Visual function at school age in children with neonatal encephalopathy and low Apgar scores

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Objective: To assess different aspects of visual function at school age in children who suffered from neonatal encephalopathy.

Method: Thirty nine full term infants with neonatal encephalopathy, low Apgar scores, and early neonatal imaging were studied using a battery of tests assessing different aspects of visual function (crowding acuity, stereopsis, visual fields) at school age. The results were compared with brain magnetic resonance imaging (MRI) findings and, when possible, with the results of the assessment of visual function performed at 5 and 12 months, available in 24 of the 39 children examined at school age.

Results: Sixteen of the 39 children (41%) had abnormal results at school age in at least one of the visual tests used. Seven of these 16 were untestable on all tests. The remaining 23 children (59%) had normal results.

Conclusions: The presence and severity of visual impairment was related to the severity of brain lesions. Moderate or severe basal ganglia lesions and severe white matter changes were always associated with abnormal visual function. Infants with normal MRI, minimal basal ganglia lesions, and minimal or moderate white matter involvement tended to have normal vision. It was also found that the assessment of visual function performed in the first year was a reliable indicator of visual function at school age. With two exceptions, the results on the 5 month visual assessment were predictive of visual outcome at school age. In the remaining two cases, a normal visual outcome at 5 years was associated with visual abnormalities at 5 months but these had already normalised by the age of 1 year.

Neonatal encephalopathy is characterised by an abnormal neurological state, with or without seizures, and affects 2–8 per 1000 term infants. Most studies in the literature have focused on infants who had neonatal encephalopathy resulting from a perinatal hypoxic-ischaemic event, generally associated with low Apgar scores.

We have previously reported that a proportion of infants with hypoxic-ischaemic encephalopathy have visual abnormalities in the first years after birth. The presence and severity of these abnormalities are related to the type and the extent of the brain lesions seen on brain magnetic resonance imaging (MRI). Although lesions affecting the cortex and white matter but sparing the basal ganglia were not always associated with abnormal visual findings, the combination of cortical and basal ganglia lesions was always associated with severe abnormalities of visual function. A short term follow up of these children showed that these abnormalities persisted in the first year after birth, whereas children with focal basal ganglia lesions without cortical involvement showed an improvement by the first year, which could therefore be classified as delayed visual maturation. There are no systematic studies assessing visual function in these children at a later age, when more mature aspects of visual function can be tested.

The aim of this study was to assess visual function at school age in children with neonatal encephalopathy with low Apgar scores, all of whom had neonatal imaging. More specifically, we wished to evaluate the correlation between: (a) various aspects of visual function, such as multiple optotypes (crowding acuity), visual fields, and stereopsis and the type and extent of the lesion, when present, as observed on neonatal MRI; (b) the results of visual assessments performed in the first year after birth and at school age.

SUBJECTS AND METHODS
This study is part of a continuing longitudinal evaluation of the maturation of visual function in full term infants with neonatal encephalopathy. The diagnosis of neonatal encephalopathy was made in infants with low Apgar scores (less than 5 at one minute and less than 8 at five minutes), who had convulsions in the first 48 hours and/or showed other neurological abnormalities during the first 48 hours after delivery. Neurological abnormalities included abnormal tone, poor feeding, and altered level of consciousness. Infants with convulsions but normal Apgar scores who were found to have neonatal cerebral infarction on brain MRI have been described separately. Encephalopathy was graded according to the classification suggested by Sarnat and Sarnat. Infants who had subsequently been diagnosed as suffering from genetic or metabolic syndromes or who presented with other neonatal complications, such as septicemia or neonatal meningitis, were excluded from the study. Infants with dysmorphic features or other clinical or brain MRI findings suggesting major congenital malformation were also excluded from the study.

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 were born at or referred soon after birth to the Hammersmith Hospital, London between October 1991 and October 1996. As part of this study, all term infants (gestation age 38 weeks or more) with neonatal

Abbreviations: MRI, magnetic resonance imaging; PLIC, posterior limb internal capsule
encephalopathy have at least one brain MRI scan between one and four weeks after delivery and detailed neurodevelopmental follow up. Since April 1993, the same infants have also been referred to the Visual Development Unit, University College London in the first months of life for serial assessments of visual function. Children who had 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 1 T HPQ magnet. All the infants had early brain MRI and serial scans. The images obtained after the first week (range 7–28 days) were used in this study, as, by this time, brain swelling, which is usually present in the first few days after birth, has cleared and the pattern of lesions is more evident. Images were obtained in the transverse plane with T1 weighted spin echo (SE 860/20), T2 weighted spin echo (SE 3000/120), and age related inversion recovery (IR 3800/30/950) sequences. Images were assessed for abnormal signal intensities by an experienced observer (MR) blinded to the outcome data. The pattern of abnormal signal intensities observed was documented as follows.

