Neurodevelopment After Perinatal Arterial Ischemic Stroke

Nienke Wagenaar, MD,[a] Miriam Martinez-Biarge, MD,[b] Niek E. van der Aa, MD, PhD,[a] Ingrid C. van Haastert, MA, PhD,[a] Floris Groenendaal, MD, PhD,[a] Manon J.N.L. Benders, MD, PhD,[a] Frances M. Cowan, MD, PhD,[b] Linda S. de Vries, MD, PhD[a]

abstract

BACKGROUND AND OBJECTIVES: Perinatal arterial ischemic stroke (PAIS) leads to cerebral palsy in ∼30% of affected children and has other neurologic sequelae. Authors of most outcome studies focus on middle cerebral artery (MCA) stroke without differentiating between site and extent of affected tissue. Our aim with this study was to report outcomes after different PAIS subtypes.

METHODS: Between 1990 and 2015, 188 term infants from 2 centers (London [*n* = 79] and Utrecht [*n* = 109]) had PAIS on their neonatal MRI. Scans were reevaluated to classify stroke territory and determine specific tissue involvement. At 18 to 93 (median 41.7) months, adverse neurodevelopmental outcomes were recorded as 1 or more of cerebral palsy, cognitive deficit, language delay, epilepsy, behavioral problems, or visual field defect.

RESULTS: The MCA territory was most often involved (90%), with posterior or anterior cerebral artery territory strokes occurring in 9% and 1%, respectively. Three infants died, and 24 had scans unavailable for reevaluation or were lost to follow-up. Of 161 infants seen, 54% had an adverse outcome. Outcomes were the same between centers. Main branch MCA stroke resulted in 100% adverse outcome, whereas other stroke subtypes had adverse outcomes in only 29% to 57%. The most important outcome predictors were involvement of the corticospinal tracts and basal ganglia.

CONCLUSIONS: Although neurodevelopmental outcome was adverse in at least 1 domain with main branch MCA stroke, in other PAIS subtypes outcome was favorable in 43% to 71% of children. Site and tissue involvement is most important in determining the outcome in PAIS.

[a]*Department of Neonatology, University Medical Center Utrecht, Utrecht University, Utrecht, Netherlands; and* [b]*Department of Paediatrics, Imperial College London, London, United Kingdom*

Dr Wagenaar is the main author and drafted the manuscript, contributed to data acquisition and interpretation, and was responsible for communication with all coauthors; Drs Martinez-Biarge and van Haastert contributed to data acquisition and interpretation and revised the manuscript for intellectual content; Drs van der Aa, Groenendaal, and Benders contributed to the analysis and interpretation of the data and read the manuscript critically for intellectual content; Drs Cowan and de Vries contributed to the study design, coordination and supervision of data collection and analysis, and drafting and critically reviewing the manuscript; and all authors have seen and approved the final manuscript as submitted and take full responsibility for the manuscript.

DOI: https://doi.org/10.1542/peds.2017-4164

Accepted for publication May 30, 2018

Address correspondence to Linda S. de Vries, MD, PhD, Wilhelmina Children's Hospital, University Medical Centre Utrecht, KE 04.123.1, PO Box 85090, 3508 AB Utrecht, Netherlands. E-mail: l.s.devries@umcutrecht.nl

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

WHAT'S KNOWN ON THIS SUBJECT: Perinatal arterial ischemic stroke often leads to adverse neurodevelopmental outcomes. Authors of most outcome studies do not differentiate between site and extent of affected tissue in their association with neurodevelopmental outcome.

WHAT THIS STUDY ADDS: With this study, we describe neurodevelopmental outcomes in different perinatal arterial ischemic stroke subtypes in a large and international cohort. Several MRI-based risk factors are provided that contribute to the prediction of neurodevelopmental outcomes in individual patients with perinatal stroke.

To cite: Wagenaar N, Martinez-Biarge M, van der Aa NE, et al. Neurodevelopment After Perinatal Arterial Ischemic Stroke. *Pediatrics*. 2018;142(3):e20174164

Perinatal arterial ischemic stroke (PAIS) is an important cause of long-lasting neurodevelopmental problems.[1,2] With increased use of neuroimaging techniques, especially MRI, the incidence from hospital-based studies is now considered to be ~1 in 2300 to 5000 live-born term neonates with a low mortality rate.[3,4]

Adverse consequences of PAIS include cerebral palsy (CP), usually of a hemiparetic type, cognitive dysfunction, epilepsy, and language, visual, and behavioral problems, which are reported to occur in 50% to 75% of infants.[1] Several groups have described MRI parameters that help in predicting adverse outcome after PAIS.[5,6] More specifically, the development of CP mainly depends on involvement of the corticospinal tracts (CSTs) at the level of the posterior limb of the internal capsule (PLIC) or cerebral peduncles.[2,7–11] Visual field defects occur most often when PAIS clearly involves the optic radiation.[12,13]

PAIS most often occurs in the territory of the middle cerebral artery (MCA), and most studies on outcome are focused on main branch MCA stroke.[1,14] Because occlusion of the proximal segment (M1) of the MCA will lead to infarction of the entire MCA region, including the basal ganglia and CST, development of unilateral CP can be reliably predicted. However, often only more distal MCA segments or the anterior cerebral artery (ACA) or posterior cerebral artery (PCA) are involved resulting in relatively characteristic lesion patterns that can be recognized on MRI.[15] Authors of most studies on outcome in PAIS do not differentiate between these lesion patterns involving various sites and extent of affected tissue. We hypothesized that outcome of PAIS primarily depends on the brain area that is affected by the stroke. Therefore, our aim with this study was to report on neurodevelopmental outcomes of different subtypes of PAIS in term infants, taking into account its lesion site and involvement of well-defined important brain structures.

METHODS

The neonates in this study comprised 2 cohorts of term newborn infants who were admitted to the NICU or referred for neurologic assessment to Queen Charlotte's or Hammersmith Hospital in London, United Kingdom (n = 79) or the Wilhelmina Children's Hospital of the University Medical Center in Utrecht (UMCU), the Netherlands (n = 117) between October 1990 and January 2015. All infants had acute symptoms in the first week after birth, most often (hemi) convulsions, but in a few infants their symptoms were less neurologically specific. All had PAIS confirmed on their neonatal MRI. Eight infants were excluded because of congenital syndromes with known adverse outcome (n = 4) or other significant brain lesions (n = 4), resulting in a total cohort of n = 187 infants. Infants who died in the neonatal period (n = 3), whose neonatal MRI scan could not be reevaluated (n = 4), or who were lost to follow-up (n = 20) were excluded from further analyses (Supplemental Table 7). This resulted in a total study cohort of 161 term neonates.

