

Early-Onset Seizures Are Correlated With Late-Onset Seizures in Children With Arterial Ischemic Stroke

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Background and Purpose—Early-onset seizures are common in children with arterial ischemic stroke, but the clinical features and effects on the outcome of early-onset seizures have been less studied in children.

Methods—Children aged 1 month to 18 years presenting with first-time and image-confirmed arterial ischemic stroke were identified for analysis.

Results—A total of 78 survivors of arterial ischemic stroke were enrolled. Twenty (25.6%) had early-onset seizures, and 90% were initial presentation. Younger children (mean, 3.4±3.9 versus 9.0±6.2 years; $P<0.001$) and cortical involvement (5% versus 63.8%; $P=0.01$) are more likely to have early-onset seizures. Thirteen of 20 survivors with early-onset seizures had late-onset seizures after the acute stage, and 12 of them were diagnosed as poststroke epilepsy.

Conclusions—Early-onset seizures occurred in 25.6% of children with arterial ischemic stroke. Younger age and cortical involvement were risk factors for early-onset seizures. Sixty-five percent of children with early-onset seizures had late-onset seizures after the acute stage. (*Stroke*. 2014;45:1161-1163.)

Key Words: children ■ epilepsy ■ seizures ■ stroke

Arterial ischemic stroke (AIS) is not uncommon in the pediatric population, with an incidence of 1.25 per 100 000 per year. Previous studies have reported that early-onset seizures are a common feature in children with AIS,¹⁻³ and ≈19% to 44% of children with AIS had early-onset seizures. Among adults, the incidence of early-onset seizures was between 2.4% and 5.4%,⁴ which was much lower than the incidence in children. Also, in adults, most stroke patients with early-onset seizures do not develop late-onset seizures or poststroke epilepsy.⁵ Therefore, in this retrospective analysis, we aimed to evaluate the epidemiology of early-onset seizures after AIS in children, as well as to determine their relationship with late-onset seizures and the outcome in children.

Methods

Subjects

We identified all children with strokes admitted to our department from the database. We enrolled only children with a first-ever and image-confirmed AIS in our study. AIS was defined as an acute focal neurological syndrome attributable to cerebral infarction in an arterial distribution. We excluded children with previous strokes and those without available image data.

Clinical Features and Seizures

Early-onset seizures were defined as seizures occurring <7 days after the stroke, and late-onset seizures were defined as unprovoked seizures occurring ≥7 days after the stroke. Poststroke epilepsy was defined by ≥2 unprovoked seizures noted after the acute stage of the stroke.

Seizure types were categorized clinically, based on the criteria of the International League Against Epilepsy.

Statistical Analysis

We used Student *t* test to compare continuous variables and χ^2 statistic to compare categorical variables. We also used the Kaplan–Meier survival analysis for cumulative incidence of subsequent unprovoked seizures. The log-rank test was used to compare the risk of subsequent unprovoked seizures for children with and without early-onset seizures. Statistical significance was considered when $P<0.05$.

Results

Study Population

A total of 94 children with first-time and image-confirmed AIS were enrolled in this study. Eleven children (11.7%) died during hospitalization for AIS, and 5 children had seizures before AIS. Therefore, only 78 survivors were enrolled for the subsequent analysis.

Early-Onset Seizures

Early-onset seizures were observed in 20 of 78 survivors (25.6%; Table). The mean onset age of early-onset seizures was 3.4±3.9 years, which was significantly younger compared with those without early-onset seizures (9.0±6.2 years; $P<0.001$). Eighteen of 20 children (90%) had early-onset seizures as initial presentation. Early-onset seizures were focal in 15 (75%) children. Three (15%) had generalized seizures, and 2 (10%) had secondary generalized seizures. Multiple

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seizures occurred in 12 (60%), and single seizures occurred in 5 (25%). Three (15%) had status epilepticus.

Of 15 children with EEG recordings, the findings showed diffuse slowing in 8 (40%), focal slowing in 7 (35%), and epileptiform discharges in 7 (35%).

Children with early-onset seizures are more likely to have infection as a risk factor (30% versus 8.6%; $P=0.03$). Cortical involvement was more common in children with early-onset seizures (95% versus 63.8%; $P=0.01$), and children with early-onset seizures were also more often associated with change in consciousness (45% versus 15.5%; $P=0.01$) in their initial presentation. Although all children had focal neurological sign, children with early-onset seizures less commonly presented with focal neurological deficits (60% versus 93.1%; $P=0.001$) in their initial presentation.

Follow-Up

The mean follow-up duration was 53.7 ± 48.8 months (range, 1–191 months). Early-onset seizures did not influence long-term mortality after the acute stage (0% versus 8.6%; $P=0.32$).

