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## Perinatal stroke and the risk of developing childhood epilepsy

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### Abstract

**Objectives**—To describe the prevalence of epilepsy after 6 months-of-age in children with perinatal stroke and examine whether perinatal data predict epilepsy onset and resolution.

**Study design**—A retrospective review of 64 children with perinatal stroke. In children with at least 6 months of follow-up data, Kaplan-Meier curves, univariate log-rank tests, and Cox proportional hazards models were used to examine predictors of time to development of seizures, and time to resolution of seizures in children with epilepsy. The association of risk factors with the presence of epilepsy at any time after 6 months-of-age was examined using Fisher's exact test.

**Results**—Forty-one of the 61 children with at least 6 months of follow-up data (67%) had epilepsy between 6 months-of-age and last follow-up, but in 13 of 41 seizures eventually resolved and anticonvulsants were discontinued. Infarct on prenatal ultrasound ( $p=0.0065$ ) and family history of epilepsy ( $p=0.0093$ ) were significantly associated with time to development of seizures after 6 months-of-age in the univariate analysis. No assessed variables were associated with time to resolution of epilepsy or with the presence of epilepsy after 6 months-of-age.

**Conclusions**—Childhood epilepsy is frequent after perinatal stroke. Evidence of infarction on prenatal ultrasound and a family history of epilepsy predict earlier onset of active seizures.

Epilepsy affects approximately 5 out of 1000 children; however, children with central nervous system injury are at increased risk<sup>1</sup>. Children with perinatal arterial ischemic stroke appear to be at increased risk for childhood epilepsy, but estimates of epilepsy after perinatal stroke vary widely. Epilepsy rates ranging from 0–50%<sup>2–9</sup> were reported for studies of 8–46 children with a median of approximately 35 months of follow-up. There are few studies examining clinical factors that predict the development of childhood epilepsy in children with perinatal stroke, and little data on when children with perinatal stroke develop epilepsy. When parents are told that their child had a perinatal stroke and the possible outcomes are described, physicians are often faced with the following three questions: will my child have epilepsy when he is older?

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If my child does have epilepsy, will the medication stop all his seizures? When would he develop seizures? The purpose of this study is to answer these questions by describing the prevalence and severity of epilepsy after 6 months-of-age in children with perinatal stroke, examine whether data present in the perinatal period predict the presence of childhood epilepsy, describe when these children develop active seizures and examine predictors of time to onset of seizure activity.

## Methods

### Population

Sixty-four children with perinatal arterial ischemic stroke were initially identified using a combination of the following techniques: review of neurology clinic records from January 1990-January 2007; patient referral; and *International Classification of Disease, 9<sup>th</sup> edition* code searches from May 1 1999-May 1 2004 using codes 767 (neonatal stroke), 433 (occlusion and stenosis/precerebral ischemia), 434 (occlusion of cerebral arteries), 435 (transient cerebral ischemia), 436 (acute but ill-defined cerebrovascular disease), 437 (other and ill-defined cerebrovascular disease), 438 (late effects of cerebrovascular disease) and 342 (acute hemiplegia)<sup>10</sup>. ICD-9 codes searches of additional years were not performed due to the limitations of these searches.<sup>11</sup> Birth years of patients ranged from 1990–2005. The perinatal period was defined as the time from the end of the 20<sup>th</sup> week of gestation to day 28 after birth<sup>12</sup>. All children had a gestational age of at least 36 weeks at birth, presented with neurological symptoms during the neonatal period (first 28 days of life) and were diagnosed with arterial ischemic stroke before discharge home from the neonatal intensive care unit (NICU). Children with radiographic evidence of generalized hypoxic ischemic injury or dysmorphic features suggestive of a genetic syndrome were excluded.

