Acutely and Retrospectively Diagnosed Perinatal Stroke
A Population-Based Study

Rael Laugesaar, MD; Anneli Kolk, PhD; Tiiu Tomberg, PhD; Tuuli Metsvaht, MD; Mare Lintrop, MD; Heili Varendi, PhD; Tiina Talvik, PhD

Background and Purpose—There are not very many epidemiological studies on perinatal stroke, and many authors suggest that this may be an underdiagnosed condition. The aim of the study was to estimate the incidence of perinatal arterial ischemic and hemorrhagic stroke in Estonia, to study the first clinical signs and to identify possible differences in predisposing factors and outcome between acutely and retrospectively diagnosed cases of perinatal stroke.

Methods—A retro- and prospective study of acutely (within the first month) and retrospectively diagnosed ischemic and hemorrhagic cases of perinatal stroke was conducted in a children population born in the eastern and southern regions of Estonia during the years 1994 to 2003. Patients were identified from a pilot study, hospital records, and an inquiry of child neurologists and general practitioners. The diagnosis was confirmed in 38 (12 were diagnosed acutely and 26 retrospectively) cases by neuroradiology (MRI or CT).

Results—The incidence rate of perinatal stroke in Estonia is 63 per 100 000 live births. Main clinical findings in the neonatal period were seizures, abnormalities of muscular tone, and disturbed level of alertness. Previously identified risk factors occurred in 32% of cases. Children with early diagnosis had more often adverse events during pregnancy and delivery (P<0.05) and developed more severe stage of hemiparesis compared with children with late diagnosis (P<0.05).

Conclusions—The incidence rate of 63 per 100 000 live birth is higher than previously reported. Detailed analysis of the first signs of perinatal stroke may improve the early diagnostics of perinatal stroke. (Stroke. 2007;38:2234-2240.)

Key Words: clinical signs incidence perinatal stroke

Perinatal stroke is a cerebrovascular event that occurs between 28 weeks of gestation and 28 days of postnatal age.1 Main clinical features in the neonatal period are seizures, apnea, and depressed level of alertness.2 Symptoms after birth lead to neuroimaging, where usually an acute insult of vascular origin is recognized.3,4 Some infants are considered neurologically normal in the neonatal period, and perinatal stroke may be diagnosed retrospectively during later months after the presentation of hemiparesis or seizures if neuroimaging demonstrates a remote vascular event.5

Only a few studies on the incidence rate of perinatal stroke have been carried out, and many authors suggest that this may be an under-diagnosed condition (Table 1).1,6 The estimated incidence rate varies largely, depending on the methodology of the study. Previously published perinatal stroke studies have typically been restricted to only arterial ischemic stroke, and most studies have included only children diagnosed in the neonatal period. They have found an incidence rate of 1.35 to 43.4 per 100 000 live births.1,7-10 Two published population-based studies which involved also retrospectively diagnosed cases demonstrated the incidence of perinatal arterial stroke 17 and 20 per 100 000 live births.11,12

The cause of perinatal stroke remains often unclear. To date 4 case-control studies11-14 of risk factors for exclusively perinatal stroke have found that lipoprotein (a), factor V Leiden mutation, hyperhomocysteinemia, protein C deficiency, preeclampsia, intrauterine growth restriction, prolonged rupture of membranes, and chorioamnionitis were independent risk factors for perinatal arterial stroke. Two other case-control studies have not shown the significant association between perinatal stroke and perinatal factors8 or trombophilia.15

The aim of the study was to estimate the incidence of arterial ischemic and hemorrhagic perinatal stroke in Estonia, to study the first clinical signs, and to identify possible differences in predisposing factors and outcome between acutely and retrospectively diagnosed cases of perinatal stroke.

Subjects and Methods
A retro- and prospective population-based study was conducted from January 1, 1994 to December 31, 2003. The study involved the
eastern and southern regions of Estonia (Figure). Estonia, with a population of 1,356,000 people, is situated in the north of Europe, on the eastern shores of the Baltic Sea. Estonia occupies an area of 45,227 km², and our study area comprised 44.6% of continental Estonia. There were 59,976 live births (30,681 males and 29,295 females) in the study region during the years 1994 to 2003. According to national statistics, 72% were born to Estonian-speaking families. Estonians belong to the Finno-Ugric ethnic group. The second most frequent ethnic group is Slavs. Our investigation was carried out in the departments of neurology and neonatology of the Children’s Clinic and Anesthesiology and Intensive Care Clinic of Tartu University Hospital. All children from eastern and southern Estonia, who have serious medical conditions, are treated in these tertiary care centers.

