Cortical Sparing in Preterm Ischemic Arterial Stroke

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Background and Purpose—Residual injury after perinatal arterial ischemic stroke in the middle cerebral artery territory usually involves the loss of cortical gray matter and subcortical white matter. In this article, we describe a different pattern of residual injury after middle cerebral artery stroke in preterm-born infants, in which the cortex is spared.

Methods—Magnetic resonance imaging scans of 40 infants (12 preterm and 28 full-term infants) with a large middle cerebral artery stroke were reviewed and correlated with outcome.

Results—Complete sparing of the cortex with cavitation of the underlying white matter was observed in 3 preterm infants, and partial sparing was noted in another 4 late preterm–born infants. One full-term infant had partial cortical sparing, and all others showed no sparing. Overall, 86% developed a hemiplegia and 30% had a developmental quotient below 85, but this did not vary between the different types of cortical injury.

Conclusions—The pattern of cortical injury after middle cerebral artery stroke changes with gestational age and may be related to maturational changes of the vascular system. Outcome did not vary between the different patterns of cortical injury. **(*Stroke*. 2016;47:869-871. DOI: 10.1161/STROKEAHA.115.011605.)**

Key Words: magnetic resonance imaging ■ middle cerebral artery ■ perinatal arterial ischemic stroke ■ preterm birth ■ stroke

Perinatal arterial ischemic stroke (PAIS) has an estimated incidence of 1 in 2300 births.[1] It is commonly seen in full-term infants, and the increased availability of neuroimaging techniques, including magnetic resonance imaging (MRI), has led to an improved diagnosis of PAIS in preterm infants.[2]

We have recently observed a different pattern of injury after middle cerebral artery (MCA) stroke in preterm-born infants. Follow-up MRI scans obtained beyond the acute phase showed relative sparing of the cortex, with cystic evolution of the underlying white matter. The aim of the current study was to review a cohort of term and preterm infants with a large MCA stroke and to investigate whether this pattern of injury was specific for preterm-born infants. We furthermore related the different types of injury to neurodevelopmental outcome.

Patients and Methods

Preterm- and term-born infants born between January 1990 and June 2015 who were admitted to the level 3 neonatal intensive care unit of the Wilhelmina Children's Hospital and diagnosed with anterior, posterior, or main branch MCA PAIS using MRI were included. Children with cortical MCA strokes (n=39) were not included because these strokes tend to be smaller, thereby hindering differentiation between sparing and loss of the cortex.

Magnetic Resonance Imaging

In full-term infants, an MRI scan was performed in the first week after birth. A second scan performed at the age of 3 months was used to evaluate residual damage. In preterm-born infants, serial cranial ultrasound was performed routinely, and an MRI scan was first performed at term equivalent age except for 2 infants. One infant was scanned at postnatal day 5 and one infant was scanned at 18 months of age.

MRI data were acquired on a 1.5 T or 3.0 T Philips MR system. Because of the long period during which children were included, the MRI protocol was not consistent over time. All protocols did, however, include axial T1- and T2-weighted imaging. In 1995, diffusion-weighted imaging was added to the MRI protocol.

MRI scans were reviewed and scored for integrity of the cortex in the former stroke area. The cortex was scored as completely spared if the cortex in the former stroke area was still intact, with cavitation of the underlying white matter (Figure 1A and 1B). If the area of white matter loss was only partially surrounded by cortex, it was scored as partially spared (Figure 1C). Finally, if no cortex surrounded the area of white matter loss, it was defined as no sparing (Figure 1D).

Neurodevelopmental Outcome

Neurodevelopmental outcome was collected from the infants' charts. This included the Griffiths Mental Development scales, which were administered between the age of 18 and 36 months. In children of ≥18 months, presence of unilateral spastic cerebral palsy was recorded, as well as development of postneonatal epilepsy.

Statistical Analysis

Differences between infants with complete sparing, partial sparing, or no sparing were analyzed using the Kruskal–Wallis, Mann–Whitney U, or Fisher Exact tests when appropriate. A P value of 0.05 was considered significant.