### Data Collection

Data were collected from the medical record on prenatal ultrasound imaging abnormalities, clinical presentation, perinatal comorbidities, initial cranial computed tomography (CT) and/or magnetic resonance imaging (MRI), initial and follow-up electroencephalograms (EEG), family history of epilepsy in first- or second-degree relatives, and epilepsy status during all available follow-up. Based on radiographic findings, stroke locations were identified, described by arterial territory, and classified as unilateral or bilateral. Unilateral middle cerebral artery (MCA) infarctions were classified as large branch (involving the M1 territory) or small branch. EEG reports were reviewed and classified as normal or abnormal. Abnormalities were classified as abnormal background consistent with encephalopathy, slowing or voltage attenuation, epileptiform discharges, or electrographic seizure activity. Epilepsy outcomes were assessed in children at least 6 months-of-age at the last clinical follow-up. All subjects had clinic notes that included the clinician's record of last seizure and estimated frequency of seizures. Children were classified as having or not having epilepsy, and were classified according to a modified form of the Engel classification<sup>13, 14</sup> adjusted by our group for a young population with limited follow-up and no surgical intervention: Class 0= seizure-free and off anticonvulsants for at least 6 months, Class 1= seizure-free for at least 6 months while on medication or seizure-free off medication for fewer than 6 months, Class 2= less than one seizure a month, Class 3= 1–4 seizures a month, Class 4= 5–30 seizures a month, Class 5= 30 or more seizures a month. Epilepsy was defined as modified Engel (ME) class 1 or higher, active seizures were defined as ME class 2 or higher, and severe epilepsy was defined as ME class 3 or higher. All children with epilepsy had at least 2 nonfebrile clinical seizures or 1 nonfebrile clinical seizure with an EEG demonstrating epileptiform discharges.

## Statistical Analysis

Totals and proportions were used to describe the clinical characteristics of the population. Time to development of first seizure after six months-of-age was the primary outcome examined. Six months-of-age was chosen as a starting point because in our clinical experience children with perinatal stroke are often maintained on phenobarbital for up to 6 months after NICU discharge; we wanted to examine what happens after that point. For children who presented with seizures at six months-of-age, the time to first seizure was zero. For children who never developed seizures, the time to first seizure was length of follow-up, and the observation was censored.

Time to resolution of seizures was also examined; in some children with epilepsy, seizures resolve and anticonvulsants can be discontinued. This analysis only included children who had seizures after six months-of-age. For children whose seizures resolved, defined as both being seizure-free for at least 6 months and being taken off anticonvulsants, the time to seizure resolution was months from start of seizures to date taken off anticonvulsants. For children whose seizures did not resolve, the time to seizure resolution was months from start of seizures to date of last follow-up, and the observation was censored.

Six variables were examined as predictors of outcome: evidence of infarction on prenatal ultrasound; initial presentation with seizures; abnormality on initial NICU EEG; presence of bilateral infarcts on radiographic imaging; in children with MCA infarcts, the presence of large-versus-small-branch infarction; and family history of seizures. Univariate log-rank tests were done to test the association of each of these factors with time to development of seizures. Last, a multivariable Cox proportional hazards model was fit to examine the association of all factors except abnormality on initial NICU EEG and the presence of large-versus-small-branch MCA infarction. Abnormality on initial NICU EEG was omitted because no children with evidence of stroke on prenatal ultrasound had a neonatal EEG. The presence of large-versus-small-branch infarction was omitted because it did not apply to children who did not have an MCA infarction. The proportional hazards assumption was tested with the Kolmogorov-type supremum test for all variables and was met in all cases.

As a secondary analysis, Fisher's exact tests were done to examine the association of the six factors with development of epilepsy at any time after six months-of-age (yes/no).

## Ethics

This study was approved by the Institutional Review Board of the Indiana University School of Medicine (Study # 0207-55)

## Results

### Patient population

Sixty-four children with perinatal arterial ischemic stroke were identified. Thirty-six (56%) were male. Forty-eight (75%) presented in the NICU with seizures. All children with seizures were treated with phenobarbital. Additional medications used included lorazepam (8), phenytoin (8), diazepam (1) and fosphenytoin (1). Additional presentations which prompted neurological evaluation included apnea (19), respiratory distress (12), abnormal tone (11), poor feeding (9), poor respiratory effort (6), and irritability (5). Comorbidities included infection in 11 (17%); cardiac abnormalities in 11 (17%); extracorporeal membrane oxygenation in 4 (6%), and renal failure in 3 (5%). Seven of the 64 children with perinatal arterial ischemic stroke (11%) had a family history of seizures.