Case Ascertainment

Patients with perinatal stroke were identified using different approaches. First, a list of children from a pilot study was used, where the hospital records from the archives of both tertiary children clinics of Estonia (the Children’s Clinic of Tartu University Hospital and Children’s Hospital of Tallinn) were searched for the following diagnoses: perinatal/neonatal stroke and hemiparesis. Second, new cases of perinatal stroke from the 1st of January 2003 were included into the study. Third, an inquiry (a letter and telephone calls) was set up among child neurologists and general practitioners in the study region to find children with hemiparesis. In addition, information was disseminated to doctors through lectures and medical seminars throughout the study period.

The following inclusion criteria were used for patient selection: (1) congenital hemiparesis or seizures, (2) computed tomography (CT) or MRI performed in the neonatal period revealing an acute or remote ischemic or hemorrhagic (subarachnoid, intraparenchymal or intraventricular hemorrhage) stroke, (3) CT or MRI performed after the neonatal period revealing a lesion consistent with remote ischemic or hemorrhagic stroke, (4) gestational age at least 32 weeks, (5) born in years 1994 to 2003, (6) birth registered in 1 of the 7 counties situated in the eastern and southern regions of Estonia. Exclusion criteria were: (1) other documented diseases with central nervous system (CNS) involvement before the diagnosis of perinatal stroke, and (2) acute stroke after 1 month of age (childhood stroke).

### Table 1. Previous Population-Based Studies on Perinatal Arterial Stroke

<table>
<thead>
<tr>
<th>Reference</th>
<th>IR per 100,000 Live Births</th>
<th>Type of Stroke Included</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perlman 1994</td>
<td>28.6</td>
<td>AIS</td>
</tr>
<tr>
<td>Estan 1997</td>
<td>24.7</td>
<td>AIS</td>
</tr>
<tr>
<td>Govaert 2000</td>
<td>35.0</td>
<td>AIS</td>
</tr>
<tr>
<td>Schulze 2005</td>
<td>43.4</td>
<td>AIS</td>
</tr>
<tr>
<td>NHDS 1980–1998</td>
<td>17.8</td>
<td>AIS</td>
</tr>
<tr>
<td>NHDS 1980–1998</td>
<td>6.7</td>
<td>HS</td>
</tr>
<tr>
<td>Wu 2004</td>
<td>17.0</td>
<td>AIS</td>
</tr>
<tr>
<td>Lee 2005</td>
<td>20.0</td>
<td>AIS</td>
</tr>
</tbody>
</table>

AIS indicates arterial ischemic stroke; NHDS, National Hospital Discharge Survey; HS, hemorrhagic stroke.
Data Abstraction
In total, 53 children (28 boys, 25 girls) with suspected perinatal stroke were identified. The medical records of these children were reviewed critically and independently by at least 2 investigators (R.L., T.T., and A.K.) to identify the diagnoses of perinatal stroke, and in uncertain cases the children were reinvestigated by one of them. Fifteen children were excluded from the study: 3 extremely premature children (<32 weeks of gestation), 4 children with other diseases of central nervous system, 7 children with negative neuroangiography, and 1 child in whom confirmative cranial imaging (MRI or CT) was not performed.

