk refixations,^{9 10} and the results were classified as:

- (i) *poor* if less than four correct refixations were recorded in any of the series of five stimuli;
- (ii) *slow* if the mean latency to make a fixation was longer than 1.5 seconds;
- (iii) *asymmetrical* if the difference between the right and left mean latency was more than 0.5 seconds

Orientation reversal and phase reversal visual evoked potentials (VEP)—These were measured recording on the surface of the scalp brain activity in response to selected stimuli. The recording electrode was placed in Oz, the reference at Fz, and the earth electrode on the vertex. Stimuli consisted of oblique square wave gratings (black and white stripes) at a spatial frequency of 0.52 cycle/degree, presented on a video monitor at a distance of 30 cm. For orientation reversal VEP, 90 degree

changes between opposite oblique orientations were embedded in a sequence of random phase shifts. For phase reversal VEP, the orientation of the gratings was fixed but their contrast was periodically reversed. The orientation reversal VEP reflects a more advanced level of cortical visual processing than the phase reversal.¹¹ Both orientation and phase reversal VEP were tested at a temporal frequency of eight reversals/second and, if no significant response was found at this frequency, the test was repeated using four reversals/second. The signal of at least 250 sweeps was averaged for each test. The results were analysed using a circular variance test of the consistency of signal phase.¹²

According to the distribution of the results obtained in a normal population in the Visual Development Unit, more than 90% of normal children show significant responses for both orientation or phase reversal VEP by 12 and 15 weeks of age.⁹⁻¹⁰ The absence of a significant response from this age onwards has to be regarded as abnormal.

MAGNETIC RESONANCE IMAGING (MRI)

MRI was performed using a Picker 1.0T HPQ system, using T1 and T2 weighted spin echo (SE) and age related inversion recovery (IR) sequences in the transverse plane. All the infants had neonatal and serial imaging performed by 6 and 12 months at least. Only the scan closest in time to the visual assessment were considered in this study.

Lesions were recorded by the consensus of two observers looking for the location and the extent of the infarction, paying particular attention to the involvement of the primary visual cortex and optic radiation.

Results

Twelve children (seven boys, five girls) with predominant unilateral cerebral infarction were selected for this study. Their age ranged from 5 months to 4 years and 2 months.

Orthoptic assessment—Eleven of the 12 children studied had normal ocular movements, one had alternating strabismus.

Vidorefractometry—All the 12 children had normal refraction.

Acuity—All the 12 children had normal acuity. *Optokinetic nystagmus*—All the 12 children showed normal and symmetrical OKN.

Visual fields—Eight of the 12 children showed

Table 3 Correlation between MRI changes and visual findings

MRI	Acuity	OKN	Fields	Fixation shift	VEP
Parietal (P) only (n=4)	oooo	oooo	oooo	oooo	●—
P + optic radiation (OR) (n=5)	ooooo	ooooo	●oooo	●oooo	●●—
P + OR + primary visual cortex (n=3)	ooo	ooo	●●	●●	●●

(VEP = visual evoked potentials; OKN = optokinetic nystagmus; o = normal; ● = abnormal; - = not performed).

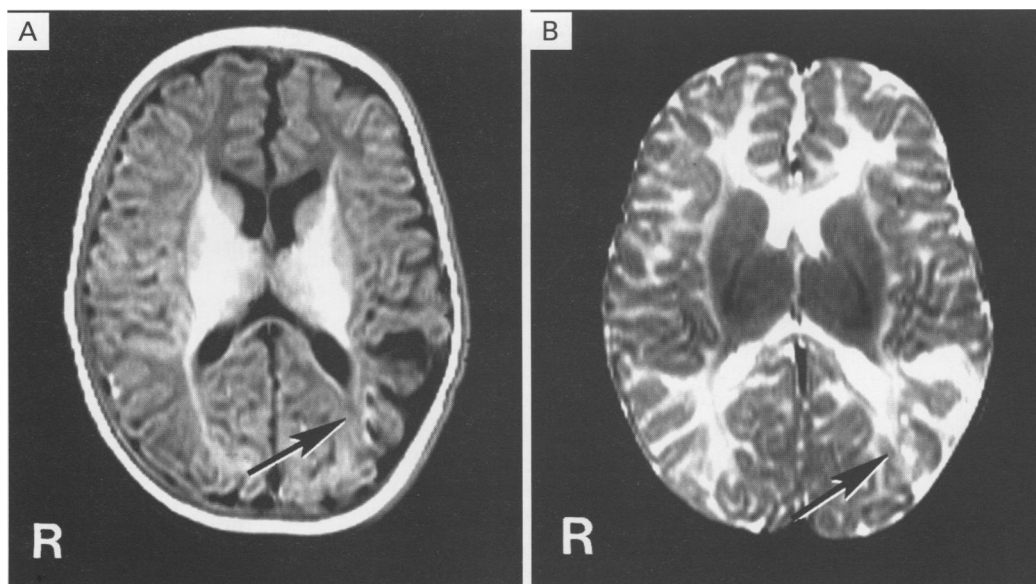


Figure 2 Boy aged 10 months with a left posterior parietal infarction. Transverse inversion recovery (IR 3800/80/800) sequence (A) and T2 weighted spin echo (SE 2700/120) sequence (B). The lesion is seen as low signal in A and increased signal in B. Involvement of the occipital radiation is also noted (arrow) compared with the contralateral side.