## Radiographic Findings

Evidence of stroke was present on prenatal ultrasound for 4 patients (6%). All patients had confirmation of infarction by cranial CT (20), MRI (20), or both (24). Forty-six children (72%) had unilateral hemispheric infarction in isolated arterial territories: 1 in the right internal carotid artery territory, 1 in the right anterior cerebral artery (ACA) territory, 4 in the posterior cerebral artery (PCA) territory (2 left, 2 right) and 40 in the MCA territory (27 left, 13 right). Of the unilateral MCA infarctions, 18 were large branch and 19 were small branch; original films could not be accessed for 3 and infarction size could not be judged from radiographic reports. Four children had multiple unilateral infarctions in multiple territories. Fourteen children had bilateral infarctions involving the following regions: the basal ganglia (1 right), brainstem (1), cerebellar (1 left, 2 right), anterior cerebral artery (2 left, 2 right), PCA (7 left, 7 right), and MCA (12 left, 11 right) territories. Four had watershed infarctions. Nineteen had infarction with hemorrhagic transformation (9 left, 3 right, 7 bilateral).

## Initial EEG findings on reports

Initial EEG reports were available for 44 of the 48 newborns that presented with seizures; 40 (91%) had at least one abnormality on initial EEG. (Table I; available at [www.jpeds.com](http://www.jpeds.com))

## Epilepsy status after 6 months-of-age

At least 6 months of follow-up data were available on 61 patients (95% of 64). Median age of these 61 patients at last follow-up was 43 months (range 9–179). Forty-one children (67%) had epilepsy (ME class 1 or higher) between 6 months-of-age and last follow-up. Eleven of those children were maintained on phenobarbital after NICU discharge for more than 6 months, but were seizure-free (ME class 1); children were maintained on phenobarbital for that length of time usually due to abnormal EEG or variations in physician practice. Eleven children had seizure activity after leaving the NICU which continued or started in the first 6 months of life (ME class 2 or higher). Nineteen children had seizure onset after 6 months of age; 6 of those children had not presented with seizures in the NICU. Median age at onset of seizures for those 19 children was 16 months (range 7–124 months). Seizures resolved in 13 (32% of 41 children with epilepsy); these children were seizure-free and off medications for at least 6 months at the last follow-up visit.

A total of 28 children (46% of the 61 included patients) were classified as having epilepsy at the time of last follow-up (Table II). Five children (8% of the 61 children) developed infantile spasms; these children have been previously described<sup>15</sup>. Most of the children with epilepsy (64%; 18 of 28) were seizure-free on medication or while being weaned off.

Twenty-five patients were on seizure medications at last follow-up; 3 had been weaned off but had been seizure-free off medication for fewer than 6 months. The most commonly used medications used at last follow up were: phenobarbital (10), lamotrigine(5), oxcarbazepine (7), valproic acid (4), and topiramate(4). Six (24% of the 25 patients with medication) patients required multiple medications to control their seizures at last follow-up.

Follow-up EEGs performed at 6 months-of-age or later were available for 42 of the children: 17 were normal; 19 had slowing and/or voltage attenuation, which was diffuse in 9 and focal in 10; 19 had epileptiform discharges. Five children had infantile spasms with onset at a median age of 7 months; three of these children later developed severe seizures (ME class 3 or higher). Several of these children were previously described.<sup>15</sup> The Kaplan-Meier curve demonstrating the probability of being seizure-free (ME class 0 or 1) over time is in Figure 1.