A neuroradiology specialist (M.L.) reviewed ultrasound (US) scans and the other neuroradiology specialist (Ti.To.) blinded to the clinical diagnosis reviewed the CT and MRI scans. For neuroradiological examinations US, CT (Siemens AG, Somatom Volume Access, or Somatom Spiral HP) and MRI (Siemens AG, Magnetom [Symphony] 1.5 T) were used. MRI sequences included T1-weighted images (TR 500 ms, TE = 14 ms), fast fluid attenuated inversion recovery (FLAIR) images (TR = 9000 ms, TE = 105 ms, inversion time TI = 2300 ms), and SE T2-weighted images (TR = 4000 ms, TE = 90 ms). Acquisition matrix = 256×224 pixels, FOV = 230, and slice thickness = 5 mm were applied. On CT the areas of decreased density, cerebral swelling and in some cases hemorrhagic compartment were indicative of an acute stroke. In the late period it corresponded to areas of hypodensity or porencephaly and brain atrophy in a vascular distribution. On MRI the distribution of the signal abnormalities in all patients was identified and classified as cerebral cortex, basal ganglia, internal capsule, and periventricular white matter involvement. Contrast medium was not used as a rule. In the late period we looked for areas of porencephaly in a vascular distribution lined by white matter, signal abnormalities, and volume loss that corresponded to the area of infarction. Local areas of cerebral atrophy and any asymmetries of cerebrospinal fluid spaces were also identified.

Electroencephalography (EEG), electrocardiography (EKG), and echocardiography (Echo-KG) were performed as part of the standard evaluation.

Study children were divided into 2 subgroups: (1) early perinatal stroke, defined as systemic or neurologic symptoms with radiographic evidence of acute or remote vascular event in the neonatal period; (2) delayed perinatal stroke, defined as no diagnosis of stroke in the neonatal period, clinically congenital hemiparesis or seizures, and radiographic evidence of remote focal infarction, encephalomalacia, or porencephaly. For comparison between these 2 subgroups, side of brain damage, prematurity, primiparity, birth weight, cardiac disorders, congenital thrombophilias, infections, maternal diseases, placental disorders, and occurrence of birth asphyxia were registered.

Cardiac disorders were investigated in 17/38 cases and included congenital diseases and arrhythmias. Congenital thrombophilias were studied in 27/38 cases and only after 2003, meaning that all samples were taken months or years after the acute event. Screening for prothrombotic conditions included full blood count, fasting cholesterol and triglycerides, total homocysteine, anticardiolipin antibodies, lupus anticoagulant, antithrombin III, protein S, protein C, activated protein C resistance, Factor V Leiden, and prothrombin 20210 gene. Laboratory method for the measurement of lipoprotein (a) levels was not available. History of ante- and perinatal events was obtained from the obstetrical reports. Infections included congenital infections as well maternal infectious episodes during pregnancy. Maternal diseases included preeclampsia, history of infertility, hyperthyroidism, surgical interventions during pregnancy, abdominal trauma, and systemic illnesses. Factors implicating placental disorders included clots, placental abruption, choioamnionitis, fetomaternal transfusion, and intrauterine growth retardation. Birth asphyxia was diagnosed by the treating physician.

Follow-up period lasted from 2 to 12 years, with an average of 7 years. Hemiparesis was assessed according to the hand function: stage I, mildly disturbed finger movements; stage II, significant disturbance of finger movements; stage III, minimal finger movements; stage IV, hemiplegia, absence of all movements. Epilepsy was defined as at least 2 unprovoked epileptic seizures after 1 week of the acute event of stroke.

Data Analysis
Statistical analysis was performed using the statistical package SAS Version 8.02. Statistical comparisons between normally distributed continuous variables were performed with Student t test. Kolmogorov-Smirnov criterion was used for the assessment of normality. To compare proportions (qualitative variables) the χ² test or the Fisher exact test (when expected values were <5%) were used. Odds ratios (OR) and 95% CI were used to estimate relative risk. We used Kaplan-Meier estimation of the proportion of subjects at any point during follow-up, and the log-rank statistic and Cox proportional hazards regression to assess differences between the epilepsy-free survival curves. All probability values were 2 sided, and differences were considered statistically significant if the probability values were less than 0.05.

The study was approved by the Medical Research Ethics Committee of Tartu University and informed consent was obtained from the parents for participation in the study.