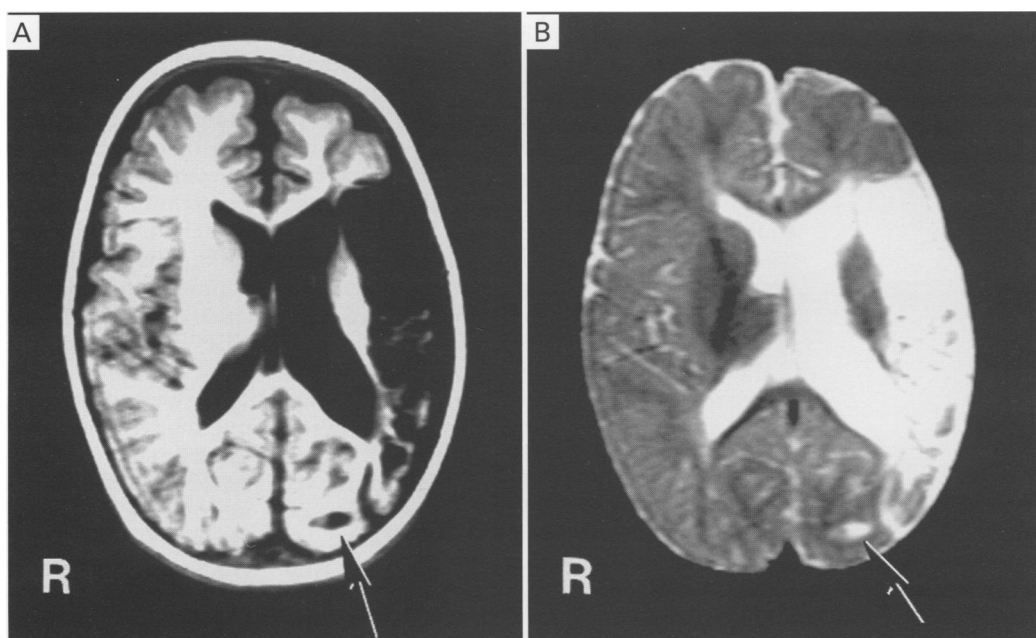


Figure 3 Boy aged 2 years. transverse inversion recovery (IR 3400/30/700) sequence (A) and T2 weighted spin echo (SE 2700/120) sequence (B). Left cerebral infarction is seen as low signal in A and increased signal in B. Part of the ipsilateral occipital radiation is missing and a lesion is also seen in the primary visual cortex (arrow).

normal and symmetrical visual fields, four showed field loss, which was partial in three of the four, and complete in one.

Fixation shift—Six of the 12 children showed normal and six abnormal fixation shift. The abnormal responses were unilateral in five of the six and bilateral in one.

Orientation reversal and phase reversal VEP—Because of lack of co-operation in some of the older infants, VEPs were performed in only seven of the children. They were normal in two and abnormal in the remaining five.

Details of the clinical findings are shown in table 1.

MRI

Eleven of the 12 infants had evidence of focal infarction in the territory of a major cerebral artery. This involved the middle cerebral artery

in 10 and the posterior cerebral artery in one. One child (case 2) showed a unilateral but bifocal lesion, involving the frontal and anterior parietal lobes and the posterior parietal and occipital lobes. Details of the site and extent of the lesions are shown in table 2.

Details of the correlation between visual findings and MRI changes are shown in table 3.

MRI changes and fixation shift

All 12 children had some involvement of the parietal lobe. Four of these had isolated parietal involvement, but a normal primary visual cortex and optic radiations. Three of the four had a normal and one an abnormal fixation shift. Five children, also had lesions in the optic radiation (fig 2): two of the five had normal and three an abnormal contralateral fixation shift. Three children had parietal

involvement and lesions in both the primary visual cortex and the optic radiation (fig 3): one of these had normal and two abnormal contralateral fixation shift.