On univariate analysis, only presence of infarct on prenatal ultrasound ( $p=0.0065$ ) (Figure 2; available at [www.jpeds.com](http://www.jpeds.com)) and family history of seizures ( $p=0.0093$ ) (Figure 3; available at

www.jpeds.com) were significantly associated with time to development of seizures after six months of age. The median time to development of seizures after 6 months-of-age was shorter in children with evidence of infarct on prenatal ultrasound (3.8 months with evidence vs 53.9 without evidence) and in children with a family history of seizures (1.1 months with a family history vs 53.9 months without). Results of the log-rank tests are shown in Table III. On multivariable analysis, none of the variables were associated with time until development of seizures, though there was a trend towards significance for presence of infarct on prenatal ultrasound and family history of seizures: presence of infarct on prenatal ultrasound ( $p=0.053$ ), NICU presentation with seizures ( $p=0.397$ ), bilateral infarcts ( $p=0.826$ ), family history ( $p=0.087$ ).

On univariate analysis, no variables were significantly associated with time to resolution of seizures after six months-of-age. Results of the log-rank tests are shown in Table IV. On multivariable analysis, none of the variables with significantly associated with time to resolution of seizures: presence of infarct on prenatal ultrasound ( $p=0.998$ ), NICU presentation with seizures ( $p=0.874$ ), bilateral infarcts ( $p=0.998$ ), or family history ( $p=0.874$ ).

None of the six factors were significantly associated with development of seizures at any time after six months of age on Fisher's exact tests. These results are shown in Table V (available at www.jpeds.com).

## Discussion

Seizures are a frequent presenting sign of perinatal arterial ischemic stroke, and childhood epilepsy is a frequent resulting morbidity. In our cohort, 75% (48 of 64) of children with perinatal stroke presented with seizures, and 67% (41 of 61 with  $\geq 6$  months of follow-up) had or developed epilepsy after 6 months-of-age. Epilepsy resolved in 13 children, so 46% (28 of 61) had epilepsy as of last follow-up. Sixty-four percent (18 of 28) of the children with epilepsy were eventually seizure-free with treatment and 25% (7 of 28) of the children with epilepsy had severe epilepsy at last follow-up with 1 or more seizures per month (ME class 3 or higher). Seizures that started or re-started after 6 months-of-age began at a median age of 16 months, but one child had seizures start at 10.3 years of age. Evidence of infarct on prenatal ultrasound and family history of epilepsy were both associated with earlier onset of seizures. We were unable to identify predictors of what caused epilepsy to resolve in some children, or whether or not children would develop epilepsy.

This prevalence of childhood epilepsy after perinatal stroke was higher than what has been reported in previous studies<sup>2-9</sup>, but we did note that seizures resolved in some children; our incidence of epilepsy at last follow-up falls within the previously described range. There are larger studies of epilepsy in the hemiplegic cerebral palsy literature, where it is reported approximately 1/3 of children have epilepsy<sup>16, 17</sup>; in this population, neonatal seizures are a predictor for later seizures<sup>18</sup>. In our cohort, neonatal seizures did not predict later epilepsy. Stroke is responsible for at least 20% of hemiplegic cerebral palsy<sup>19, 20</sup>, but the wide range of other etiologies included in this population makes it difficult to draw conclusions on the outcomes after perinatal stroke from published cerebral palsy data.

The median age at time of seizure development for children over 6 months-of-age in our cohort was 16 months (range 7 months to 10 years and 4 months). Sran et al<sup>2</sup> described children with perinatal stroke who were seizure-free for 1-8 years, then developed epilepsy. It is possible that the incidence of epilepsy after perinatal stroke in our cohort will rise as we continue to follow these children over the next several years.

Evidence of infarction on prenatal ultrasound predicted the earlier onset of epilepsy in our cohort. There are few large studies of fetal stroke, but the data that have been published suggest

that these children may be at increased risk for neurological impairment. Ozduman et al<sup>21</sup> described epilepsy in 2 of 3 children with fetal stroke who had at least 18 months of follow-up; they reviewed the previous literature but few details on the long-term neurological outcomes were available.

Family history was also a predictor of the development of seizures over time; children developed epilepsy earlier if they had a family history of epilepsy. This suggests that genetic background may influence outcome, but may also reflect increased awareness and detection of seizures in families with prior experience with epilepsy.

