

ORIGINAL ARTICLE

Neonatal cerebral infarction and visual function at school age

E Mercuri, S Anker, A Guzzetta, A Barnett, L Haataja, M Rutherford, F Cowan, L Dubowitz, O Braddick, J Atkinson

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See end of article for authors' affiliations

Correspondence to: Dr Mercuri, Department of Paediatrics, Imperial College School of Medicine, Hammersmith Hospital, Du Cane Road, London W12 0HN, UK; e.mercuri@ic.ac.uk

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Objective: To assess various aspects of visual function at school age in children with neonatal cerebral infarction.**Patients and methods:** Sixteen children born at term, who had cerebral infarction of perinatal onset on neonatal magnetic resonance imaging (MRI) were assessed using a battery of visual tests. This included measures of crowding acuity (Cambridge Crowding Cards), stereopsis (TNO test), and visual fields. The results of the visual assessment were compared with the type and the extent of the lesion observed on neonatal MRI.**Results:** Only six of the 16 children (28%) had some abnormalities of visual function on these tests. Visual abnormalities were more common in children with more extensive lesions involving the main branch of the middle cerebral artery and were less often associated with lesions in the territory of one of the cortical branches of the middle cerebral artery. The presence of visual abnormalities was not always associated with the involvement of optic radiations or occipital primary visual cortex. Abnormal visual fields were only found in children who also developed hemiplegia.**Conclusions:** Abnormality of visual function is not common in children who had neonatal infarction and, when present, tends to be associated with hemiplegia and more extensive lesions.

Recent population based data report an incidence of neonatal cerebral infarction of 1 in 4000 term infants.¹ There have been several reports that these lesions are not always associated with an abnormal outcome, but most only assessed motor and language sequelae.^{2–4} Less attention has been paid to visual outcome. Most studies have only reported abnormal visual function in children with cerebral infarction who developed hemiplegia.^{5–6}

In 1996 we reported a short term visual follow up in a cohort of infants with neonatal cerebral infarction,⁷ including infants with both normal and abnormal motor outcome. Using a battery of tests specifically designed to evaluate visual function in the first year of life, we showed that, whereas acuity and ocular movements were always normal, visual fields and visual attention (tested by saccadic shifts of fixation between targets) were abnormal in about 50%. We also found that not all the infants in whom involvement of the structures of the visual pathway was found on magnetic resonance imaging (MRI) developed abnormal visual function. Half of the infants with involvement of the optic radiation had abnormal fields, and only 50% of the infants with parietal lobe lesions had an abnormal fixation shift in the first year of life. These findings suggested that other pathways and areas in the immature brain to some extent, compensated for early lesions affecting the visual pathway.

No systematic study has been performed to assess visual function at school age, when more mature aspects of visual function, such as stereopsis and crowding acuity, can be assessed.

The aim of this study was to assess various aspects of visual function at school age in children who suffered neonatal cerebral infarction and to examine the correlation between vision and (a) the type and extent of the infarction, and (b) the results of the early visual assessments performed in the first year of life.

SUBJECTS AND METHODS

This study is part of a continuing longitudinal study aimed at evaluating the maturation of visual function in full term infants with focal perinatal infarction. Permission for the study was obtained from both the Royal Postgraduate Medical School and the University College ethics committee. Informed consent was obtained from parents in each case.

The children recruited in this study were born at, or referred soon after birth to, the Hammersmith Hospital, London in the period October 1991 to October 1996. As part of this study all infants who suffered neonatal cerebral infarction had early and serial brain MRI in the first year of life and, since April 1993, were also referred to the Visual Development Unit of University College London in the first months of life for serial assessments of visual function. Four children who were also found to have cerebral infarction on neonatal MRI and were assessed at school age but did not attend the visual development unit in the first year of life were also included in the study.