MRI changes and visual fields

All the four children with a normal primary visual cortex and optic radiations had normal fields. Three children showed involvement of both the primary visual cortex and optic radiations: one of the three showed normal fields and the other two contralateral field loss. Five children had involvement of the optic radiation only: three of the five had normal and two abnormal fields which were contralateral to the lesion in one but ipsilateral in the other.

VEPs were abnormal in five of the seven children in whom they were recorded, although no specific association was found with the extent of the lesion.

Discussion

Several studies have investigated the correlation between unilateral cerebral infarction and neuromotor outcome.¹³⁻¹⁹ Although the incidence of sequelae varied because of different selection criteria and methodology, all these studies reported a low incidence of hemiplegia, suggesting that the effect of an early unilateral brain lesion can be compensated for by the plasticity of the developing brain. This has been further confirmed by the fact that, unlike adults with acquired lesions, children with congenital unilateral lesions do not always show impairment of lateralised functions such as language or visuo-spatial abilities in relation to the side of hemispheric injuries.

Using a battery of tests specifically designed to evaluate visual function in infants we were unable to show a constant association between involvement of the visual structures and abnormal function of the kind observed in adults, yet we observed a considerable incidence of visual abnormalities. Narrower unilateral visual fields were found in two thirds of the children who showed involvement of both the primary visual cortex and the optic radiation while the incidence was lower in children with involvement of the optic radiation alone.

None of our children showed abnormal acuity, irrespective of the extent of their unilateral lesions. This agrees with previous studies reporting normal acuity in infants with unilateral involvement of the optic radiation and primary visual cortex on MRI.^{20 21}

Although adult and animal studies implicate the parietal lobe in controlling shifts of visual attention,^{7 22-24} we found that only one of the four children with isolated parietal involvement showed abnormal fixation shift. In contrast, the higher incidence of abnormal fixation shift in children who had involvement of optic radiation and primary visual cortex in addition to the parietal lesions, suggests that these structures may also have an important role in this function of selective attention.

We were also able to demonstrate that although visual abnormalities were common in our cohort, in some cases early lesions of the visual pathway could be compensated by the

developing brain; thus the visual outcome cannot always be predicted by the presence or the extent of the lesion. It is still unclear why and how certain infants compensate for their lesions while others do not, or why other children show clinical signs which are apparently not related to the lesions. One of the children in our cohort, for instance, showed a large infarct of the right middle cerebral artery involving the fronto-parieto-occipital region, but only a punctate lesion in the contralateral internal capsule (case 3). This child showed both visual field and fixation shift abnormalities ipsilateral to the infarction and perfectly normal visual function in the contralateral field. At 1 year of age this child showed some minor signs of motor impairment which were again ipsilateral to the lesion. While the motor impairment might be explained by the involvement of the contralateral internal capsule, it is more difficult to explain why the very extensive lesion does not produce any abnormal contralateral motor sign and why visual abnormalities are ipsilateral to the involvement of the parieto-occipital lesions on MRI.

Interestingly, in this study the abnormal results on all the tests were mainly noted in the children who were tested between 5 and 10 months, while only one of the five children who was older than 19 months at the time of the assessment showed abnormal results. According to our normative data, at 5 months all normal children show brisk refixations on fixation shifts (in both competition and non-competition situations), and significant responses on both orientation and phase reversal VEP at 8 rev/second. From this age onwards these tests show very little further progression. The presence of a lesion in these children might be responsible for delayed maturation of these functions which may still achieve normal levels by the end of the first year of life. This is in contrast to what has been found in other aspects of development in children with unilateral lesions. Several studies investigating neurodevelopmental outcome in these children have reported a very low incidence of sequelae in the first year of life.^{14-16 25} However, more recent studies, based on longer longitudinal follow up, have reported that the long term outcome in these children is less favourable, and that motor sequelae, epilepsy, and other abnormalities of development generally emerge only after the first year of life.^{17 26 27} Such subsequent emerging deficits were not apparent in visual function in our cohort, but it will be of interest to evaluate higher levels of visual function which can be tested in older children.

In conclusion, although the presence of a focal unilateral lesion was not always associated with abnormalities of various aspects of visual function, the high incidence of children who were abnormal on at least one of the tests used, suggests that all the children with such lesions need to be longitudinally investigated with a detailed assessment of various aspects of vision. Further longitudinal studies, following the evolution of both visual and imaging findings, are also needed to evaluate whether

the abnormalities found in these children in the first year of life are permanent, or only represent a sign of maturational delay.