Informed verbal parental consent was obtained to perform an MRI for clinical purposes. The Institutional Review Board of the UMCU approved the use of MRI data for anonymous data analysis and waived the requirement to obtain written informed consent. In London, neonatal MRI scans were performed after obtaining written informed consent and permission to use these scans and clinical data for research.

MRI

In both centers, MRI was performed on a 1.0, 1.5, or 3T whole-body system (Philips Medical Systems, Best, Netherlands, or Picker System, Cleveland, OH) by using a scanning protocol including at least T1-weighted, T2-weighted, and diffusion-weighted imaging (DWI). In general, infants were sedated to minimize movement artifacts. Because we included infants over a long time period, the MRI protocol was not always the same; imaging details have been reported previously.[6,9,16]

Evaluation of MRI Data

Neonatologists experienced in neonatal brain MRI (F.C. and L.dV.) reevaluated each (of both centers) MRI scan. The lesions were assessed in 3 planes, if possible. On the basis of shape, extent, and localization of the area of signal intensity changes, all infants were classified to 1 of the stroke subtypes shown in Fig 1 on the basis of their most predominant stroke pattern.

Classification was mostly based on vascular territory of specific named arteries that resulted in characteristic infarctions as described by Govaert.[15] However, we felt that consistency of involvement of particular anatomic structures was more important, and the involvement of specific anatomic hallmarks was also used for classification. A hemispheric lesion in the MCA territory located posterior to the central sulcus was attributed to the posterior branch of the MCA, whereas involvement anterior to the central sulcus was attributed to the anterior branch. When the full central sulcus was involved, but not regions more anterior or posterior, this was attributed to the middle branch MCA. If the anterior or posterior areas and middle branch MCA were involved, the most predominant branch was chosen, and central sulcus involvement was noted separately. Involvement of the central sulcus region was best assessed in the parasagittal plane. Where >1 MCA branch artery was involved this was also noted separately as multiple

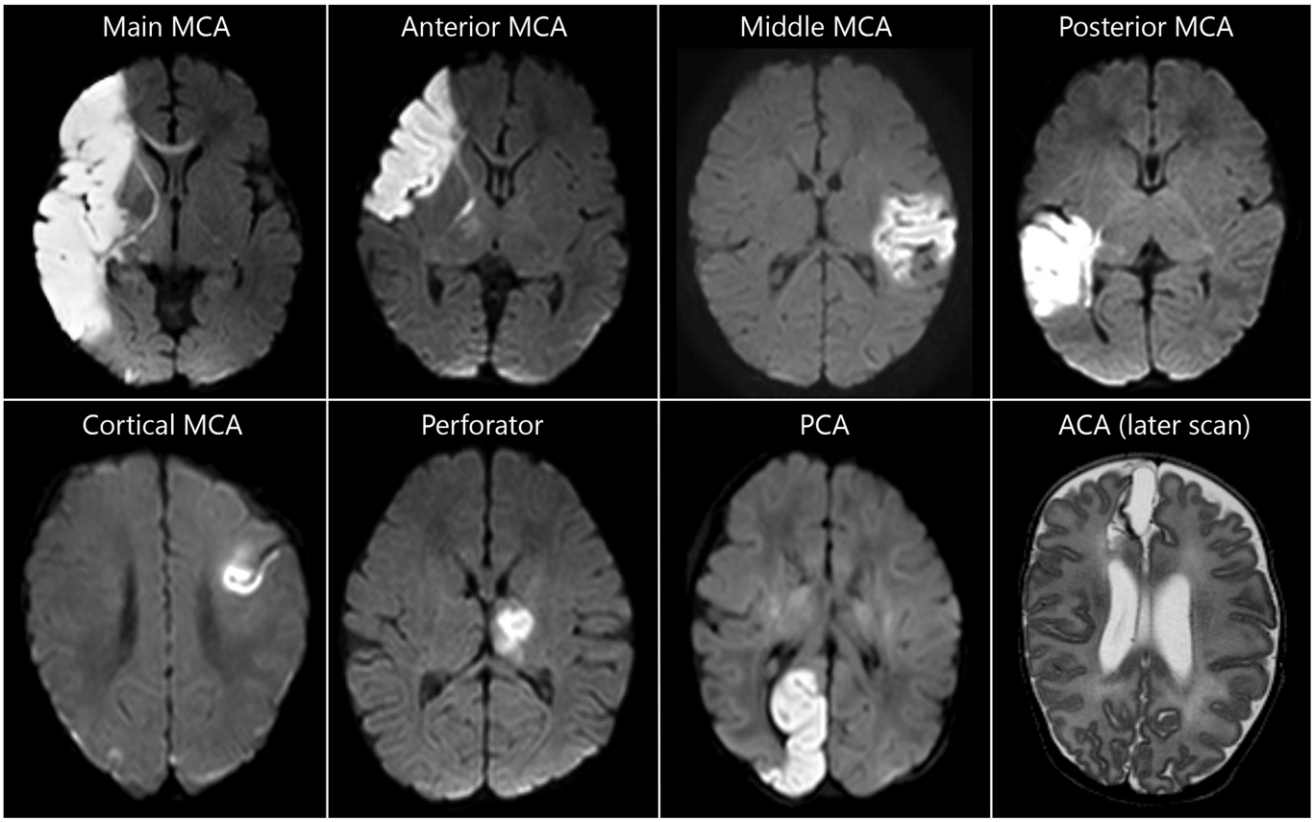

FIGURE 1

Classification of stroke territory subtypes. Stroke subtypes were classified on the basis of the following infarction territories: main MCA (complete MCA infarction); anterior MCA branch (partial MCA infarction anterior to the central sulcus); middle MCA branch (partial MCA infarction involving the central sulcus); posterior MCA branch (partial MCA infarction posterior to the central sulcus); cortical MCA branch (superficial MCA infarction involving only the cortex, without involvement of the striatum); perforator branch (perforator stroke involving only the deep gray matter [thalamus and/or basal ganglia]); PCA or ACA (non-MCA infarction). In these examples, CST involvement is seen in the main MCA stroke and the anterior and posterior MCA branch strokes. Secondary network injury to the thalamus is seen with the main branch and the anterior MCA stroke.

lesions. Small punctate lesions were not considered part of the spectrum of "multiple lesions."