- The basal ganglia and thalami were assessed as normal, minimal, moderate, or severe: minimal, focal abnormalities but normal signal within the posterior limb internal capsule (PLIC); moderate, focal abnormalities involving the posterior lentiform nuclei and ventrolateral nuclei of the thalami with equivocal or abnormal signal intensity within the PLIC; severe, widespread abnormalities in all regions of the basal ganglia and thalami and abnormal signal intensity within the PLIC.
- White matter abnormalities were assessed as minimal, moderate, or severe: minimal, mild generalised long T1 and prolonged T2 within the periventricular white matter; moderate, small focal lesions with a short T1 and short T2, consistent with haemorrhage and/or areas with a clear T1 long T1 and long T2 but no loss of grey/white matter differentiation; severe, more pronounced areas of abnormality with larger haemorrhage or exaggerated long T1 and T2 with loss of grey/white matter differentiation.
- The cortical abnormalities consisted of “highlighting” with an abnormally high signal on T1 weighted images and were graded according to how many cortical sites were involved.

The scans were classified according to the predominant pattern of changes in the white matter and basal ganglia. Abnormalities in optic radiations and the primary visual cortex were also noted and classified as normal, abnormal, or asymmetrical.

Assessment of visual function
Visual assessment at school age
All children had a detailed assessment which included orthoptic examination and the following tests.

Acuity and crowding ratio
The Cambridge Crowding Cards were used to obtain a measure of binocular crowding acuity as this gives a measure in children that is equivalent to that obtained in adults testing with standard Snelling linear charts. This measure reflects visual functioning in everyday life better than monocular or single letter acuity.12 13 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 measurement 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 was 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,12 13 and in agreement with previous studies,14 15 the crowding effect was considered abnormal when the ratio was equal to or greater than 2.

Stereopsis
This was tested using the TNO test, which is specifically designed for screening for defects of binocular vision.16 It consists of seven three dimensional images (plates) of increasing difficulty. The first four plates provide a quick and easy way to establish whether stereopsis is present at all, and plates V–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 5 (240 seconds of arc) were passed, and normal if at least two out of four stimuli on plate VI were detected (120–60 seconds of arc).

Visual fields
These were tested by gradually moving a small white ball (a Stycar ball 40 mm in diameter) from 90° laterally towards the child’s midline. The child was asked to indicate when they first saw the ball. The child’s eye movements 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 adults by the end of the first year.17 18

Early visual assessment
This was evaluated using the Atkinson Battery of Child Development for Examining Functional Vision (ABCDEFV)19 20 which includes, among its “core” vision tests, assessment of orthoptic status (cover test, ocular movements, pupil response), acuity (tested using preferential looking), and visual fields. Details of the early assessment in this cohort have been published previously.10 Overall results are reported in relation to our present findings.

RESULTS
Fifty children met the inclusion criteria for the study. Seven were traced but were not available for follow up, and two could not be traced. Two children had behaviour problems and would not cooperate with the assessments. The remaining 39 were included in this study and were assessed at
school age. Of these 39, 15 were born before April 93 and did not have an early visual assessment in the first year.

**Neonatal brain MRI**

Eight of the 39 children (21%) had normal scans. Nine (23%) had minimal, five (13%) moderate, and three (8%) severe white matter lesions without basal ganglia involvement. Three children (8%) had minimal basal ganglia lesions, five (13%) moderate basal ganglia lesion, with or without white matter changes, and six infants (15%) had severe basal ganglia lesions, all with associated white matter changes. Twenty eight children had normal, and 11 had abnormal optic radiations and/or primary visual cortex.

**Visual assessment**

Table 1 shows details of the assessment of visual function at school age. Seven children had severe visual impairment with inability to fix and follow and could not be tested. There were no reported abnormalities of fundus oculi or other ocular abnormalities. The results of the remaining 32, tested between 5 years and 6 years of age are reported below.

**Table 1** Details of the assessment of visual function at school age of 39 children with neonatal encephalopathy

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<tr>
<th>Case No</th>
<th>Grade of enceph</th>
<th>Pattern of lesion</th>
<th>OR</th>
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<th>Age at test</th>
<th>Orthop</th>
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<th>Stereo</th>
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Abn, abnormal; Athet CP, athetoid cerebral palsy; BG, basal ganglia; Bil, bilateral; Dys, dystonic; enceph, encephalopathy; m, months; Min, Minimal; Mod, moderate; MR, mental retardation; MRI, magnetic resonance imaging; Neuro, neurological; OR, optic radiations; Orthop, orthopsis; PVC, primary visual cortex; Sev, severe; Stereo, stereopsis; Tetra, tetraplegia; Untest, untestable; WM, white matter; y, years.

*Unable to fix and follow; –, not tested.

**Acuity and crowding ratio**

Two of the 32 children (6%) had refractive errors and wore glasses when tested. Twenty four children (75%) showed normal results (3/3), assessed on both single and crowded optotype. The crowding ratio was always below two. One of the 24 had myopia and had abnormal results on both single optotype and crowding cards. Eight children (25%) had normal results on single optotype but abnormal results on the crowding cards, with a ratio above 2.

