Cognitive Outcome at Early School Age in Term-Born Children With Perinatally Acquired Middle Cerebral Artery Territory Infarction

Daniela Ricci, MD; Eugenio Mercuri, MD; Anna Barnett, PhD; Rachel Rathbone, MSc; Francesco Cota, MD; Leena Haataja, MD; Mary Rutherford, FRCR; Lilly Dubowitz, MD; Frances Cowan, PhD

Background and Purpose—To assess cognitive outcome at early school age in term-born children with middle cerebral arterial (MCA) territory infarction of perinatal onset and examine the correlation between cognitive abilities and the extent of lesions as seen on neonatal MRI, epilepsy, and hemiplegia.

Methods—Thirty-one children were seen as newborns with an acutely evolving MCA territory infarction documented on neonatal MRI scan. IQ was assessed (WIPPSI/WISC where appropriate) and they had a standardized neurological examination at early school age. Lesion(s) site was recorded from the neonatal images.

Results—Twenty-eight of 31 children were assessed (median age 5.75 range 5.33 to 10.33 years); 1 child died and 2 were abroad. IQ was within the normal range (mean 104, range 82 to 144) in 21 (78%); 1 child did not complete all tests but had a normal PIQ; 3 had a low and 3 an exceptionally low IQ. Verbal IQs were more varied and lower than performance IQs especially in children from multilingual backgrounds. There was no consistent association between cognitive impairment, side, or extent of the MCA lesion. Cognitive impairments were more frequent in children with seizures or hemiplegia. All 6 children with low IQ also had behavioral problems or unusual associated clinical or scan features.

Conclusions—in our cohort a low IQ at early school age did not occur in children with the common presentation of neonatal unilateral MCA territory infarction. Cognitive impairment appeared more frequently when an MCA arterial territory infarction, even if relatively small, was associated with other risk factors. (Stroke. 2008;39:403-410.)

Key Words: cognitive outcome ■ infarction ■ middle cerebral artery ■ MRI ■ neonate

Neonatal arterial ischemic stroke was considered an uncommon condition frequently associated with motor and cognitive deficits. Lesions were usually identified after the child presented with hemiplegia or epilepsy in early infancy and were and often still are assumed to be of late antenatal onset. The wider availability of neonatal imaging has allowed the detection of acutely evolving lesions in the first postnatal days, usually in infants with neurological symptoms, and this has given insights into their timing and into identification of risk factors.1–4 It is now recognized that arterial territory infarction in neonates is not usually associated with evidence of intrapartum asphyxia or neurological signs other than convulsions or evidence for the antenatal onset of lesions in symptomatic neonates.2,4–9

Not all infants with arterial territory infarction of perinatal onset have an abnormal outcome. Several studies have reported on the prevalence of motor impairment and hemiplegia, the most obvious potential motor sequela, which in our studies occurs in about 30% of children and can be predicted from the site of the lesion.6,10,11 Less structured follow-up at school age has been reported on other aspects of development including the pattern of cognitive outcome. Studies that have investigated cognitive development and some aspects of verbal development in infants and children with focal lesions are, in the main, retrospective,9 have included different types of focal lesions,4,12–14 imaging with CT,4 do not differentiate between lesions occurring pre- and postnatally,9–12 and have not always given the results of specific and appropriate testing.3–6,9

The aim of this study was to assess the cognitive outcome at early school age of a cohort of term born children, with an acutely evolving arterial territory cerebral infarction detected on early neonatal MRI brain scan, who were prospectively followed. We also wished to establish the correlation between cognitive abilities and the side and extent of lesions on neonatal MRI and other clinical signs such as epilepsy and hemiplegia.

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Subjects and Methods

Ethical permission for this study was obtained from the Hammersmith Hospital Research Ethics Committee. The children described are part of a large prospective cohort of term infants born at or referred to the Hammersmith Hospital, London, for MRI between 1991 and January 2001 who all underwent neonatal brain MRI.