Magnetic resonance imaging

MRI was performed using a Picker 1.0T HPQ system using T1 and T2 weighted spin echo and age related inversion recovery sequences in the transverse plane. All the infants had serial imaging in the neonatal period and at least at 6 and 12 months of age. Lesions were recorded by the consensus of two observers looking for the location and extent of the infarction. The infarcts were classified according to the arterial distribution of the lesions. This was based on the location, extent, and shape of the lesions.^{8–9}

Abbreviation: MRI, magnetic resonance imaging

Infarcts were characterised as being in the territory of the main arteries or in a borderzone distribution. The infarcts in the territory of the middle cerebral artery were further subdivided according to whether they occurred in the territory of the main branch or in one of the cortical branch arteries.

The scans were also assessed for involvement of the primary visual cortex and optic radiation.

Assessment of visual function

Early visual assessment

This was evaluated by using the Atkinson battery of child development for examining functional vision (ABCDEFV),¹⁰ which includes among its "core" vision tests assessment of orthoptic status (ocular movements, pupil response), acuity (tested using preferential looking), visual fields, and fixation shift. Details of the early assessment in this cohort have been published.⁷

Visual assessment at school age

Acuity and crowding ratio

The Cambridge crowding cards were used to obtain a measure of binocular crowding acuity. This gives an equivalent measure in children to adults testing with standard Snelling linear charts, and best reflects visual functioning in everyday life rather than monocular or single letter acuity.¹¹ In this test, letters are presented, both alone on the cards (single optotype) and surrounded by four other letters which are half a letter width away (crowded optotype). Each child was tested on the single before the crowded optotype. When crowded optotypes were shown, only the central letter had to be identified. They were tested monocularly and binocularly.

The child was tested at a distance of 3 m and asked to name or match the letter shown. If the response was correct, the tester showed a card with decreased letter size and continued until the child was unable to correctly identify the central letter. As the aim of this study was not to identify refractive errors but to evaluate possible cerebral visual impairment by measure of crowding, children with known refractive errors were tested using their prescription glasses.

A maximum of three letters of each size was shown. The third letter was shown only if in the previous two trials using the same size one letter had been correctly identified and one had not. The result of the third letter was the deciding one: if the score was 2 out of 3, then the tester proceeded to a smaller letter; if the score was 1 out of 3, then the test ended

and the last letter size where the criterion of 2 out of 3 was reached taken as the measure of acuity.

The results of the single and crowded optotype were compared and their ratio calculated by dividing acuity for crowded by acuity for single optotypes. According to our normative data,^{11,12} and in agreement with previous studies,^{13,14} the crowding effect was considered abnormal when the ratio was equal to or greater than 2.

Stereopsis

This was tested using the TNO test, a test specifically designed for screening for defects of binocular vision.¹⁵ The test consists of seven three dimensional images (plates) of increasing difficulty. Plates I to IV provide a quick and easy way to establish whether stereopsis is present at all, and plates V to VII enable a quantitative assessment of stereoscopic sensitivity. According to age specific normative data, stereopsis was classified as absent if the children did not pass any plates, weak if some of the first five (240 s/arc) were passed, and normal when at least plate VI was completed (60 s/arc).

Visual fields

These were tested by gradually moving a small white ball (a Stycar ball of 40 mm in diameter) from 90° laterally towards the child's midline. The child was asked to indicate when they first saw the ball. Eye movements of the child were also observed to estimate the angle of the visual fields and their symmetry. The findings were compared with age specific normative data. According to these data, the extent of visual fields develops during the first years of life, and the right and left sides of the binocular visual fields extend from about 30° at birth to 90°, reaching values similar to those for adults by the end of the first year.¹⁶⁻¹⁸

RESULTS

Sixteen children with neonatal cerebral infarction were assessed at between 5.5 and 7 years of age. Ten had a normal motor outcome, and six had hemiplegia.

Magnetic resonance imaging

Table 1 shows details of the side and extent of the lesion on the MRI scans performed after the first week of life.

Thirteen children had an arterial infarction in the territory of the middle cerebral artery, involving the main branch in four of the 13 and one cortical branch in the other nine. The remaining three children had a borderzone lesion.