Magnetic resonance images were also evaluated for involvement of specific regions we considered likely to be of major importance in predicting outcome (ie, the CST, the central sulcus region, thalami, and basal ganglia, as described previously[2,8]), mainly by visual inspection of the DWI from MRI scans done in the MRI from the first week and from T1- and T2-weighted images when the MRI was acquired later.[7] Involvement of the CSTs has been described previously.[11] Only when the middle part of PLIC and cerebral peduncle were affected, carrying the main motor tracts, was this classified as involvement (Fig 2) for the purposes of this study.

Often with hemispheric strokes, signal changes were also seen in the thalami, particularly the pulvinar, that are likely secondary to "network" injury rather than part of the primary stroke.[17] Examples of primary thalamic stroke (perforator stroke) and secondary network injury to the thalamus are shown in Fig 1 (anterior MCA). Bilateral lesions were described as bilateral stroke when stroke lesions were equally severe or as smaller contralateral lesions when 1 region of stroke predominated.

Neurodevelopmental Outcome

Neurodevelopmental outcome was determined during routine follow-up appointments. We only used data from after 12 months until 7 years.

Cognitive development was determined by using the developmental quotient of the Griffiths Mental Development Scale (GMDS), calculated by using all subscale scores except locomotion, the Bayley Scales of Infant and Toddler Development, Third Edition (BSITD-III), or the Wechsler Preschool and Primary Scale of Intelligence second or third edition.[18–20] For all cognitive tests, *z* scores were calculated to allow comparison of the data for statistical analyses. Cognitive delay was defined as a *z* score below −1, corresponding to −1 SD. Language delay was defined as a language score on the GMDS of <−1 SD, >15 points on the Dutch

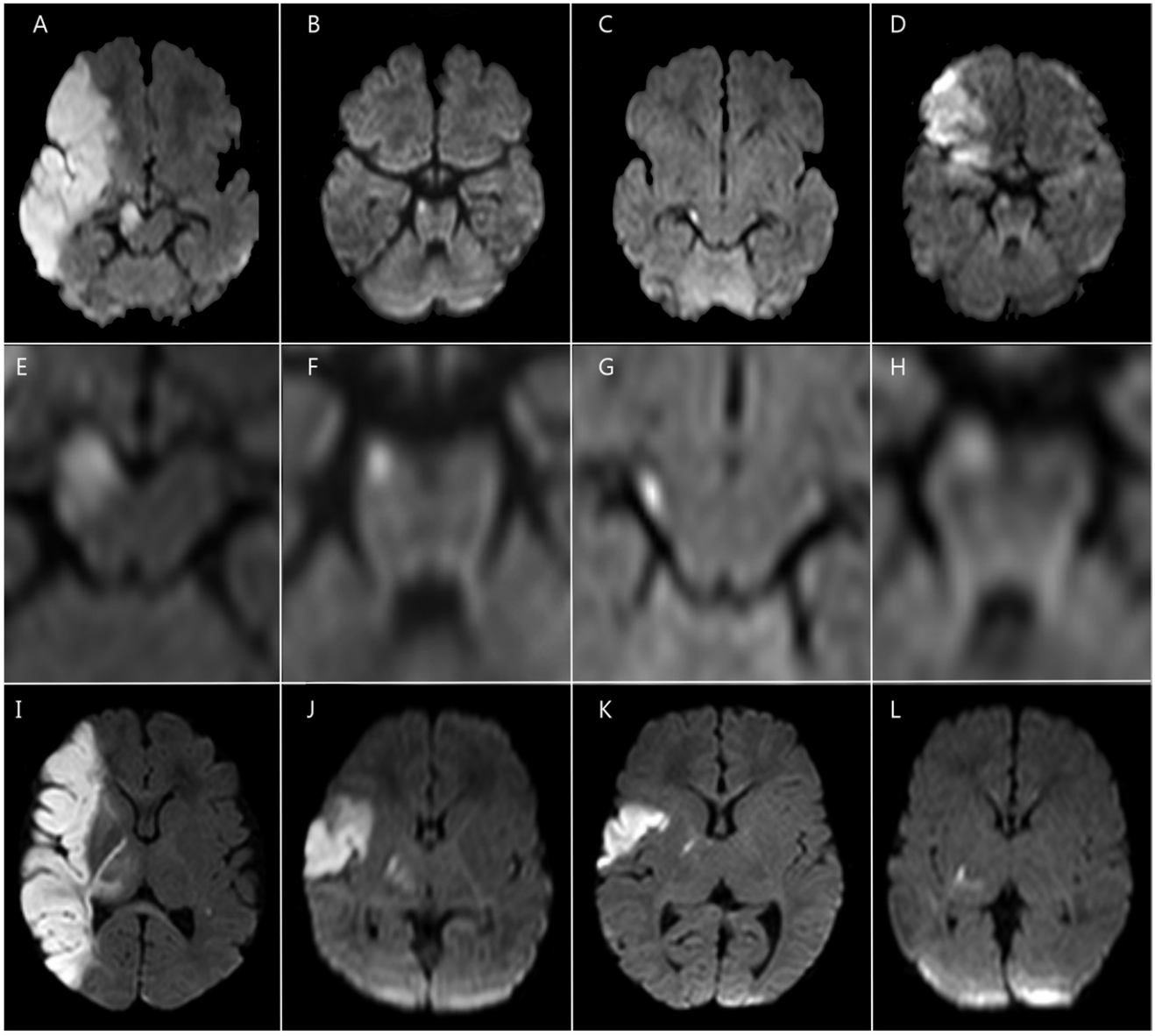

FIGURE 2

Classification of cerebral peduncle involvement. Involvement of the cerebral peduncle was only scored when the full (A and E) or middle third of the cerebral peduncle was involved (B and F), as described by Kirton et al.[11] Lateral (C and G) or median (D and H) peduncle abnormalities were not defined as "cerebral peduncle involvement" in our analyses. Involvement of the PLIC was only scored when the full (I) or middle (J) part of the PLIC was involved and not when there was only anterior (K) or posterior (L) PLIC involvement.

language screening instrument,[21] or a diagnosis of speech and/or language disorders.