Thirty-one term infants with evidence of middle cerebral artery (MCA) territory infarction on neonatal MRI were prospectively enrolled in the neonatal period. Sixteen infants were inborn and 15 were referred for a neurologic assessment and MRI. Only one child (infant 18) had an Apgar <7 at 5 minutes. Only in 3 of the 21 children with a recorded cord pH was this <7.1 and none was <7.1. Six children had a cord pH between 7.1 and 7.2. Details are given in Table 1. Four infants were ventilated, 1 for meconium aspiration (infant 17), 1 for mild tachypnoea and grunting (infant 22), 1 for persistent pulmonary hypertension (infant 20), and 1 after

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GA indicates gestational age; BW, birth weight; min. minutes; M, missing; EmCS, emergency caesarean section; SVD, spontaneous vaginal delivery; VDF, vaginal delivery/forceps; VDV, vaginal delivery/ventouse; VDV-F, vaginal delivery/forceps after failed ventouse; BGT, basal ganglia and thalami; PLIC, posterior limb internal capsule; N, normal; L, left; R, right; F, frontal lobe; P, parietal lobe; T, temporal lobe; O, occipital lobe; abn, abnormal; SI, signal intensity; bil, bilateral; PV, periventricular; WM, white matter; haem, haemorrhage; *<9thC; **<0.4thC.

Table 1. Perinatal Data and Lesion Site in Children With MCA Territory Infarction

Subjects and Methods

Ethical permission for this study was obtained from the Hammersmith Hospital Research Ethics Committee. The children described are part of a large prospective cohort of term infants born at or referred to the Hammersmith Hospital, London, for MRI between 1991 and January 2001 who all underwent neonatal brain MRI.

Thirty-one term infants with evidence of middle cerebral artery (MCA) territory infarction on neonatal MRI were prospectively enrolled in the neonatal period. Sixteen infants were inborn and 15 were referred for a neurologic assessment and MRI. Only one child (infant 18) had an Apgar <7 at 5 minutes. Only in 3 of the 21 children with a recorded cord pH was this <7.1 and none was <7.1. Six children had a cord pH between 7.1 and 7.2. Details are given in Table 1. Four infants were ventilated, 1 for meconium aspiration (infant 17), 1 for mild tachypnoea and grunting (infant 22), 1 for persistent pulmonary hypertension (infant 20), and 1 after
receiving anticonvulsants (infant 26). None were thought to have severe asphyxia. In all but 2 the lesion was detected after the onset of seizures between days 1 and 3 after birth; 1 infant (case 22) did not have seizures and another infant was enrolled for a MRI scan as a normal control. In all infants the lesions were obvious on their first brain MRI scan done within a week after birth, and conventional and diffusion-weighted imaging suggested that the timing of onset of the lesions was likely to be perinatal. One infant additionally had signs of unexplained prenatal onset of Wallerian degeneration in the brain stem together with an acutely evolving infarction in the ipsilateral hemisphere on the scan performed in the first postnatal week and another had a very small punctate lesion in the lentiform nucleus consistent with an antenatal infarction. One of the 31 children enrolled died as a neonate from bilateral MCA infarction associated with thrombus in an internal carotid artery, and 2 who had unilateral lesions in the territory of branch MCA arteries were not seen at school age having moved abroad; when last seen by us at 4 years they were performing in the normal range. One of these children had a seizure at 9 years but has a normal EEG and is not on antiepileptic medication.

The remaining 28 patients were regularly seen at 6- to 12-month intervals irrespective of whether they had any detectable sequelae on short term follow-up. The 2-year follow-up of these children has been reported as have details of their neuromotor abilities at 5.5 years.15

**Magnetic Resonance Imaging**

The infants were imaged on a 1.0 Tesla Picker HPQ system using conventional T1-weighted spin echo (SE 860/20 ms) inversion recovery (IR 3800/30/950 ms), T2-weighted spin echo (SE 3000/120 ms) sequences, and diffusion-weighted imaging.

The MCA territory infarctions were classified according to the extent of the lesions, dividing involvement within the MCA territory into parietal, frontal, temporal, and occipital areas and noting the extent of involvement of the basal ganglia, thalamus, and the anterior and posterior limbs (PLIC) of internal capsule. We also noted whether they were main, cortical branch, or lenticulostriate territory lesions subdivided according to a modified version of the criteria suggested by de Vries et al.5 In addition we classified separately the infarcts associated with contralateral lesions.