Table 1 Side and extent of the lesions on brain magnetic resonance imaging

Type	Side	Cortex	VC	OR	BG	
1	Cortical branch	L	PO	N	N	N
2	Cortical branch	L	P	N	N	N
3	Cortical branch	L	PTO	N	N	N
4	Cortical branch	L	P	N	N	N
5	Cortical branch	L	P	N	N	N
6	Cortical branch	L	FP	N	N	N
7	Cortical branch	L	PO	N	L	N
8	Cortical branch	L	P	N	N	N
9	Cortical branch	Bil (L>R)	R:P - L:PO	N	L	L thalamus
10	Main branch	L	TFPO	L	L	L lentiform & thalamus
11	Main branch	R	FPO	N	N	R lentiform
12	Main branch	L	FPTO	N	L	L lentiform & thalamus
13	Main branch	L>R	L:TFPO - R:P	N	N	L lentiform & thalamus
14	Borderzone	L	FP/PO	L	L	N
15	Borderzone	Bilateral	PO	N	L	N
16	Borderzone	L>R	L:PO - R:O	N	L	L caudate & lentiform

N, Normal; L, left; R, right; P, parietal; O, occipital; T, temporal; F, frontal; VC, primary visual cortex; OR, optic radiations; BG, basal ganglia.

Table 2 Assessment in the first year of life

	Age at test (months)	Orthop	Acuity	Fixation shift	Fields
1	5.5	N	N	N	N
2	5.5	N	N	Abn	L field narrower
3	5.5	N	N	Abn	R field narrower
4	3.5	N	N	N	N
5	5	N	N	Abn	R field narrower
7	7	N	N	Abn	R field narrower
9	14	N	N	N	na
11	4.5	N	N	Abn	Total neglect R
12	7	N	N	N	R field narrower
14	4.5	N	N	N	N
15	3	N	N	Abn	R field narrower
16	5	N	N	N	N

N, Normal; Abn, abnormal; L, left; R, right; na, not assessed.

Visual assessment

Early assessment

Twelve of the 16 children had an early visual assessment in the first year of life. Table 2 shows details of the findings.

Acuity, tested by preferential looking, was normal in all 12, but seven of the 12 had abnormal visual fields, associated with abnormal fixation shift in six of the seven.

Details of the early assessment in 10 of the 12 have been published.⁷

Assessment at school age

Table 3 shows details of the assessment of visual function at school age.

Acuity and crowding ratio

Twelve children showed normal results (3/3), assessed on both single and crowded optotype. The crowding ratio was always below two. Two children had myopia and had abnormal results on both single optotype and crowding cards, and two had normal results on single optotype but abnormal results on the crowding cards, with a ratio above 2.

Stereopsis

Fourteen children showed normal results (≥ 60 seconds of arc), and two had weak stereopsis. One of the two had difficulties in understanding the task. In the other subject the abnormal stereopsis was associated with strabismus.

Comparison of visual and MRI findings

Figures 1 and 2 show details of the association between visual abnormalities and different types of neonatal cerebral infarction.

Five children showed involvement of the primary visual cortex and/or the optic radiations on MRI. Two had abnormal fields, one strabismus, and the other two had normal visual function (tables 1 and 2).

Comparison of visual and motor outcome

Figure 3 shows details of the association between visual abnormalities and motor outcome. Ten children had normal motor outcome and six developed hemiplegia. Normal and abnormal visual function could be observed in both groups but abnormal visual fields were only found in children with hemiplegia.

Comparison of early and late visual assessments

Figure 4 shows details of early and late assessments in the 12 children who were assessed in the first year of life and at school age.

DISCUSSION

We assessed visual function at school age in children who were found to have cerebral infarction on neonatal MRI. Only six of 16 children (28%) had some abnormality of visual function assessed (acuity, stereopsis, visual fields, and eye movements), and four of the six showed abnormalities on only one of these tests.