Although we found predictors of time to onset of epilepsy, none of the risk factors we evaluated predicted time to resolution of seizures or whether children would develop epilepsy. Lee and colleagues also found it difficult to identify predictors of epilepsy<sup>6</sup>. Our sample size may have limited our ability to identify strong predictors. We may be able to revisit this in future, larger studies.

There are several limitations in this study. Most of the data are retrospective. We started to collect prospective data on some of these children two years ago, but the rarity of perinatal stroke makes it difficult to collect information on large numbers of children at a single center. Our cohort may have been too small to detect variables predictive of later epilepsy due to type II error. We have limited follow-up, with a median age at last follow-up of 43 months; some of the children developed epilepsy as late as 10 years of age, so we may have underestimated the rate of childhood epilepsy. It is also possible that some of the children whose epilepsy “resolved” will have their epilepsy restart later in life. This cohort may be biased towards sicker patients who have higher rates of epilepsy. Some children with perinatal stroke have normal neurological outcomes<sup>22</sup>; their parents might be less likely to return for follow-up. Some of the children who were “well-controlled on one medication” may have had resolution of their epilepsy that was not detected because follow-up EEG was not performed. We had 11 children who were maintained on phenobarbital for more than 6 months after NICU discharge, in part because there are no well-established guidelines on how long to maintain anticonvulsant therapy in children with neonatal stroke. However, for a parent, a child who has epilepsy and is “well-controlled on medication” and a child who is actually epilepsy-free but still on medication require the same amount of work. For parents, the experienced outcome is the same, so we felt it was reasonable to group them together. For the Kaplan-Meier curves and Cox proportional hazards models, we chose to examine time to development of active seizures after 6 months-of-age because it was not always clear when epilepsy began and ended for children maintained on phenobarbital while seizure-free for prolonged periods. The object of this paper was to provide information to counsel parents about future care their children would require. In the future, when we have more follow-up data on these children, we may find it easier to identify predictors of chronic epilepsy.

Previous work has suggested that abnormal background on neonatal EEG or early seizures may be predictive of later poor neuromotor outcome<sup>3, 7</sup>. The next step in our research will be to examine other outcome measures and see if this holds true in our cohort. We will also assess the association of epilepsy with other disability.

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## Abbreviations

<b>NICU</b>	neonatal intensive care unit
<b>CT</b>	computed tomography
<b>MRI</b>	magnetic resonance imaging
<b>EEG</b>	electroencephalogram
<b>MCA</b>	middle cerebral artery
<b>ME</b>	modified Engel
<b>PCA</b>	posterior cerebral artery