CP was diagnosed by using criteria from the European CP Network,[22] and severity was determined by using the Gross Motor Function Classification System.[23] Behavioral problems were asked about at each clinic visit, and, when appropriate, children were referred to a clinical psychologist; additionally, in the UMCU cohort, parents completed the Child Behavior Checklist.[24] Only behavioral assessments after 2 years of age were taken into account. Postneonatal epilepsy was classified as (recurrence of) seizures diagnosed on EEG for which regular medication was given. Visual field defects included hemianopia and quadrantanopia, diagnosed by a specialized visual development unit in London or pediatric ophthalmologist specialized in assessing visual field defects in infancy in Utrecht. An adverse outcome was defined as the presence of 1 or more of the following: CP, cognitive deficit, language delay, epilepsy, behavioral problems, or visual field defect at latest follow-up.

Statistical Analyses

Descriptive statistics are summarized as percentages of the available study

TABLE 1 General Characteristics of the Study Population

Characteristics	Total, $N = 161$
Gestational age, median (IQR)	40.3 (39.0–41.1)
Birth wt, median (IQR)	3440 (3040–3700)
Birth wt *z* score <—1 SD, *n* (%)	41 (26)
Head circumference at birth, median (IQR)	34.8 (33.5–36.0)
Male sex, *n* (%)	103 (64)
Apgar score at 1 min, median (IQR)	7 (5–9)
Apgar score at 5 min, median (IQR)	9 (7–10)
Seizures, *n* (%)	142 (88)
Postnatal d at first seizures, median (IQR)	1 (0–2)
Hypoglycemia,[a] *n* (%)	28 (17)
Postnatal d at MRI, median (IQR)	5 (3.5–7)
MRI >7 d after first symptoms or birth, *n* (%)	22 (14)
Side of stroke lesion, *n* (%)	
Right	51 (32)
Left	103 (64)
Bilateral	7 (4)
Lesion subtype, *n* (%)	
Main MCA	31 (19)
Anterior MCA branch	17 (11)
Middle MCA branch	21 (13)
Posterior MCA branch	28 (17)
Cortical MCA branch	21 (13)
Perforator branch	27 (17)
PCA or ACA	16 (10)

[a] Hypoglycemia was defined as a blood glucose <2 mmol/L.

cohort or as median and interquartile range (IQR) where appropriate. Stroke subtypes and other imaging features were compared with outcome parameters by using χ^2 tests, independent *t* tests, or Mann–Whitney *U* tests (for nonparametric variables). Binary logistic regression analysis was performed to determine independent MRI predictors for adverse outcome, which were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). These regression analyses were performed for the total cohort and also separately for those without main MCA branch infarction.

Statistical analyses were performed with SPSS, version 21 (IBM SPSS Statistics, IBM Corporation). *P* values <.05 were considered to be statistically significant.

RESULTS

The total study cohort consisted of 161 term neonates born at a median of 40.3 weeks' gestation and a median birth weight of 3440 g (Table 1). There were no differences in infant clinical parameters between the 2 centers, so results are reported for the total cohort. In Utrecht, 30 infants received erythropoietin as part of an intervention study or off-label use.[25] These infants did not differ in stroke patterns and also had equal rates of adverse outcome (unpublished data N.W., N.A., F.G., M.B. and L.dV.) and were therefore not reported separately.

MRI Findings

MRI was performed at a median of 5 (IQR: 3.5–7) days after birth. The MCA was most commonly involved, and most often affected were the main branch, posterior, and perforator branches (19%, 17%, and 17%, respectively) and less often the anterior, middle, or 1 of the cortical branches (11%, 13%, and 13%, respectively). PCA stroke was found in 14 cases (9%) and ACA stroke in 2 cases (1%). Clinical characteristics are given in Table 1 and details of involvement of specific regions in Table 2. Involvement of the CST could not be determined in 5 infants (3%), who had an MRI in the second week after birth without DWI abnormalities and T1- or T2-weighted imaging of insufficient quality to assess the CST. Infants that were lost to follow-up (Supplemental Table 7) did not differ in terms of stroke pattern classification, basal ganglia and thalami (BGT), or CST involvement.

Clinical Characteristics per Stroke Subtype

Infants with cortical MCA infarction were born at significantly later gestational age (mean 40.7 ± 1.3 vs 40.0 ± 1.4 weeks; $P < .03$) compared with other subtypes.

Hypoglycemia was more often found in infants with PCA infarction compared with the other subtypes (58% vs 16%; $P < .0001$) and more often in main branch MCA strokes compared with other subtypes (36% vs 16%; $P < .02$), whereas the incidence of hypoglycemia was not significantly different between PCA and main branch MCA stroke ($P > .1$).

Seizures at presentation were less common in perforator stroke compared with the other subtypes (62% vs 94%; $P < .0001$). Also, perforator stroke was less often left sided compared with the other subtypes (48% vs 71%; $P < .03$). Other characteristics from Table 1 were not significantly different between stroke subtypes.

Neurodevelopmental Outcome

All infants were seen between 12 months and 7 years with a median age of 41.7 months when last seen (Table 3). There were no differences in outcomes between centers. At their latest follow-up, 49 infants (30%) had developed CP; Gross Motor Function Classification System levels were determined for 40 infants with 90% at level I, 8% at level II, and 3% at level IV (1 child with bilateral main branch MCA). There were no infants in this study who were first diagnosed with CP beyond