**Follow-Up Assessment**

Cognitive development was assessed using the Wechsler Preschool and Primary Scale of Intelligence–Revised (WPPSI) or the Wechsler Intelligence Scale for Children (WISC) – Third Edition UK (1990) depending on the age of the child. The results of the tests are expressed as a full intelligence quotient (FIQ), a verbal intelligence quotient (VIQ), and a performance intelligence quotient (PIQ) based on age specific normative data and classified as follows: IQ ≥120, high intelligence; 90 to 119, average to high average; 80 to 89, low average; 70 to 79, low intelligence; ≤69, exceptionally low intelligence.16 All the children additionally had a detailed neuromotor examination.

**Statistical Analysis**

Testing for differences of continuous variables between groups was done using the Mann–Whitney U test. For categorical variables, comparison between groups was performed using Fisher exact test. All of the probability values resulted from 2-sided statistical tests, and P<0.05 was considered to be significant.

**Results**

Twenty-eight children (18 males) were assessed at school age (range 5.5 to 10.5, median 5.66 years). Mean gestational age was 39.8 (range 37 to 42) weeks and birth-weight 3.152 (range 1.7 to 4.64) kg. Five infants were <9th percentile for weight including 3 <0.4th percentile. None of the children was microcephalic at birth. Perinatal details are given in Table 1.

Eight of the 28 (29%) had a hemiplegia and 20 had a normal symmetrical examination and function. Six children (21%) developed seizures (age range at onset 5 months to 7 years, median 2 years). The child who presented at 5 months had infantile spasms, 1 had generalized seizures, 3 had partial seizures, and 1 had febrile seizures. Four required regular antiepileptic drugs, currently continuing in 3; details are given in Table 2.

Two children were mildly dysmorphic, 1 also had a mild bleeding tendency. No specific syndrome or hematological abnormality could be identified despite extensive investigation.

**Magnetic Resonance Imaging**

Table 1 give the details of the extent of the lesions. All infarcts were in MCA territory, 6 (21%) on the right side and 22 (79%) on the left. Six (21%) were infarcts in the territory of the main branch, 20 (71%) in one of the cortical branches and 2 (8%) in the territory of the lenticulostriate branch alone. Examples of lesions and associated outcome are shown in Figures 1 and 2.

Two of the 6 children with a main branch territory infarction also had a smaller lesion in the contralateral hemisphere and one had a small lesion in the contralateral PLIC. Seven of the 20 children with a cortical branch territory infarction also had some abnormal signal intensity in the contralateral white matter. In 5 of the 10 children with bilateral lesions the smaller contralateral lesion was in the same arterial territory as the major area of infarction. For the 10 children with bilateral abnormality only 2 of the smaller lesions were small focal infarctions; 4 children had small areas of nonspecific long T2 in the white matter, 1 had focal hemorrhage in the white matter and the PLIC, and 1 each had small regions of long T2 in the PLIC, the thalamus, or the lentiform nucleus.

**Cognitive Assessment at School Age**

**Full IQ**

Twenty of the 28 children were assessed using the WPPSI and 8 using the WISC; one child completed the performance but did not complete the verbal part of the test because of tiredness and did not wish to be assessed again.

Twenty-one of the remaining 27 children (78%) had an IQ within the normal range (mean 104, range 82 to 144). Three children (11%) had an IQ in the range of the low intelligence and 3 (11%) in the exceptionally-low intelligence range, including one child with autistic spectrum disorder who had difficulties in performing any test items. Details are given in Table 2.

**Verbal IQ**

Twenty two of the 27 (81.3%) children had a verbal IQ in the normal range (mean 100, range 81 to 133), 1 (3.7%) in the low intelligence range, and 4 (15%) in the exceptionally-low intelligence range. Figure 3a shows the mean score of each verbal subtest.

**Performance IQ**

Twenty four of the 28 children (86%) had a performance IQ within the normal range (mean 103, range 80 to 143), 1
In the low intelligence range, and 3 (10.4%) in the exceptionally-low intelligence range. Figure 3b shows the mean score of each performance subtest.

Eleven of the 27 children (41%) completing the full testing showed a significant difference between VIQ and PIQ (12 points or more depending on age at testing) with a lower VIQ in 9 and a lower PIQ in 2. The profile for the verbal scores was more uneven than for the performance scores.