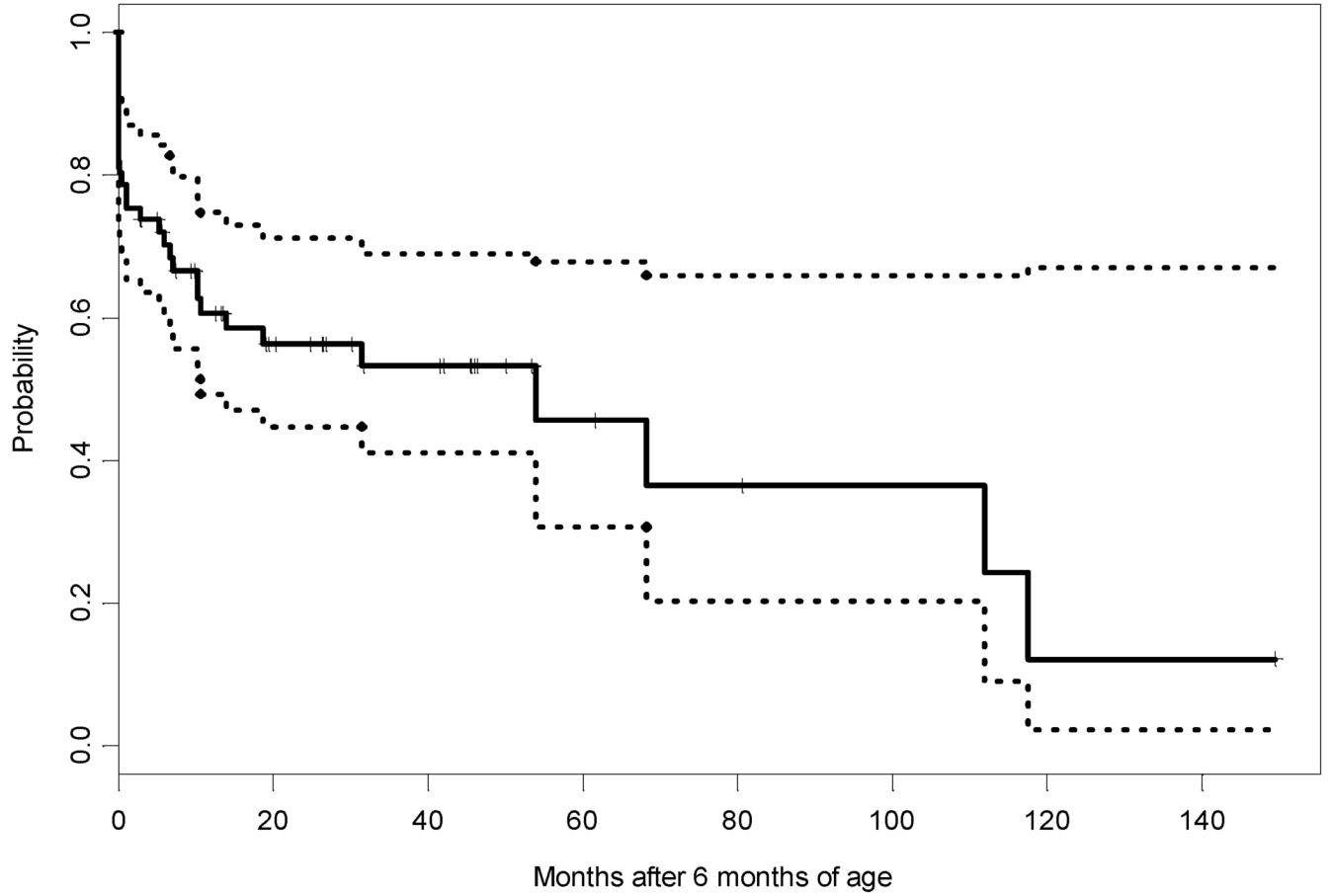
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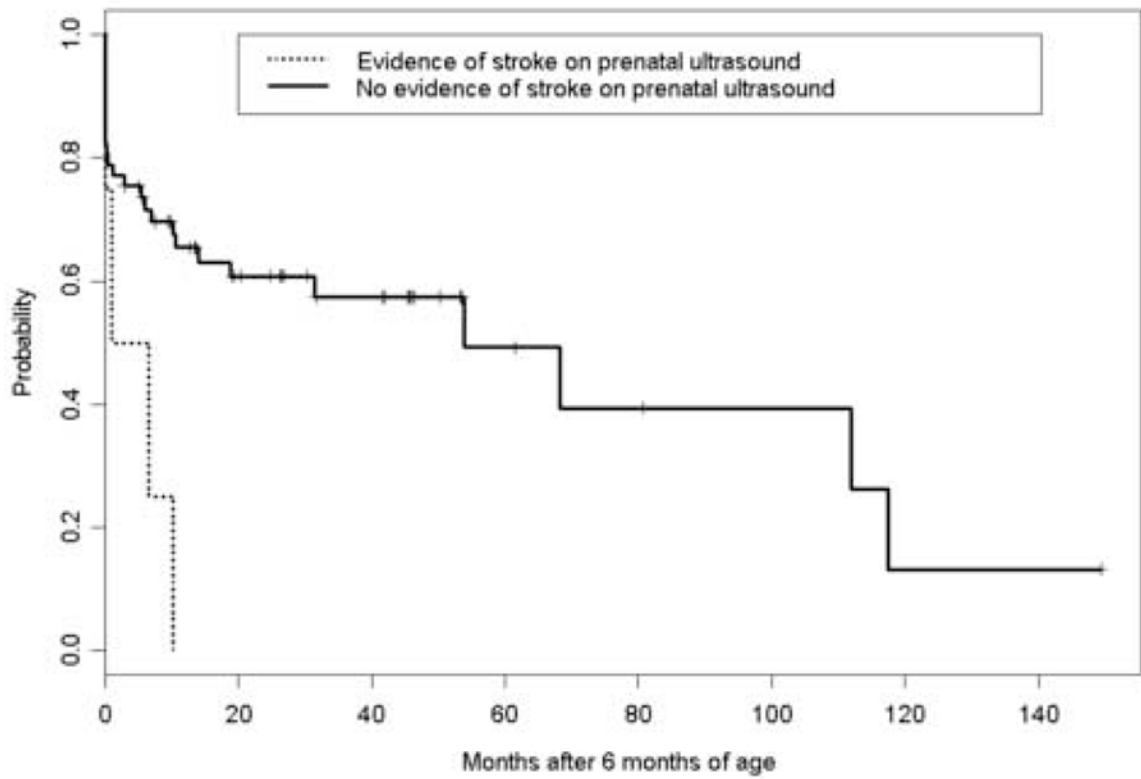
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## Probability of being seizure-free