TABLE 2 MRI Features per Stroke Territory Subtype

	Total, *n* = 161	Main MCA, *n* = 31	Anterior MCA Branch, *n* = 17	Middle MCA Branch, *n* = 21	Posterior MCA Branch, *n* = 28	Cortical MCA Branch, *n* = 21	Perforator Branch, *n* = 27	PCA or ACA, *n* = 16
CST involvement								
PLIC alone	28 (18)	0 (0)	8 (47)	5 (24)	9 (32)	0 (0)	6 (26)	0 (0)
PLIC and peduncle	46 (30)	28 (100)	3 (18)	6 (29)	4 (14)	0 (0)	2 (9)	0 (0)
Basal ganglia and/or thalamic involvement								
BG alone	25 (16)	1 (3)	5 (29)	1 (5)	1 (4)	0 (0)	17 (63)	0 (0)
Thalamus alone	17 (11)	0 (0)	1 (6)	3 (14)	2 (7)	0 (0)	8 (30)	3 (21)
BGT	41 (26)	30 (97)	2 (12)	1 (5)	6 (21)	0 (0)	2 (7)	0 (0)
Central sulcus involvement	68 (43)	31 (100)	7 (41)	21 (100)	9 (35)	0 (0)	0 (0)	0 (0)
Bilateral lesions								
Smaller lesions	26 (18)	10 (39)	1 (6)	1 (5)	5 (19)	4 (19)	2 (8)	3 (21)
Bilateral stroke	7 (5)	2 (8)	1 (6)	1 (5)	0 (0)	0 (0)	2 (8)	1 (7)
Multiple lesions	58 (39)	12 (46)	5 (31)	6 (30)	12 (46)	7 (33)	7 (28)	9 (64)

Neonatal magnetic resonance images were reevaluated for involvement of the CSTs at the peduncle and the PLIC (*n* = 156), basal ganglia (*n* = 159), and central sulcus region (*n* = 157). In 148 infants, we could assess the presence of multiple and/or bilateral lesions. BG, basal ganglia.

TABLE 3 Cognitive Developmental Score After the Age of 12 Months per Time Point

	Age at Testing, mo, Median (IQR)	GMDS: DQ (Without Locomotor Subscore), Median (IQR)	BSITD-III: Cognitive Composite Score, Median (IQR)	WPPSI: Total IQ Score, Median (IQR)	*z* Score, Median (IQR)	*z* Score <−1 SD, *n* (%)
12–18 mo, *n* = 83	15.2 (13.0 to 17.6)	98.2 (92.2 to 110.0)	—	—	−0.15 (−0.65 to 0.83)	15 (18)
~2 y, *n* = 123[a]	24.0 (21.1 to 25.0)	98.5 (91.1 to 104.7)	105.0 (95.0 to 113.8)	—	−0.03 (−0.67 to 0.67)[b]	17 (13)
~3–4 y, *n* = 71	41.1 (36.0 to 42.4)	98.9 (88.6 to 107.5)	—	—	−0.09 (−0.95 to 0.64)	14 (19)
~5–7 y, *n* = 64	67.0 (65.0 to 70.0)	—	—	102.0 (88.0 to 111.0)	0.10 (−0.80 to 0.73)	11 (17)
Latest follow-up, *n* = 160	41.7 (24.6 to 66.0)	—	—	—	−0.04[c] (−0.95 to 0.68)	37 (23)

DQ, developmental quotient; WPPSI, Wechsler Preschool and Primary Scale of Intelligence; —, not applicable.
[a] At ~2 y, 106 tested with the GMDS, and 28 tested with the BSITD-III.
[b] When tested with both GMDS and BSITD-III, a *z* score was calculated for the latest test.
[c] *z* score could not be calculated in 3 infants because of severe delay (<−2 SD).

2 years of age. Cognitive test results were available for 157 infants, and 3 infants could not be tested because of severe delay (<−2 SD). This resulted in 37 infants (23%) with a cognitive *z* score <−1 SD and 13 infants (8%) with a cognitive *z* score <−2 SD (Table 3). At their latest follow-up, 87 of 161 infants (54%) had an adverse outcome; 38 infants (24%) had 1 or a combination of adverse outcomes without having CP. More details on adverse outcome domains per stroke subtype are given in Table 4. Further analyses were performed by using outcome results from each patient's last follow-up.

Overall, 50 of 87 (57%) infants with adverse outcome developed sequelae in multiple domains. Of the 49 infants with CP, 35 (71%) had another adverse outcome, most commonly a cognitive deficit (*n* = 22; 45%). Visual field defects did not occur in isolation, and most often, they occurred in combination with CP (13 of 17). Although adverse outcomes commonly co-occurred, only 4 children were affected in all 6 developmental domains.

Infants with language delay had increased risk of cognitive delay (OR: 11.8; 95% CI 4.7–29.2), but excluding those with main MCA branch stroke, the odds for cognitive delay were 6.5 times increased with language delay (95% CI 2.1–20.1). Postneonatal epilepsy also increased the risk for cognitive delay (OR: 9.1; 95% CI 3.1–26.6), but this was only significant in the main MCA branch stroke group.

MRI Parameters Associated With Neurodevelopmental Outcome

Analyzing all infarcts together, univariate analyses revealed

TABLE 4 Adverse Outcome Domains per Stroke Territory Subtypes

PAIS Type and Outcomes (No. With Data)	Total (*n* = 161), *n* (%)	Main MCA (*n* = 31), *n* (%)	Anterior MCA Branch (*n* = 17), *n* (%)	Middle MCA Branch (*n* = 21), *n* (%)	Posterior MCA Branch (*n* = 28), *n* (%)	Cortical MCA Branch (*n* = 21), *n* (%)	Perforator Branch (*n* = 27), *n* (%)	PCA or ACA (*n* = 16), *n* (%)
CP, *N* = 161	49 (30)	31 (100)	2 (12)	4 (19)	6 (21)	0 (0)	4 (15)	2 (13)
Cognitive deficit, *n* = 160	37 (23)	17 (57)	1 (6)	3 (14)	8 (29)	3 (14)	2 (7)	3 (19)
Language delay, *n* = 145	34 (23)	15 (58)	4 (25)	2 (10)	5 (20)	3 (17)	3 (11)	2 (17)
Postneonatal epilepsy, *n* = 151	18 (12)	12 (41)	1 (6)	0 (0)	3 (12)	0 (0)	0 (0)	2 (13)
Behavioral problems, *n* = 126	31 (25)	10 (37)	4 (31)	1 (6)	6 (25)	2 (13)	3 (17)	5 (42)
Visual field defect, *n* = 96	17 (18)	12 (48)	0 (0)	0 (0)	2 (14)	0 (0)	0 (0)	3 (27)
Combination of adverse outcomes, *n* = 161	50 (31)	26 (84)	3 (18)	2 (10)	8 (29)	2 (10)	2 (7)	7 (44)
Within normal range, *n* = 161	74 (46)	0 (0)	9 (53)	13 (62)	12 (43)	15 (71)	18 (67)	7 (44)

Number of infants tested per outcome domain are presented in the first column.