Correlation Between Cognitive Development and Additional Contralateral Lesions

When the cohort was subdivided according to the extent of the infarction, all groups showed variation in their scores. Low IQ occurred in 1 child with a main branch territory lesion alone (subject 16), 1 with a main branch territory infarction and contralateral lesion (subject 27), and 1 with a cortical branch and contralateral lesion (subject 22). The children with an isolated lenticulostriate infarction (subject 2) or isolated cortical branch infarction (subject 8) that had a low global IQ were the 2 children with dysmorphic features and 1 whose mother also had a low IQ (subject 10). Box plots showing the range of the data are given in Figure 4a and 4b, and details are given in Table 3.

Correlation Between Cognitive Development and Lesion Side–Unilateral Lesions

When the cohort was subdivided according to the side of the infarction all groups showed variable scores. A low IQ was associated with left-sided lesions in 4 of the 15 children. Details are given in Figure 4b and Table 3.

Correlation Between Cognitive Development and Hemiplegia

Eight children developed a hemiplegia; 2 had a low global IQ and 1 an exceptionally low global IQ. These 8 included the...
child who did not complete the VIQ testing but had a normal PIQ; he is doing well in school and is unlikely to have a low global IQ. Of the 20 children not developing a hemiplegia, 1 had a low and 2 an exceptionally-low global IQ; these were the 2 children with dysmorphic features and 1 whose mother had a low IQ. Details are given in Figure 4c and Table 3.

Analysis of the correlation between cognitive development and hemiplegia was not found to be significant ($P=0.31$).

Correlation Between Cognitive Development and Epilepsy

Five of 6 children who developed postneonatal seizures completed the assessment. Three of the 5 had a global IQ within the normal range, (2 average, 1 low average), 2 had a low global IQ, 1 with an exceptionally-low IQ in performance. The remaining child who had an autistic spectrum disorder had difficulties in performing any of the subtests. Details are given in Figure 2c and Table 2. Analysis of the correlation between cognitive development and epilepsy was not found to be significant ($P=0.09$).

Discussion

Approximately three-quarters of our cohort of term-born infants with perinatally acquired MCA infarction were cognitively in the normal range at early school age on testing using the WPPSI/WISC. Only 11% (3 children) had an exceptionally-low intelligence and another 11% (3 children) a low IQ. We were unable to find a clear association between cognitive impairment and the specific regions and extent of tissue affected within the MCA arterial territory. Although low IQs seemed more frequent in children with a main branch territory infarction, numbers are small and both normal cognition and cognitive impairment were found in all lesion groups, with 2 of the children with an exceptionally-low IQ having a small cortical branch or lenticulostriate lesion. Commenting on the effect of lesion side was difficult as there were only 6 children with a predominantly right-sided lesion and one had low IQ contrasting with low IQ in 5 children of the 22 with a left-sided lesion.

The incidence of cognitive impairment in our cohort is much lower than that reported in other studies of children with neonatal stroke and support the study of Wulfeck et al who did not find evidence of marked global delay in their cohort. This variance in results may be explained by differences in ascertainment of children with neonatal stroke, that many studies are retrospective and include only children with hemiplegia, and that ages and the type of tests used vary between studies. Our findings are also apparently in contrast with a study reporting significant neurodevelopmental problems in preschool children with perinatal stroke on a background of neonatal encephalopathy. However the lesions seen in that study included not only arterial territory infarction but also watershed infarction and lesions related to...
sagittal sinus thrombosis. Another difference is that, although all the children in our study had infarction of perinatal onset, as proven by early MR imaging, only 1 had low Apgar scores whereas in the cohort reported by Ramaswamy et al, \(^\text{14}\) the median 5-minute Apgar score was 5 and most infants needed major resuscitation. It is likely that the differences in outcome between the 2 studies are attributable to the evidence for a global insult and different types of lesion rather than to the effects of the arterial territory stroke alone.\(^\text{18–19}\)