Results

During the 25-year period, 187 infants were diagnosed with PAIS. Stroke in the MCA was observed in 161 infants, with

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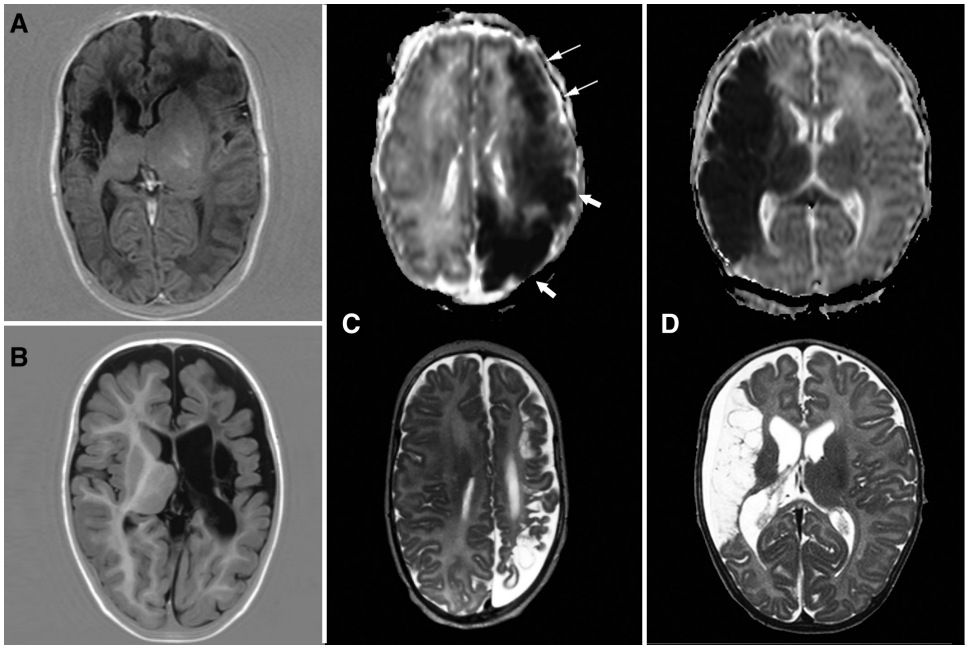

Figure 1. Magnetic resonance imaging (MRI) scans of 4 infants with a middle cerebral artery (MCA) stroke and a different degree of cortical sparing. Complete sparing was seen in 2 infants, born at 32 (**A**) and 28 (**B**) weeks and scanned at the age of 3 and 18 months, respectively. The apparent diffusion coefficient (ADC) map of an infant born at $35^{3/7}$ weeks (**C**) shows a combined middle and posterior cerebral artery stroke. Although the ADC map shows involvement of both the cortex and the white matter in the occipital and parietal regions (thick arrows), the cortex appears to be spared in the frontal lobe (thin arrows). This pattern of partial sparing was also seen at 3 months, with almost complete destruction of the occipital lobe, but cortical sparing of some parts of the frontal cortex. This child later developed refractory epilepsy and required a hemispherectomy. The ADC map in a full-term infant (**D**) shows a main branch MCA stroke, with both cortical and subcortical involvement. MRI at 3 months of age shows a completely absent cortex in the former stroke area.

involvement of the anterior, posterior, or main MCA branch in 49 infants. Six infants were excluded from further analyses because they died within the first 2 weeks after birth (n=5) or refused a second MRI at the age of 3 months (n=1). Three additional infants were excluded because of an antenatal stroke, resulting in a total of 40 infants (28 full-terms and 12 preterms; Table).

Full-Term Infants

An MRI at the age of 3 months was available in 28 full-term infants. Review of their neonatal scans showed a main branch MCA stroke in 17 infants, an anterior MCA branch stroke in 5 infants, and a posterior MCA branch stroke in 6 infants. The MRI scan obtained at 3 months showed partial sparing in 1 infant born at $37^{1/7}$ weeks. In all other infants, no cortical sparing was observed (Figures 1D and 2).

Preterm Infants

Twelve preterm infants were born at a median gestational age of $34^{1/7}$ weeks (range 28–$35^{6/7}$), and MRI showed a main branch MCA stroke in 11 infants and an anterior MCA branch stroke in 1 infant. Complete cortical sparing was observed in 3 infants (Figure 1A and 1B), and partial sparing was observed in 4 other infants (Figure 1C). In the 5 remaining infants, no sparing was observed (Figure 1D).