TABLE 5 Univariate Associations Between the MRI Parameters and Neurodevelopmental Outcome Domains

	Involvement on MRI							
	PLIC, OR (95% CI)	Cerebral Peduncle, OR (95% CI)	Basal Ganglia, OR (95% CI)	Thalamus, OR (95% CI)	BGT, OR (95% CI)	Central Sulcus, OR (95% CI)	Bilateral Lesions, OR (95% CI)	Multiple Lesions, OR (95% CI)
CP	6.7 (1.2–38.7)	115.6 (35.2–379.4)	5.5 (1.6–19.4)	NS	102.2 (27.8–376.2)	16.7 (6.7–41.6)	2.3 (1.0–5.2)	NS
Cognitive deficit	NS	6.1 (2.7–13.5)	NS	NS	5.9 (2.5–14.1)	4.2 (1.9–9.4)	NS	NS
Language delay	NS	4.7 (2.0–10.8)	NS	NS	7.2 (2.7–18.8)	4.1 (1.7–9.4)	NS	NS
Postneonatal epilepsy	NS	11.4 (3.5–37.4)	NS	NS	11.8 (3.1–44.9)	4.1 (1.4–12.2)	4.4 (1.5–12.9)	2.9 (1.0–8.6)
Behavioral problems	NS	NS	NS	NS	3.8 (1.5–9.5)	NS	NS	NS
Visual field defect	NS	8.4 (2.4–28.6)	NS	NS	7.8 (2.0–30.7)	3.5 (1.0–11.8)	NS	NS
Adverse outcome in any domain	NS	17.7 (5.9–52.9)	NS	NS	68.6 (8.9–526.5)	4.9 (2.4–9.7)	NS	NS

NS, nonsignificant.

associations between several MRI parameters and neurodevelopmental outcome domains (Table 5). Involvement of the cerebral peduncles and combined involvement of the BGT were both related to almost all adverse outcome domains with ORs ranging between 3.8 and 115.6 (Table 5).

Multivariable Modeling

For the total cohort, several MRI parameters were significantly and independently associated with different outcome domains, as described in Table 6. Because there was involvement of the CST, basal ganglia, and central sulcus in all main MCA branch infarcts, multivariable analyses were repeated separating all infants with main MCA branch infarction from the others (Table 6).

In infants with main MCA branch infarction, no specific MRI parameters were associated with different adverse outcome domains. In the other subgroup (*n* = 130), CP was still associated with involvement of the cerebral peduncle (OR: 34.4; 95% CI 5.6–208.9) and combined BGT involvement (OR: 6.9; 95% CI 1.1–45.1). Adverse cognitive outcome was associated with combined BGT involvement (OR: 4.4; 95% CI 1.2–16.9). Language delay and visual field defects were no longer associated with MRI features, but postneonatal epilepsy remained associated with involvement of the cerebral peduncle (OR: 9.7; 95% CI 1.0–101.1) and

TABLE 6 Logistic Regression Models for Neurodevelopmental Outcome Domains With Best Fit

Outcome Domain	MRI Parameters	Total Cohort, $N = 161$		Subgroup ($n = 130$) Excluding Main Branch MCA Stroke	
		OR	95% CI	OR	95% CI
CP	Cerebral peduncle	63.0	10.7–369.4	34.4	5.6–208.9
	BGT	21.0	4.1–106.6	6.9	1.1–45.1
Cognitive deficit	BGT	5.9	2.5–14.1	4.4	1.2–16.9
Language delay	BGT	7.1	2.7–18.8	NS	NS
Postneonatal epilepsy	Cerebral peduncle	13.9	2.9–67.6	9.7	1.0–101.1
	Bilateral lesions	3.6	1.1–11.7	15.9	2.3–110.8
Behavioral problems	BGT	3.8	1.5–9.5	8.9	1.9–41.2
Visual field defect	BGT	7.8	2.0–30.7	NS	NS
Adverse outcome in any domain	Cerebral peduncle	4.0	1.1–14.7	NS	NS
	BGT	27.9	3.2–244.0	17.1	2.1–141.1

NS, nonsignificant.