Results
Incidence
The diagnosis of perinatal stroke was confirmed in 38 children (18 boys, 20 girls). Among them 2 retrospectively diagnosed children, who were born in the study area but treated in the Children’s Hospital of Tallinn, were included into the study. Thirty-two cases (84%) were of Estonian nationality and 6 cases (16%) of Slavic origin. Twelve of these 38 children, (9 boys, 3 girls) were diagnosed in the neonatal period, whereas the remaining cases (9 boys, 17 girls) where diagnosed retrospectively during the later months of life, because they did not develop symptoms in the neonatal period. With 59 976 live births over the 10-year study period, the incidence rate of perinatal stroke in Estonia is 63.4/100 000 or 1 per 1578 live births; 58.7/100 000 for boys and 68.3/100 000 for girls. The incidence rate of perinatal stroke recognized in the newborn period is 20.0/100 000 or 1 per 4998 live births; 29.3/100 000 for boys and 10.2/100 000 for girls. The incidence rate of retrospectively diagnosed perinatal stroke is 43.4/100 000 or 1 per 2307 live births; 29.3/100 000 for boys and 58.0/100 000 for girls.

Clinical Presentation
All children with early diagnosis presented symptoms within the first days from birth (12/38; Table 2). Most frequently registered symptoms were seizures (11/12), changes in muscular tone (9/12), and disturbed level of alertness (8/12). In patients with neonatal seizures epileptic dischargers on EEG were confirmed in 3/11 cases. Hypoxic-ischemic encephalopathy was diagnosed in 10/12 newborns: grade I in 1, grade II in 7, and grade III in 2 cases. Nine neonates needed treatment in intensive care, and 5 were intubated and needed artificial ventilation.

Among the 26 retrospectively diagnosed cases, only 6 children (23%) presented mild clinical signs in the neonatal period (Table 2). Most often (5/26) mild changes of muscular tone were documented. After the neonatal period 22/26 children required medical attention because of hemiparesis and 4/26 because of seizures. Mean age at the emergence of symptoms was 8.0 months (range: 1 month to 2 years).
Cranial Radiology
Cranial radiology (US, MRI, or CT) was performed in all children with perinatal stroke diagnosed in the neonatal period (12/38). Acute arterial ischemic lesions were identified in 4/12 neonates in the initial images during the neonatal period—all infarcts were in the region of the left middle cerebral artery. In the other 7/12 children hemorrhagic lesions were diagnosed: subarachnoidal hemorrhage with periventricular edema in 1, parenchymal bleeding in 2, and intraventricular hemorrhage in 4 children. Intraventricular hemorrhage was unilateral in 3 (3/4) cases. In 1 case (1/12), MRI on the 8th day of life revealed asymmetrical porencephalic dilatation of the lateral ventricles and hemiatrophy referring to antenatal onset of the vascular event. After the neonatal period neuroimaging demonstrated a large porencephalic lesion as a result of the arterial ischemic or hemorrhagic insult as the main finding in 11/12 and small unilateral periventricular cysts in 1 case.

In children with retrospectively diagnosed perinatal stroke neuroimaging (CT or MRI) was performed at a mean age of 25 months (range: 1 month to 5 years). Eleven (11/26) children had cortical damage; basal ganglia or internal capsule were affected without cortical damage in 4/26 children and lesions of the periventricular white matter alone were present in 11/26 cases. Porencephaly was described in 13 cases, T2-hyperintensities in another 7 cases. Four children had more than one risk factor. 

All children had evidence of hemiparesis: right-sided in 32/38 (84%) and left-sided in 6/38 (16%) cases, grade I (mild) in 9, grade II (moderate) in 17, and grade III (severe) in 12 children. Thirteen children of the study group (34%) had developed epilepsy by the mean age of 3 years (range: 9 months to 7 years). Six children had complex focal seizures, 5 had simple focal seizures, and 2 had complex focal seizures with secondary generalization.

Subgroup Comparison
Comparison between children with early (group I) and delayed diagnosis of perinatal stroke (group II) revealed male predominance within children with early diagnosis. Newborns in group I were born statistically more often from the first delivery and were with bigger birth weight (P<0.05, Table 3). Placental pathology and asphyxia occurred significantly more often in group I (P<0.01).

Severe hemiparesis (stage III) occurred more often among patients who were diagnosed in the neonatal period (OR=6.9; 95% CI 1.40; 33.57). Epilepsy occurred in the same proportion of children with early and delayed diagnosis (log-rank P=0.916).