Neurodevelopmental Outcome

The neurodevelopmental outcome of 36 children who reached the age of 18 months is shown in Table. No differences in the Griffiths' developmental quotient or presence of hemiplegia were observed. Postneonatal epilepsy was present in 2 out of 3 (66%) children with complete sparing compared with 9

Table. Clinical Characteristics and Neurodevelopmental Outcome

	Complete Sparing (n=3)	Partial Sparing (n=5)	No Sparing (n=32)	Significance
Gestational age, wk	$30^{5/7}$ [28–32]	$33^{4/7}$ [$33^{3/7}$–$37^{1/7}$]	$39^{5/7}$ [34–42]	<0.001
Sex (m/f)	1/2	2/3	20/12	n.s.
Side (l/r)	2/1	4/1	17/15	n.s.
Neonatal seizures	0 (0)	2 (40)	31 (97)	<0.001
Follow-up >18 months	3 (100)	4 (80)	29 (90)	
Griffiths' DQ	99 [66–114]	85 [52–98]	90 [55–112]	n.s.
USCP	3 (100)	3 (75)	25 (86)	n.s.
Epilepsy	2 (66)	1 (25)	9 (31)	n.s.

Data are depicted as median and [range] or as (percentage). Neurodevelopmental outcome, reported from the age of 18 months onwards, was available in 36 children. DQ indicates developmental quotients; l/r, left/right; m/f, male/female; and USCP, unilateral spastic cerebral palsy.

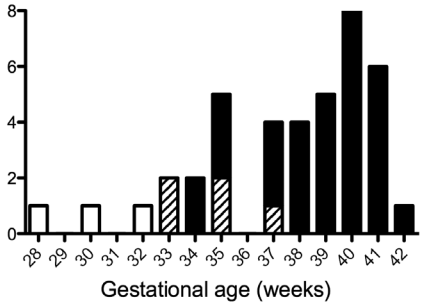

Figure 2. Frequency distribution of the different types of patterns observed for the different gestational ages. Complete sparing (white) was only seen in infants born before 33 weeks of gestation. Partial sparing (shaded) was observed between 33 and 37 weeks, whereas infants born after 37 weeks showed no sparing (black).

out of 29 (31%) without sparing, though this was not significantly different.

Discussion

In the current study, we have shown different patterns of residual injury after MCA stroke, which seems to depend on gestational age. The change in injury pattern occurs with a concomitant change of the developing leptomeningeal arteries.[3] By the end of the first trimester, the anterior, middle, and posterior cerebral arteries and their branches gives rise to a complex of arteries that fan out into one large network of leptomeningeal arteries.[3] Arterial branches arising from the MCA uninterruptedly continue into branches of the posterior and anterior cerebral artery. This network persists until 30–32 weeks of gestation, when a regression of the arterial system occurs, which continues until after birth. This regression involves the interruption and constriction of the initially uninterrupted arterial loops, resulting in the formation of smaller anastomoses. One could expect that more circumscribed irrigation areas are formed for each of the 3 cerebral arteries, with watershed areas in between these areas. This change may explain the change in patterns observed. Until 30–32 weeks, following occlusion of the MCA, the large network of arterial connections between the 3 areas may provide sufficient blood to perfuse the cortex, normally provided via the leptomeningeal arteries of the MCA. In older infants, the formation of 3 separate territories will prevent the retrograde filling and is therefore more likely to result in ischemia of the cortex.[3]

Despite complete sparing of the cortex in some children, their neurodevelopmental outcome was not better. Two of the children with complete sparing who did not have neonatal seizures developed postneonatal epilepsy. Their remaining cortex is likely to be dysplastic and, therefore, does not contribute to a better outcome.[4]

Diffusion-weighted imaging was only acquired in one infant with partial sparing and in none of the infants with complete sparing. The single diffusion-weighted imaging obtained showed no diffusion restriction in some parts of the cortex in the MCA territory, supporting our hypothesis (Figure 1C). More recently developed magnetic resonance sequences, including perfusion-weighted imaging, were not acquired in these infants, but might provide further insight in the pathophysiological mechanism.[5]

The cortical sparing after PAIS should be differentiated from cystic leukomalacia, especially from subcortical leukomalacia, which also involves the white matter with sparing of the cortex.[6] Leukomalacia tends to be bilateral, however, and serial cranial ultrasound can be used to examine the temporal evolution and differentiate between the two.

Summary

Different patterns of residual damage after MCA stroke in newborns can be observed depending on gestational age at which they arise. Embryological vascular changes may explain this phenomenon, which might be confirmed by future imaging studies, including diffusion-weighted imaging, perfusion-weighted imaging, and high-resolution magnetic resonance angiography.

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Disclosures

None.

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