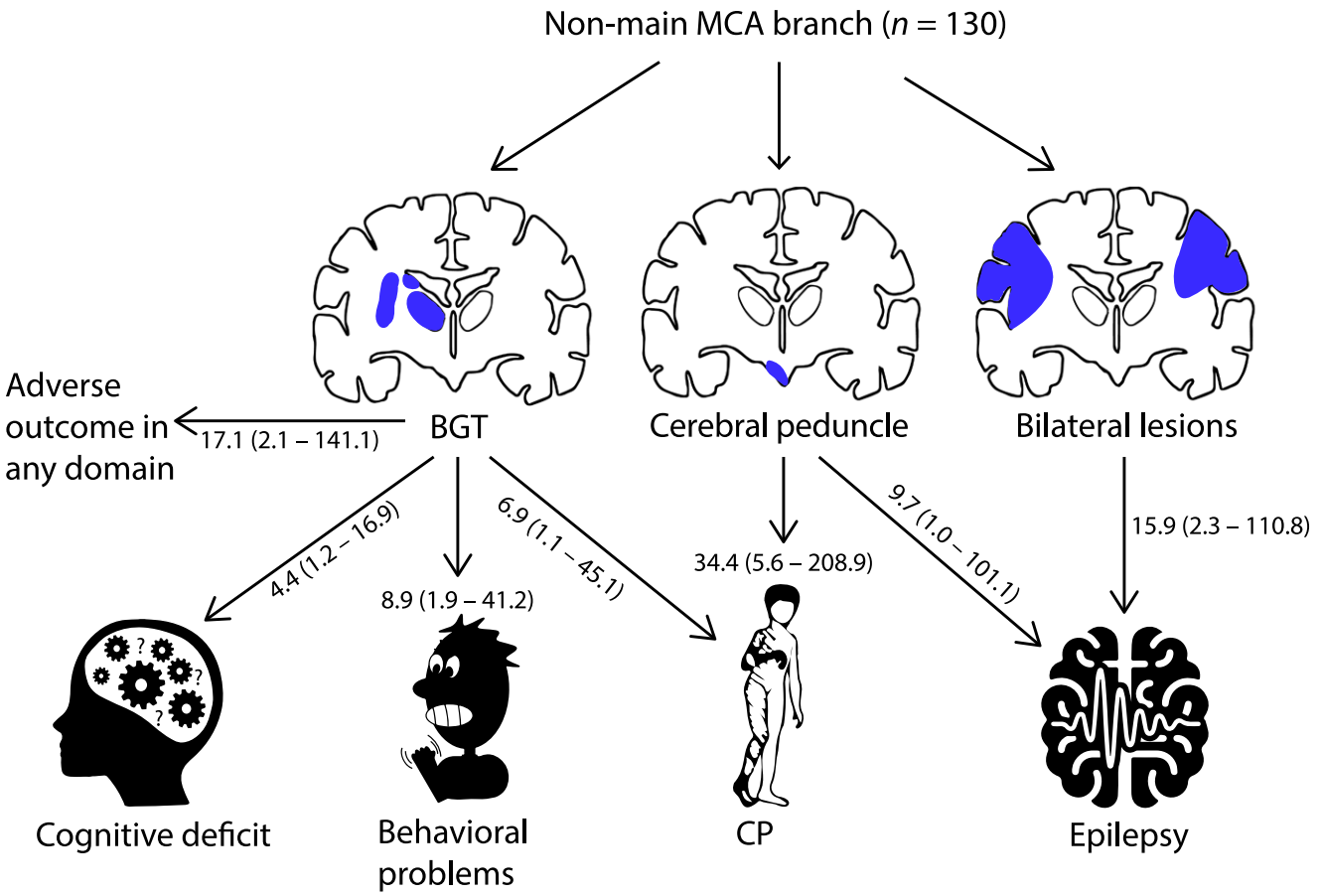

FIGURE 3
Graphic representation of the logistic regression models for neurodevelopmental outcome domains. Specific brain regions as seen on early MRI increase the odds for CP, epilepsy, and behavioral problems in a subgroup of 130 infants excluding those with main branch MCA stroke. Data are presented as OR with 95% CI.

bilateral lesions (OR: 15.9; 95% CI 2.3–110.8). Behavioral problems were associated with combined BGT involvement (OR: 8.9; 95% CI 1.9–41.2). Combined involvement of the BGT increased the risk of adverse outcome in at least 1 domain (OR: 17.1; 95% CI 2.1–141.1; Table 6; Fig 3).

DISCUSSION

In this study, we have demonstrated that an adverse outcome in term infants with PAIS depends on stroke territory (the site, extent, and location of the lesion). To the best of our knowledge, this is the first study in which is provided a precise overview of a spectrum of different outcome domains per stroke pattern

in a large cohort of term infants from 2 centers. Additionally, with our study, we highlight the use of early neonatal MRI, and especially DWI, to predict neurodevelopmental outcome, because outcome is not only dependent on stroke territory but also on the involvement of specific brain regions, such as the CST.

It is of great importance to clinicians and parents to evaluate promptly the risk of an adverse outcome in patients with PAIS, because early intervention strategies, which may attenuate unfavorable development, need to be appropriately focused.[26] It is also important when possible to reassure parents that outcomes are likely to be good. Several studies on neurodevelopment after PAIS are available, but authors of these studies report a wide range of abnormal neurodevelopment, mainly because there is no distinction between specific stroke subtypes.[27,28] This makes risk estimation difficult for the individual child. With our study, we have distinguished several specific PAIS subtypes and described incidence rates per outcome domain for them, enabling more personalized prediction of long-term development. In the literature, the incidence rate of CP after PAIS is ∼30%, comparable to our study.[6,8,27,28] However, infants with main MCA branch infarction will all develop CP, whereas this percentage ranges between 0% and 21% in other stroke subtypes. With our data, we provide a firm basis for informing parents of infants with main MCA branch infarction differently about future prospects than parents of infants with other stroke subtypes.

Involvement of the CST on neonatal MRI was seen in the majority of patients with more extensive stroke subtypes, as reported in other studies.[8,29] The CST signal changes are best seen on early DWI and have been described as "pre-Wallerian degeneration." When they are seen in the middle third of the cerebral peduncle they are always associated with the development of hemiplegic CP.[7,9] Because pre-Wallerian degeneration is the result of anterograde degeneration of the descending axons of injured cell bodies within the infarcted areas, it was found more often in infants with larger infarctions (affecting the complete motor cortex). Infants with other stroke subtypes not resulting in involvement of the CST in our cohort did not develop CP. We performed multivariable modeling separately for those without main MCA branch infarction, to determine individual MRI risk factors for adverse outcome in milder subtypes. For these subtypes, involvement of the cerebral peduncle was still a risk factor for CP and epilepsy, illustrating the importance of pre-Wallerian degeneration in the prediction of adverse outcome in those with less widespread stroke.

Involvement of the BGT increased the risk for CP, in agreement with the literature.[8,30,31] In our cohort, BGT involvement most commonly occurred with larger infarcts (main and partial MCA branches) and was most often part of the primary stroke. But BGT involvement could also be a manifestation of secondary injury to connectivity pathways (eg, corticothalamic or corticostriatal networks) particularly in the thalami and best seen on DWI.[17,30,32] The increased risk for CP most likely stemmed from the larger stroke than just the BGT involvement. This is supported by several studies revealing that primary stroke lesions restricted to the BGT (ie, perforator stroke) are usually not associated with adverse motor outcome.[6,33] In our cohort, only 15% of infants with perforator stroke developed unilateral spastic CP, all related to additional involvement of the PLIC.