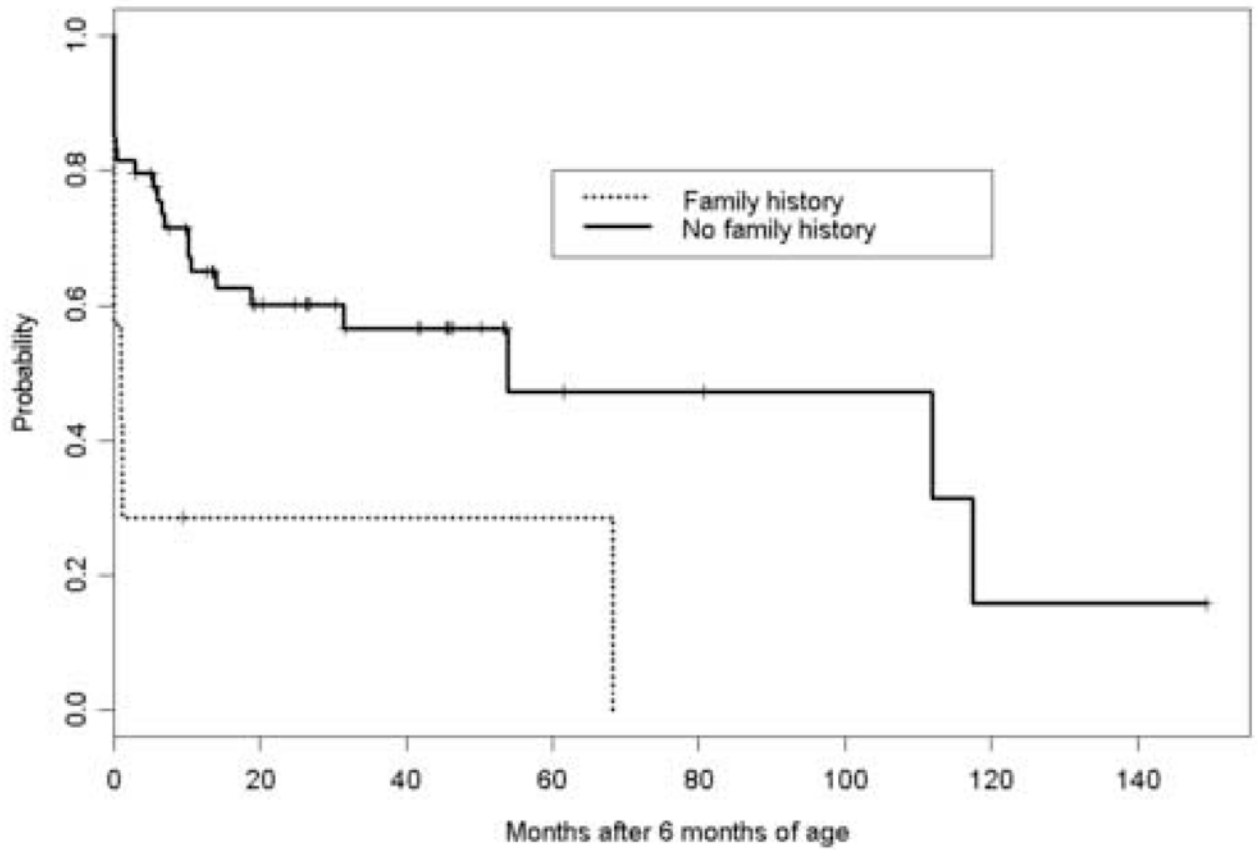


**Figure 1.**  
The light dotted lines represent 95% confidence intervals.



**Figure 2.** Comparison of children with and without evidence of infarction prenatal ultrasound, difference is significant,  $p= 0.0065$

## Probability of being seizure-free by family history of seizures



**Figure 3.** Comparison of children with and without family history of epilepsy, difference is significant,  $p=0.0093$ .

**Table I**

EEG findings on initial EEG (n= 44\*)

EEG finding	# (%)
Abnormal background	26 (59.1%)
Slowing/voltage attenuation	26 (59.1%)
Epileptiform discharges	35 (79.5%)
Electrographic seizures	17 (38.6%)
Normal	4 (9.1%)

\* Not all children had initial EEG performed

**Table II**

Epilepsy outcomes at last follow-up (N=61)

<b>Outcome</b>	<b># (%)</b>
ME Class 0	33 (54%)
ME Class 1	18 (30%)
ME Class 2	3 (5%)
ME Class 3	4 (7%)
ME-Class 4	2 (3%)
ME-Class 5	1 (2%)
Infantile spasms	5 (8%)

ME= Modified Engel

Class 0= seizure-free and off anticonvulsants for at least 6 months

Class 1= seizure-free on medication for at least 6 months or seizure-free off medication for fewer than 6 months

Class 2= less than one seizure a month

Class 3= 1–4 seizures a month

Class 4= 5–30 seizures a month

Class 5= 30 or more seizures a month.

**Table III**

Log-rank tests- Prediction of time to seizure onset after 6 months

	<b>N</b>	<b>Median months</b>	<b>p-value</b>
Evidence of infarct on ultrasound	4	3.8	0.007