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**Figure 1** Comparison between early and late visual assessment in 24 children: correlation with magnetic resonance imaging (MRI) results. WM, White matter; BG, basal ganglia.
Stereopsis
Twenty six children (81%) showed normal results (< 120 seconds of arc), and six (19%) had weak stereopsis. One of the six had difficulties in understanding the task, and in four other subjects the abnormal stereopsis was associated with strabismus.

Visual fields
Twenty six children (81%) had normal and symmetrical visual fields, and six (19%) had bilateral narrow fields.

Comparison of visual and MRI findings
All of the 11 children with normal MRI or minimal basal ganglia except one (90%) had normal results on all the tests assessing various aspects of visual function.

Eleven of the 14 children (79%) with minimal or moderate white matter had normal results on all the tests, while the remaining three (21%) had abnormal results in one of the tests.

The three children with severe white matter lesions all had severe visual abnormalities (100%).

Four of the five children (80%) with moderate basal ganglia lesions had abnormal results, irrespective of whether there were additional white matter changes or not.

All of the six children (100%) with severe basal ganglia and white matter lesions had severe visual impairment and would be classified as “cortically” blind.

Eleven of the 39 children (28%) had abnormal optic radiations and/or primary visual cortex and all had abnormal visual function. Of the 28 with normal optic radiations and primary visual cortex, 23 (82%) had normal and five (18%) had abnormal visual function.

Figure 1 illustrates the results from those 24 infants who had both early assessment in the first year and assessment at school age. All the children who had normal results on the tests performed in the first year also had normal results at school age (100%).

Of the 17 children with some abnormalities on the early assessment, all but two (88%) also had abnormalities at school age. In the remaining two (12%), the abnormalities found at 5 months had already normalised by the end of the first year.

DISCUSSION
The aim of this study was to assess various aspects of visual function in children who suffered neonatal encephalopathy and had low Apgar scores. We only included children in whom metabolic, genetic, infective, or syndromic diseases had been excluded, and we focused on those who had evidence of perinatal insults on neonatal scans. We have already reported that, when tested in the first year after birth, a proportion of children with neonatal encephalopathy have visual impairment, and this is related to the type of lesion observed on neonatal MRI. More specifically, we found that lesions involving the basal ganglia were more likely to be associated with impaired visual function in the first year of life than lesions of the occipital cortex.9 10

We here confirmed our previous observation that visual function is related to the presence of basal ganglia lesions, and we have also been able to provide more details on the correlation between severity of visual impairment and basal ganglia involvement. When we analysed in more detail the degree of severity of the basal ganglia lesions, it was obvious that moderate or severe lesions were always associated with visual impairment. All the children with severe basal ganglia lesions were very much more severely visually impaired and only showed a response to light. In contrast, children with moderate basal ganglia lesions had abnormal results on crowding acuity, fields, and stereopsis, but they could still be tested and had visual function that could be used in everyday life. If the lesions affecting the basal ganglia were minimal, such as those only affecting the posterior aspects of the lentiform, these were associated with normal visual function at school age.

In contrast, the presence of white matter lesions is not always a reliable marker for identifying children who are likely to develop abnormal visual function, as only the children with severe white matter changes had visual abnormalities. The presence or the severity of visual abnormalities was not always related to the involvement of the primary visual cortex or optic radiations, as five children with normal optic radiation and visual cortex had abnormal visual function.

Although this study was not primarily designed to ascertain the prognostic value of early assessment of visual function in this cohort, we found that in more than 90% (22/24) of the cases there was a concordance between the assessments performed in the first year of life and those performed at school age. In the two patients who had false positives on the early assessment, the early abnormalities of visual attention had already normalised by the end of the first year, and can therefore be described within the spectrum of “delayed visual maturation”.21

Two of the 24 children followed longitudinally showed that once their visual delay was overcome at the end of the first year of life, normal visual development was achieved, even when the more mature aspects of visual function such as crowding acuity and stereopsis were tested. The results from 90% of this longitudinal group suggest that both MRI and the assessment of visual function in the first months of life can reliably predict visual outcome at school age. This allows identification at an early stage of infants who may benefit from pre-school rehabilitation programmes.22

Stereopsis was associated in all but one case with squint or other abnormal ocular movements. This finding is important, as previous studies have reported that stereopsis is often associated with perceptual motor impairment.19 It is of interest that the abnormalities of visual function, when present, tended to be severe and involve various aspects such as stereopsis, visual fields, and ocular movements. Further studies are in progress to establish the association between abnormal function and perceptual motor abilities at school age in these children. Other studies are also needed to establish whether the children who have normal acuity, stereopsis, and visual fields may still present with other abnormalities of visual processing, such as motion coherence or mature aspects of visual attention.

ACKNOWLEDGEMENTS
This study was supported by grants from Action Research, SCOPE, and the Medical Research Council.

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