Authors of a limited number of studies reported on long-term cognitive outcome in infants with PAIS.[27,34–36] We found that cognitive delay occurred in 23% of all PAIS patients but in 57% of those with a main branch MCA stroke when last seen at a median age of 41 months. Authors of other studies have reported even higher rates of cognitive impairment after PAIS at school age.[36,37] Because most infants were still young when last seen, we did not see a trend over time. Multivariable analysis revealed that cognitive delay was related to BGT involvement. However, this seemed to reflect larger strokes, because BGT involvement was most often seen in main and partial branch MCA strokes. Other studies have revealed that larger infarct volume was associated with adverse cognitive development in PAIS.[38–41] We also found that posterior MCA branch and PCA strokes had higher rates of cognitive delay compared with other nonmain MCA subtypes, indicating that not only volume but also location of affected tissue plays an important role in cognitive development. In a recent study, Stephan-Otto et al[42] reported that stroke in regions posterior to the central sulcus, close to the arcuate fasciculus, may account for language deficits after PAIS. In our cohort, rates of language delay were not higher in posterior compared with anterior MCA branch strokes, but many children were too young for detailed speech or language assessment. It was of interest that infants with language delay had 6.5 to 10 times increased risk of cognitive delay, revealing that language and cognition are closely related. However, cognitive delay might also precede language delay or share a common origin, and exact causative mechanisms need to be studied further. Development of postneonatal epilepsy increased the risk for cognitive delay as described previously, but this was limited to infants with main MCA stroke.[43]

This study has several limitations inherent to its retrospective design.

Infants were only eligible if they were admitted to the NICU or referred for neurologic assessment, excluding infants with (smaller) infarcts that may not have caused neonatal symptoms; also, preterm infants were not included.[44] However, our strict inclusion criteria resulted in a homogeneous group of term infants with PAIS. This study was focused on DWI from MRI, whereas early DWI may not always be possible in all institutions. However, we were often able to see signal intensity changes in CST on T2-weighted sequence as well, especially when the MRI was done in the second half of the first week. The use of apparent diffusion coefficient (ADC) maps from DWI to assess acute ischemic injury is recommended to avoid T2 shine-through and other artifacts. Because the ADC map was not always available for our cohort, we used DWI for all infants. When ADC maps were available, they were used to verify DWI signal abnormalities, as is recommended in clinical practice. Infants that performed well were sometimes discharged from follow-up, and cognitive, language, and behavioral problems may have been underdiagnosed.[36,37] Long-term outcome studies with a prospective design are needed to determine whether early predictions in PAIS patients remain stable over time. Even with this large study, some subgroups were small, and we cannot exclude that some associations between brain regions and outcomes might have been significant.

CONCLUSIONS

In a large cohort of term-born infants from 2 centers, we have demonstrated that neurodevelopmental outcomes vary between PAIS subtypes. Although neurodevelopmental outcome was invariably adverse in at least 1 domain with main branch MCA stroke, in other PAIS subtypes, outcome was normal in 43% to 71% of children. With this study, we provide clinicians with important information for more precise risk evaluation of neurodevelopment in PAIS patients on the basis of the tissue involved, assessed from early MRI allowing better counseling of parents in the neonatal period, personalized planning of therapeutic interventions, and long-term support for behavioral and cognitive difficulties.

ABBREVIATIONS

ACA: anterior cerebral artery
ADC: apparent diffusion coefficient
BGT: basal ganglia and thalami
BSITD-III: Bayley Scales of Infant and Toddler Development, Third Edition
CI: confidence interval
CP: cerebral palsy
CST: corticospinal tract
DWI: diffusion-weighted imaging
GMDS: Griffiths Mental Development Scale
IQR: interquartile range
MCA: middle cerebral artery
OR: odds ratio
PAIS: perinatal arterial ischemic stroke
PCA: posterior cerebral artery
PLIC: posterior limb of the internal capsule
UMCU: University Medical Center in Utrecht

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: No external funding.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

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Supplemental Information

SUPPLEMENTAL TABLE 7 Additional Information on the Subgroup of Excluded Infants

Infarct Subtype	Reason for Exclusion	Details
PCA stroke	Syndrome	Cerebellar hemorrhage, infarction, and hydrocephalus after vitamin K deficiency related to α1-antitryptin
PCA stroke	Syndrome	CHARGE syndrome association
Perforator stroke	Syndrome	Cystic fibrosis
Perforator stroke	Syndrome	22q11 with hypoplastic left heart syndrome
PCA stroke	Other significant brain lesion	Large sinovenous thromobosis and thalamic hemorrhage
Cortical stroke	Other significant brain lesion	Severe watershed injury
PCA stroke	Other significant brain lesion	Large cerebral aneurysm
Perforator stroke	Other significant brain lesion	Intraparenchymal hemorrhage in temporal lobe
Main MCA stroke	Died	Main MCA stroke with severe asphyxia; Vein of Galen AVM; died as a result of hemorrhage
PCA stroke	Died	PCA with severe asphyxia; withdrawal of care due to severe hypoxic-ischemic encephalopathy injury to the deep gray matter
Main MCA stroke	Died	Bilateral MCA stroke; died as a result of these lesions
Perforator stroke	Lost to follow-up	Tested only at 12 mo; until then, normal development
Posterior MCA branch	Lost to follow-up	Tested only at 12 mo; until then, normal development
Posterior MCA branch	Lost to follow-up	Normal development at 10 mo, then discharged from follow-up
Posterior MCA branch	Lost to follow-up	Moved abroad before 3 mo of age
Cortical stroke	Lost to follow-up	Refused all follow-up
Perforator stroke	Lost to follow-up	Moved abroad before 6 mo of age
Posterior MCA branch	Lost to follow-up	Seen only at 8 mo with normal symmetrical development
Posterior MCA branch	Lost to follow-up	Seen only at 9 wk; until then, normal development
Anterior MCA branch	Lost to follow-up	No follow-up available
Posterior MCA branch	Lost to follow-up	No follow-up available
Posterior MCA branch	Lost to follow-up	Seen only at 5 mo with signs of hemiplegia but no follow-up available afterward
No information available	Lost to follow-up	No follow-up available
No information available	Lost to follow-up	No follow-up available
Middle MCA branch	Lost to follow-up	No follow-up after 3 mo
Posterior MCA branch	Lost to follow-up	Seen only at 6 mo; until then, normal development
Cortical stroke	Lost to follow-up	No follow-up available
PCA stroke	Lost to follow-up	No follow-up available
Main MCA stroke	Lost to follow-up	No follow-up available
Posterior MCA branch	Lost to follow-up	No follow-up available

AVM, arteriovenous malformation; CHARGE, coloboma, congenital heart disease, choanal atresia, mental and growth retardation, genital anomalies, and ear malformations and hearing loss.