- 1 Barmada MA, Mossy J, Schumann RM. Cerebral infarcts with arterial occlusion in neonates. *Ann Neurol* 1979; 6:495-502.
- 2 Govaert P. Cranial haemorrhage in the term newborn infant. *Clinics in Developmental Medicine*, 129. London: McKeith Press, 1993:118-25.
- 3 de Vries L, Regev R, Connell J, Bydder G, Dubowitz L. Localized cerebral infarction in the premature infant: an ultrasound diagnosis correlated with computed tomography and magnetic resonance imaging. *Pediatrics* 1988; 81:36-40.
- 4 Filipeck PA, Krishnamoorthy KS, Davis KR, Kuehnle K. Focal cerebral infarction in the newborn: a distinct entity. *Paed Neurol* 1987; 3:141-7.
- 5 Posner MI, Walker JA, Friedrich FJ, Rafal R. Effects of parietal injury on covert orienting of visual attention. *J Neurosci* 1984; 4:1863-74.
- 6 Lavadas E, Del Pesce M, Provinciali L. Unilateral attention deficits and hemispheric asymmetries in the control of visual attention. *Neuropsychol* 1989; 27: 353-66.
- 7 Rafal RD. Neglect. *Curr Opin Neurobiol* 1994; 4: 231-6.
- 8 Griffiths R. *The abilities of babies*. London: University of London Press, 1954.
- 9 Atkinson J. The Cambridge assessment and screening of vision in high risk infants and young children. In: Anastasiw NJ, Harel S, eds. *At risk infants: interventions, families and research*. Baltimore: Brookes Publish Co Inc, 1993:33-46.
- 10 Atkinson J, Van Hof- van Duijn J. Assessment of normal and abnormal vision during the first year of life. In Fielder A, Bax M, eds. *Management of visual handicap in childhood*. London: MacKeith Press, 1993:9-29.
- 11 Braddick O. Orientation and motion-selective mechanisms in infants. In Simons K, ed. *Infant vision: basic and clinical research*. Oxford: Oxford University Press, 1993:163-77.
- 12 Wattam-Bell J. Analysis of infant visual evoked potentials (VEPs) by a phase sensitive statistics. *Perception* 1983; 14: A33.
- 13 Levy SR, Abrams IF, Marshall PC. Seizures and cerebral infarction in the full term newborn. *Ann Neurol* 1985; 17: 366-70.
- 14 Trauner D, Mannino F. Neurodevelopmental outcome after neonatal cerebrovascular accident. *J Pediatr* 1986; 108: 459-61.
- 15 Roodhooft AM, Parizel PM, von Acker KJ, Deprelterre AJ, Reempts PJ. Idiopathic cerebral arterial infarction with paucity of symptoms in full term neonate. *Pediatrics* 1987; 80: 898-905.
- 16 Clancy R, Malin S, Laraque D. Focal motor seizures heralding stroke in fullterm neonates. *Am J Dis Child* 1985; 139: 601-6.
- 17 Fujimoto S, Yochoci K, Togari S. Neonatal cerebral infarction: symptoms, CT findings and prognosis. *Brain Dev* 1992; 14:48-52.
- 18 Bouza H, Dubowitz LMS, Rutherford M, Cowan F, Pennock J. Late magnetic resonance imaging and clinical findings in neonates with unilateral lesions on cranial ultrasound. *Dev Med Child Neurol* 1994; 36: 951-64.
- 19 Koelfen W, Freund M, Varnholt V. Neonatal stroke involving the middle cerebral artery in term infants: clinical presentation, EEG and imaging studies, and outcome. *Dev Med Child Neurol* 1995; 37: 204-12.
- 20 Cioni G, Fazzi B, Poggianti M, Boldrini A, Canapicchi R, Van Hof-van duin J. Predictive value of cranial ultrasound and MRI findings in infants at risk for cerebral visual impairment. *Gaslini* 1995; 27 (suppl 1): 27-30.
- 21 Cioni G, Fazzi B, Ippata A, Canapicchi R, Van Hof-van duin J. Correlation between cerebral visual impairment and MR imaging in children with neonatal encephalopathy. *Dev Med Child Neurol* 1995; 38:120-32.
- 22 Linch JC, Mountcastle VB, Talbot WH, Yin TCT. Parietal lobe mechanisms for directed visual attention. *J Neurophysiol* 1977; 40: 362-89.
- 23 Posner MI, Petersen SE. The attention system of the human brain. *Annu Rev Neurosci* 1990; 13: 25-42.
- 24 Hood B, Atkinson J. Disengaging visual attention in the infant and adult. *Infant Behav Devel* 1993; 405-22.
- 25 Bouza H, Rutherford M, Acolet D, Pennock JM, Dubowitz LMS. Evolution of early hemiplegic signs in full term infants with unilateral brain lesions in the neonatal period: a prospective study. *Neuroped* 1994; 25: 201-7.
- 26 Lanska M, Lanska D, Horwitz S, Aram D. Presentation, clinical course and outcome of childhood stroke. *Ped Neurol* 1991; 7: 333-41.