Discussion
According to our study, the incidence rate of perinatal stroke in our population is 63.4 per 100,000 live births. To our knowledge this is the third research study with the aim to find the incidence rate for retrospectively diagnosed perinatal stroke. We admit this is ambitious. But Estonia is a small country with well-developed medical care system, which facilitates epidemiological studies. Two previous population-based studies of perinatal stroke considering both acutely and retrospectively diagnosed cases found the incidence rate lower than we did. Both studies included only arterial ischemic strokes, whereas our study comprises also children with arterial hemorrhagic strokes as well as children with arterial ischemic stroke presented as unilateral periventricular white matter lesions as classified earlier.

For comparison with prior studies of early diagnosed neonatal stroke, we have to analyze separately the incidence of perinatal arterial stroke diagnosed in the neonatal period (20.0 per 100,000 live births), which is lower than in earlier studies (Table 1), even though we have included hemorrhagic cases. At the moment the consensus is missing about whether to include only ischemic or also hemorrhagic cases in the epidemiological studies of perinatal stroke. We decided to include hemorrhagic cases of perinatal stroke into our study, as the pathogenetic mechanisms are often combined in perinatal damage: the neuroradiological follow-up showed porencephaly in arterial distribution in later stage in 6 of 7
cases with intracranial bleeding diagnosed in the neonatal period.

As in two-thirds of cases the diagnosis of perinatal stroke is delayed, we were interested whether it is feasible to promote earlier diagnostics. We found in our study that neonatal seizures were the most common clinical finding that led to further investigations, which is in good correlation with previous studies.3,7,8,10 –12,22–25 In no case of delayed diagnosis of perinatal stroke, neonatal seizures were mentioned in the medical records, implicating that to improve the early diagnostics of perinatal stroke we have to look carefully for clinical signs other than neonatal seizures. One in 5 of the retrospectively diagnosed children presented with changes of muscular tone in the neonatal period, meaning that more attention should be paid to the issue by doctors, treating the neonate immediately after birth.

Among neonates with early diagnosis 11/12 cases demonstrated evidence of an acute brain insult in neuroradiology. These data are in good correlation with the study of Cowan et al.,4 who showed that 80% of term newborns with encephalopathy had evidence of acute hypoxic-ischemic brain lesions in MRI, a finding that contradicted the previous opinion about the brain damage during the fetal period. In our study group with early diagnosis of stroke, encephalopathy was diagnosed in 83% of cases. This supports the need for MRI investigation in all children with clinical symptoms of encephalopathy. In our study group left-sided brain damage occurred more often than right-sided, which is consistent with the results of other investigators.3,5,7–9,12,23 In one-third of cases the other side of brain was also affected, but to a smaller extent. Studies on animal models of neonatal stroke have shown that after large unilateral neonatal hypoxic brain injury, apoptotic processes are present in both hemispheres.26 No difference in side of brain damage was observed between children with early or delayed diagnosis of perinatal stroke.

The estimation of the exact timing of brain lesion is difficult in children with retrospectively diagnosed perinatal stroke when first neuroradiological study is performed several months after the acute event. Our study did not include children with congenital brain malformations as holoprosencephaly, agenesis of corpus callosum, and migrational abnormalities (heterotopias and lissencephaly) which are associated with brain damage occurring earlier than 28 weeks of gestation.27,28 Eleven children with late diagnosis showed mainly periventricular white matter lesions, which are considered to happen during the early 3rd trimester of gestation.29 Gray matter lesions seems to occur toward the end of the 3rd trimester and in the term-born infant.29 Further investigations are needed to specify whether perinatal stroke with delayed clinical presentation takes place rather before, during, or after the delivery.