Visual acuity was abnormal in four of the 16 children studied, but two of the four had abnormal results on both single optotype and crowding and were found to have a refractive uncorrected error. The other two children had normal results when tested with single optotype but had an abnormal crowding ratio, suggesting that the poor acuity results from cerebral visual impairment rather than ocular

Table 3 Assessment of visual function at school age

	Motor outcome	Age at test	Orthop	Stereo	Crowding acuity	Fields
1	N	5 y 5 m	N	N	N	N
2	N	5 y 6 m	N	N	N	N
3	N	5 y 5 m	N	N	N	N
4	N	6 y 4 m	N	N	N	N
5	N	6 y	N	N	N	N
6	N	5 y 8 m	N	N	N	N
7	Hemiplegia	5 y 7 m	N	N	N	N
8	N	5 y 11 m	N	Abn	N	N
9	Hemiplegia	5 y 3 m	Strab	N	N	N
10	Hemiplegia	5 y 9 m	N	N	N	Abn R
11	N	5 y 8 m	Strab	Abn	N	N
12	Hemiplegia	5 y	N	N	Abn	Abn R
13	Hemiplegia	5 y	N	N	N	N
14	N	4 y 6 m	N	N	N	N
15	N	5 y 7 m	N	N	Abn	N
16	Hemiplegia	5 y 8 m	N	N	N	N

N, Normal; y, years; m, months; Strab, strabismus; Abn, abnormal; R, right.

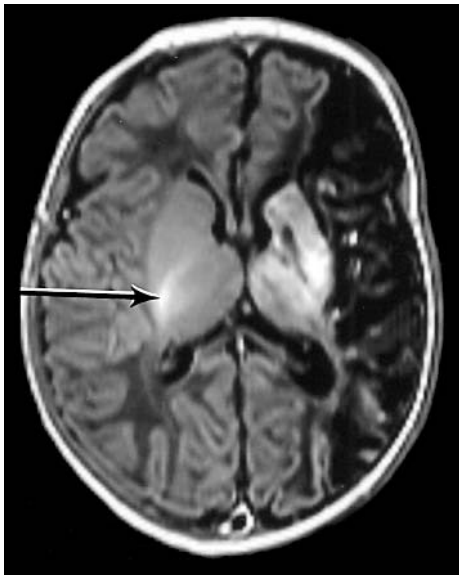


Figure 1 Inversion recovery sequence (IR 3800/30/950). Infant aged 14 days (case No 12). There is a large infarct involving the left hemisphere. There are additional abnormal high and low signal intensities within the basal ganglia, thalamus, and optic radiation on the left.

problems. High crowding ratios are also characteristic of amblyopia, but this explanation is unlikely for cases such as these where the effect was found in each eye and in binocular.

Visual fields were asymmetrical in two of the 16 children studied. The assessment of visual functions performed, however, only gives a broad estimate of the extent of visual fields. Other techniques such as the perimeter developed by van Hof-van Duin *et al*¹⁸ would have probably detected more subtle abnormalities of visual fields than the assessment used here. Nevertheless, our assessment can still reliably detect children who would have a significant restriction of visual fields that may affect their everyday life. Surprisingly, when we correlated the results of the assessment performed in the first year of life and at school age, we found that six of the seven children with abnormal visual fields in the first year of life had normal fields when tested at school age. This difference may partially be explained by the sensitivity of the assessment at school age. However, an alternative explanation may be the different techniques used to assess the two age groups. In the first year it is difficult to test visual fields without initially attracting the attention of the infant to the midline using a coloured toy. The extent of the visual fields is then tested by assessing the response of the infant's eyes and head to a stimulus presented at the periphery. This technique is also used in other tests to assess visual fields such as the van Hof perimeter. The infant is required to disengage his/her attention from a central to a peripheral stimulus, a task requiring the integrity of other cortical areas involved in shift

	Cortical branch	Main branch	Borderzone
Ocular movements	○○○○○○○○●	○○○○	○○○
Stereopsis	○○○○○○○○●○	○●○○	○○○
Acuity	○○○○○○○○○	○○●○	○●○
Fields	○○○○○○○○○	○○●●	○○○

Figure 2 Comparison of visual and magnetic resonance imaging findings.

	Normal motor outcome	Hemiplegia
Ocular movements	○○○○○○○○○●	○○○○○●
Stereopsis	○○○○○○○○●●	○○○○○○
Acuity	○○○○●○○○○	○○●○○○
Fields	○○○○○○○○○	○●●○○○

Figure 3 Comparison of visual and motor outcome.