No evidence of infarct on ultrasound	57	53.9	
Initial presentation with seizures	45	53.9	0.890
No initial presentation with seizures	16	111.8	
Abnormal NICU EEG	40	31.4	0.701
Normal NICU EEG	5	>53.5	
Bilateral infarcts	13	31.4	0.772
No bilateral infarcts	48	53.9	
MCA infarct- Large branch	18	111.8	0.718
MCA infarct- Small branch	18	53.9	
Family history	7	1.1	0.009
No family history	54	53.9	

NICU= neonatal intensive care unit; EEG= electroencephalogram;

MCA= middle cerebral artery

**Table IV**

Log-rank tests- Predictors of resolution of epilepsy

	<b>N</b>	<b>Median months</b>	<b>p-value</b>
Presence of infarct on prenatal ultrasonography	4	>178.8	0.2535
No presence of infarct on prenatal ultrasonography	26	>152.9	
Initial presentation with seizures	21	>88.0	0.2609
No initial presentation with seizures	9	>178.8	
Abnormal NICU EEG	20	>150.5	0.3830
Normal NICU EEG	2	>78.4	
Bilateral infarcts	7	>152.9	0.2619
No bilateral infarcts	23	>178.8	
Family history of epilepsy	6	>178.8	0.7023
No family history of epilepsy	24	>152.9	
Large branch	9	>178.8	0.0984
Small branch	8	65.4	

**Table V**

## Fisher's exact test- predictors of epilepsy

	<b>p-value</b>
Evidence of infarct on ultrasound	0.293
Initial presentation with seizures	0.356
Abnormal NICU EEG	0.136
Bilateral infarcts	0.742
MCA infarcts: Large vs. small branch	0.443
Family history	0.409

NICU= neonatal intensive care unit; EEG= electroencephalogram;

MCA= middle cerebral artery