Our study revealed previously identified risk factors for perinatal stroke in 32% children. Unfortunately only a few

<table>
<thead>
<tr>
<th>TABLE 3. Comparison Between Children With Early and Late Diagnosis</th>
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<tbody>
<tr>
<td>Group I (n=12)</td>
</tr>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Boys</td>
</tr>
<tr>
<td>Girls</td>
</tr>
<tr>
<td>Side of damage</td>
</tr>
<tr>
<td>Left</td>
</tr>
<tr>
<td>Right</td>
</tr>
<tr>
<td>Prematurity</td>
</tr>
<tr>
<td>Protein C deficiency</td>
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<tr>
<td>Hyperhomocysteinemia</td>
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<tr>
<td>Preeclampsia</td>
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<tr>
<td>IUGR</td>
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<tr>
<td>Chorioamnionitis</td>
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<tr>
<td>First delivery</td>
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<tr>
<td>Mean birth weight of term neonates (95% CI)</td>
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<tr>
<td>3798 g (3510; 4086)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
</tr>
<tr>
<td>4 (33%)</td>
</tr>
<tr>
<td>Trombophilia</td>
</tr>
<tr>
<td>Infection</td>
</tr>
<tr>
<td>Maternal disorders</td>
</tr>
<tr>
<td>Placenta disorders</td>
</tr>
<tr>
<td>Birth asphyxia</td>
</tr>
<tr>
<td>Grade of hemiparesis</td>
</tr>
<tr>
<td>Severe</td>
</tr>
<tr>
<td>Mild-moderate</td>
</tr>
<tr>
<td>Epilepsy</td>
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</tbody>
</table>
*Relative risk (RR).
case-control studies have been carried out to identify risk factors for perinatal stroke.8,11–15 This is a large field for further investigations.

It remains to question why some children with perinatal stroke are symptomatic in the newborn period and others are not. Comparison between the 2 study subgroups revealed that several perinatal factors previously associated with perinatal vascular brain damage,1,2,5,18,19 including placental pathology and perinatal asphyxia, were significantly more frequent among children with early diagnosis. Only coagulopathies were more common, but not significantly, among retrospectively diagnosed children, reflecting that inherited disorders rather than adverse events around the delivery play an important role in the pathogenesis of retrospectively diagnosed perinatal stroke.

Our study has a number of limitations. First, to a large extent the study was retrospective by nature and we may have missed some lethal cases during the study period. Second, not all children were tested for cardiac and prothrombotic factors, so the prevalence of these causes could be different within the entire study cohort. The strengths of our study are good preconditions that facilitate epidemiological studies: a country with a small population and well developed health care system with one medical research center.

All children in our study had clinically manifested hemiparesis. On one hand, this rises from our study design, because the presence of hemiparesis was a prerequisite for inclusion in the retrospective study as a marker of focal brain damage.30 In contrast to adult population, lesions of the left hemisphere during childhood rarely result in pronounced speech and language disorder.30,31 However, we may have missed children with perinatal stroke and speech disorder as the only clinical manifestation.

Reports of neonates with stroke presenting with seizures but without significant birth asphyxia and encephalopathy have demonstrated favorable neurodevelopmental outcome,7,24,25 whereas neurodevelopmental outcome was abnormal in all encephalopathic neonatal stroke patients in a cohort study.3 Our study revealed that early diagnosis of perinatal stroke is more likely to be followed by severe stage of hemiparesis (P<0.05). This is consistent with a previous finding that more severe symptoms in the newborn period correlate with more significant disabilities on long-term follow-up.22

In our outcome study we found that besides the persistent hemiparesis, one-third of cases developed epilepsy with the same occurrence among children with early and delayed diagnosis. This is contradictory to a previous study, where infants who were diagnosed in the neonatal period were more likely to develop epilepsy.31 Other investigators have found persistent epilepsy in 0% to 92%11,22,25 of children with early and in 23% to 36% of patients5,11 with delayed diagnosis. Our earlier study found that 35% of children with hemiparetic form of cerebral palsy develop epilepsy.32 Studies on epilepsy in Estonia have revealed that in 57.5% of cases the initial seizure took place at the age of more than 4 years,33 and therefore some children from our study population with later birth years may develop epilepsy in the future.

Summary

The incidence of perinatal stroke in Estonia is 1 per 1578 live births. One-third of cases present with neonatal seizures, which lead to further investigations and early diagnosis of perinatal stroke. The other two-thirds do not develop neurologic symptoms in the immediate postnatal period and are diagnosed later when hemiparesis or seizures are noted and neuroimaging reveals evidence of a remote vascular event. Motor outcome is worse after the early diagnosis of perinatal stroke, and one-third of children both with early and late diagnosis of perinatal stroke develop epilepsy.

Acknowledgments

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Disclosures

None.

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