	1 year assessment	5 year assessment
Ocular movements	○○○○○○○○○○○	○○○○○○○●○○○
Acuity	○○○○○○○○○○○	○○○●○○○○○●○
Fields	○●●○●●●○●○○	○○○○○○○○○●○

Figure 4 Comparison of early and late visual assessments.

of visual attention. This is a similar “disengage” process to that required for the fixation shift paradigm. A deficit in disengagement has been linked to parietal lobe functioning in Balint's syndrome¹⁹ and in infants who have undergone hemispherectomy.²⁰ Interestingly all six children who had abnormal fields in the first year of life which normalised by school age showed parietal lesions on MRI with sparing of the optic radiations and primary visual cortex. Five of the six also had abnormal fixation shift in infancy. The only child who showed persistent field abnormalities also had optic radiation involvement and had shown normal results on fixation shifts. These findings suggest that problems indicated by field testing in infancy should not be taken as prognostic indicators of long term field defects, although it is possible that they reflect attention mechanisms that manifest in a different form in later childhood.

The prevalence of abnormal visual fields in our cohort (12.5%) was apparently lower than that reported in two previous studies reporting abnormal visual fields in 30% and 50% of children with neonatal cerebral infarction.^{5 6} Those studies, however, only included children who had hemiplegia, whereas we included all the children who had neonatal infarction irrespective of their motor outcome. When we looked at the incidence of abnormal visual fields in children with hemiplegia in our cohort, this was similar to the previous studies (33%). Hemiplegia has also recently been found to be associated with more subtle deficits of global motion perception in school age children.²¹

The relatively low prevalence of abnormal visual findings in our cohort may partly be explained by the type and extent of the lesions. More extensive lesions involving the main branch of the middle cerebral artery were more often associated with abnormal visual findings than localised lesions in the territory of one of the cortical branches of the middle cerebral artery (75% v 32%). The presence and severity of visual impairment, however, did not always depend on the involvement of the optic radiations and/or occipital visual cortex, which are more often affected in patients with more extensive lesions. This was also confirmed by the low association of abnormal visual findings and borderzone lesions, which were always associated with involvement of the optic radiations.

It is of interest that in this study the presence of unilateral basal ganglia lesions was not always associated with abnormal visual function. These findings are at variance with what has previously been reported in children with bilateral basal ganglia lesions, who always showed severe and bilateral abnormalities of visual function.^{22 23}

In conclusion, we found that abnormality of acuity, visual fields, and stereopsis are not common in children who had neonatal infarction and, when present, tend to be associated with hemiplegia and more extensive lesions. Further studies are in progress to assess in more detail other aspects of visual function, such as visual attention and defects of spatial cognition, as suggested by the early abnormal results on fixation shifts in these children.

Authors' affiliations

E Mercuri, A Barnett, L Haataja, M Rutherford, F Cowan, L Dubowitz, Department of Paediatrics, Hammersmith Campus, Imperial College School of Medicine, London, UK

E Mercuri, Department of Child Neurology and Psychiatry, Catholic University, Rome, Italy

S Anker, A Barnett, O Braddick, J Atkinson, Visual Development Unit, University College, London, UK

A Guzzetta, Department of Child Neurology and Psychiatry, IRCCS Stella Maris Foundation, Pisa, Italy

L Haataja, Department of Paediatrics and Child Neurology, Turku University Central Hospital, Turku, Finland

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PostScript

LETTERS

Neonatal necrotising enterocolitis and perinatal exposure to co-amoxycylav

Two recent studies have reported an association between antenatal exposure to co-amoxycylav, either alone or in combination with erythromycin, and neonatal necrotising enterocolitis (NEC).^{1,2} Based on the analyses of secondary outcomes in these studies, the authors raised concerns about the use of co-amoxycylav antenatally and recommended further investigation of its use in the neonatal period.