One of the advantages of our study is that, although not population based, all the children were followed from birth, with early and serial neonatal brain imaging, and all were assessed at school age. All had lesions of perinatal onset and they had Apgar scores and early neonatal behavior that did not suggest global asphyxia; we therefore emphasize that we cannot extrapolate our conclusions about cognitive outcome to infants with MCA territory infarction of antenatal onset, with signs of a more global insult and neonatal encephalopathy or with parasagittal infarction. Most infants with neonatal arterial territory infarction have near normal Apgar scores and then present with seizures in the first 1 to 3 days after birth,\(^\text{7–9,18}\) and our findings would suggest that for infants with an infarct in the territory of the MCA who present in this way, cognitive impairment, or even low intelligence, occurs infrequently. Of note all the 6 children in our cohort who had low or exceptionally-low intelligence had, together with an acute MCA territory infarction, additional imaging or unusual clinical features; 2 had mild dysmorphic features but were without a syndromic diagnosis despite extensive investigation, another 1 was very shy and difficult to test, and 1 has a mother with cognitive impairment. Another child lost his nonhemiplegic arm in the neonatal period because of arterial thrombosis leaving him very limited in terms of upper limb function, and he has also developed an autistic spectrum disorder. The remaining child had evidence of Wallerian degeneration and atrophy in the brain stem together with an acutely evolving infarction in the ipsilateral hemisphere on the MRI scan performed in the early neonatal period, and she developed infantile spasms at 5 months. Thus our data suggest that although cognitive impairment does not appear to be a common sequel for infants with the typical presentation of neonatal MCA cerebral infarction, one has to be...
more circumspect about outcome when an arterial territory infarction, even if relatively small, occurs in an unusual context.18–20

The relationship between cognitive abilities and epilepsy or hemiplegia was complex. A low or exceptionally-low IQ was found in 3 of 8 children with a hemiplegia and 3 of 22 without. It is our experience that a hemiplegia results when 3 tissue sites are involved, the cerebral hemisphere, basal ganglia, and PLIC.6,13 This may not necessarily involve an extensive amount of tissue and may account for the relatively poor relationship between the occurrence of hemiplegia and cognitive outcome. In contrast and perhaps not surprisingly a low or exceptionally-low IQ was found more frequently in children who had seizures (3 of 6 children) compared with those without (3 of 22 children). Seizures were most frequently associated with hemiplegia (5 of 6 children) and with lesions in the main branch territory (4 of 6 children).

The overall profile in the VIQ was much more varied than for the PIQ. Almost half of the children (n=11, 41%) showed a significant difference between VIQ and PIQ with the majority having lower VIQ scores with the lowest mean score being for vocabulary. This supports work documenting a high incidence of verbal delay after perinatal infarction. Some reports suggest that children with a left-sided lesion are slower to acquire vocabulary in the first 2 years and had more problems with verbal expression.12–13 In our cohort the data are too skewed toward left-sided lesions for a meaningful statistical analysis, but we could not detect evidence suggestive of a correlation between language development and lesion laterality; VIQ was significantly lower than PIQ in 5 of the 13 children with left-sided lesions and 1 of the 3 with right-sided lesion.

Although the number of children enrolled in our study was relatively large, it is still too small to establish not only the effects of the extent and location of the lesions but also the possible effects of other variables, such as ethnic, cultural, and educational backgrounds and especially, in relation to language development, multilingualism of the families. Nearly 50% of our study came from a multilingual background, typical for the area that we serve. Seven of the 9 children with a significantly lower VIQ than PIQ were from such a background. We could not say whether lesion side affected this observation because so few children had right-sided lesions. It may be that the presence of any focal lesion, regardless of laterality limits cerebral plasticity and makes it more difficult to cope with more than 1 language. However, we cannot discount that the different ethnic, social, and education backgrounds may also influence language development or that the tests used, although standard, may not be optimal for such a varied group. Larger cohorts are needed to help establish the effect of possible confounding factors and to subclassify further the lesions to achieve a better correlation between specific areas of the brain and specific aspects of cognitive function even when the global IQ is within normal range.

In conclusion we found that children at early school age with MCA territory infarction of perinatal origin had IQs in the normal range except when there were additional unusual features. Further follow-up is needed to understand how these children cope with more academic tasks and complex social demands when they are older and whether seizures develop later. Follow-up data also needs to be correlated with the studies investigating the response of the brain to perinatally acquired injury in terms of its ability to revascularize and regenerate tissue,22 the relocation of control of function,23–24 and the time course of developmental processes in the face of focal lesions.25–26

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Disclosures

None.

References


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