We have completed a case-control study designed to test the hypothesis that perinatal exposure to co-amoxycylav is associated with an increased risk of NEC. During a 17 year period (1983–2000), 32 cases of NEC were diagnosed in preterm infants born to mothers inbooked at Liverpool Women's Hospital. Of these, 17 were diagnosed at laparotomy, 12 had classical radiological features, and in three the diagnosis was made on clinical grounds alone. Two gestation matched controls were selected for each index case. Information on potentially relevant perinatal variables, including antenatal and postnatal exposure to co-amoxycylav, were collected from maternal and infant case notes.

Infants who developed NEC tended to be lighter at birth (median birth weight 853 (interquartile range (IQR) 717–1248) g v 1037 (IQR 779–1613) g in controls, $p = 0.065$) and were more often delivered after absent or reversed flow identified on umbilical artery Doppler studies ($p = 0.007$). Postnatally, Gram negative septicaemia preceding NEC was significantly more common in cases than controls ($p = 0.005$). However, the frequency of perinatal exposure to co-amoxycylav was similar in both groups (table 1).

In summary, there is no evidence from this study of a link between perinatal exposure to co-amoxycylav and NEC. Our findings do not support the hypothesis that treatment with co-amoxycylav is causally associated with the development of NEC.

A Al-Sabbagh, S Moss, N Subhedar

Correspondence to: Dr Subhedar, NICU, Liverpool Women's Hospital, Crown Street, Liverpool L8 7SS, UK; nvsubhedar_lwh@yahoo.com

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Birth weight of Chinese babies born in Italy

Fok *et al*¹ note that the birth weight (BW) of the Chinese neonates they studied is lower than that of babies born in some western countries and state that a genuine genetic predisposition exists leading to the smaller size of Chinese infants.

In Tuscany, an Italian region with 3.4 million inhabitants, about 0.5% of the population are immigrants from the People's Republic of China. Since the early 1990s, Chinese immigrants in Tuscany have formed a stable, endogamic, culturally defined, and economically well integrated community. They receive the same full free medical care as Italian citizens.

Using the registry of the Regional Cystic Fibrosis Neonatal Screening Programme, which covers 99.9% of the Region's neonates,² we extracted the data for all the 4787 ethnic Chinese babies born in Tuscany from 1 July 1991 to 31 December 2002 to two ethnic Chinese parents. The forms that accompany the blood sample for the screening test are completed at birth by an obstetrician or nurse and contain the neonate's sex, BW, and gestational age (GA). We calculated the mean BW of the Chinese babies for each sex and GA starting from the 35th week (missing data: 638 babies). To avoid errors in estimates, we excluded as unlikely for GA those

BWs that were more than 1.5 interquartile ranges above the 75th or below the 25th centile for each GA and sex.³

Compared with native Tuscan newborns,⁴ Chinese babies born in Tuscany have a higher mean BW at almost all GAs; only at the 40th, 41st, and 42nd weeks for boys and 42nd week for girls is the mean BW of the Chinese babies slightly lower, but not significantly so. Compared with those born in China,¹ Chinese babies born in Tuscany have a higher mean BW at all GAs, except for the 42nd week (girls). The differences we found are in many cases statistically significant, despite the small size of our population.

Our data conflict with the hypothesis of Fok *et al* that Chinese newborns have a genetic predisposition to a smaller size than their white counterparts and suggest that, to explain the differences in BW they found, maternal and environmental factors should be taken into consideration.

F Festini, M F Reali, G Taccetti, T Repetto, M de Martino

Cystic Fibrosis Centre of Tuscany, Meyer Hospital, University of Florence, Italy; filippo.festini@iol.it

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Table 1 Exposure of infants with necrotising enterocolitis (NEC) and controls to co-amoxycylav

	NEC (n = 32)	Controls (n = 64)	p Value*
Antenatal exposure	5	11	1.0
Postnatal treatment	19	30	0.25
Any perinatal exposure	20	34	0.38

* χ^2 or Fisher's exact test.

CORRECTION

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Neonatal cerebral infarction and visual function at school age

E Mercuri, S Anker, A Guzzetta, et al.

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