Over the course of 4.5 years of follow-up, subsequent unprovoked seizures occurred in 13 children with early-onset

seizures, and in 5 without early-onset seizures. The cumulative incidence of subsequent unprovoked seizures in children with and without early-onset seizures was 52.5% (95% confidence interval [CI], 28.3–76.7%) and 3.5% (95% CI, 0–8.3%) at 1 year; 52.5% (95% CI, 28.3–76.7%) and 6.2% (95% CI, 0–13.4%) at 2 years; and 72.3% (95% CI, 49.7–94.9%) and 14.4% (95% CI, 1.6–27.2%) at 4.5 years. Children with early-onset seizures had a significantly higher risk of subsequent unprovoked seizures compared with children without early-onset seizures ($P<0.001$; log-rank). The subsequent seizures mostly occurred <1 year (67%). However, 27% developed after 2 years (Figure).

Early-Onset Seizures and Poststroke Epilepsy

Thirteen of 20 survivors with early-onset seizures had subsequent late-onset seizures. One child had recurrent seizures and concomitant new ischemic lesions. According to the definition, this seizure was not counted as late-onset seizures. Twelve of 13 (92%) children with late-onset seizures had ≥ 1 episode of subsequent unprovoked seizures and hence were diagnosed with poststroke epilepsy. Four children had refractory epilepsy and needed the use of multiple antiepileptic drugs (AEDs).

Seventeen (21.8%) survivors with AIS had poststroke epilepsy after the acute stage. There was a significant association between early-onset seizures and poststroke epilepsy ($P<0.001$). Besides, the mean age of onset of strokes in children with poststroke epilepsy was significantly younger (3.6 ± 5.6 versus 8.7 ± 5.9 years; $P=0.002$). Moreover, the use of AED prophylaxis after early-onset seizures did not prevent the recurrence of seizures (50% versus 37.5%; $P=0.67$).

Table. Main Features of Stroke Survivors With and Without Early Poststroke Seizure

	Total, N (%)	With Early Seizure, N (%)	Without Early Seizure, N (%)	P Value
No. of patients	78	20 (25.6)	58 (74.4)	
Age, y	7.6 ± 6.2	3.4 ± 3.9	9.0 ± 6.2	<0.001
Male sex	35 (44.9)	10 (50)	25 (43.1)	0.61
Risk factors				
Cardiac disorder	23 (29.5)	7 (35.0)	16 (27.6)	0.58
Coagulopathy	20 (25.6)	6 (30.0)	14 (24.1)	0.77
Vasculopathy	19 (24.4)	4 (20.0)	15 (25.9)	0.77
Infection	11 (14.1)	6 (30.0)	5 (8.6)	0.03
Vasculitis	7 (9.0)	0 (0)	7 (12.1)	0.18
Metabolic disorder	6 (7.7)	3 (15.0)	3 (5.2)	0.17
Hematologic disorder	2 (2.6)	0 (0)	2 (3.4)	1.0
Clinical data				
Cortical involvement	56 (71.8)	19 (95.0)	37 (63.8)	0.01
Bilateral location	15 (19.2)	5 (25)	10 (17.2)	0.52
Initial presentation				
Focal neurological deficit	66 (84.6)	12 (60)	54 (93.1)	0.001
Change in consciousness	18 (23.1)	9 (45.0)	9 (15.5)	0.01
Follow-up				
Mean follow-up length, mo	55.6 ± 48.4	73.0 ± 52.2	49.0 ± 45.6	0.62
Onset time of epilepsy, mo		10.7 ± 13.7	17.9 ± 17.7	0.39
Subsequent death	5 (6.4)	0 (0)	5 (8.6)	0.32

Discussion

In our study, 25.6% of children with AIS had early-onset seizures. Previous studies showed early-onset seizures in 19% to 44% of children with ischemic stroke.^{1–3} Compared with

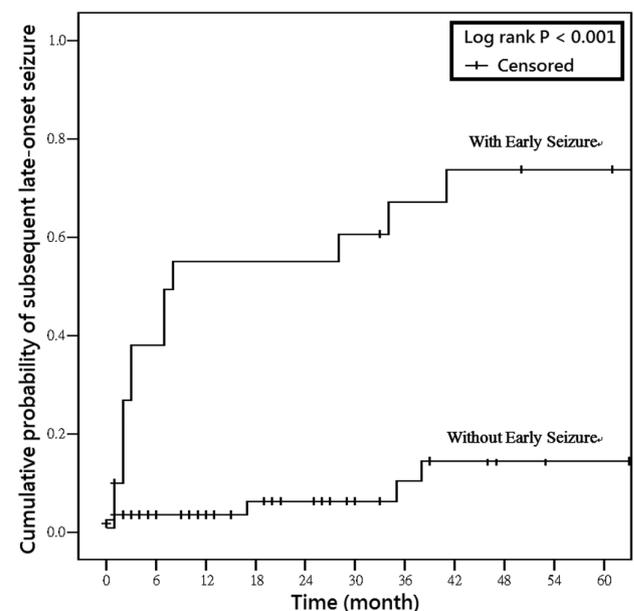


Figure. Cumulative probability of subsequent late-onset seizures in children with/without early seizures.

previous studies of adult stroke, in which the incidence of early-onset seizures was found to be between 2.4% and 6%,⁵ children are more likely to develop early-onset seizures compared with adults. Our study also showed that early-onset seizures are associated with a younger age of onset of stroke similar to previous studies.^{1,6}

In our study, early-onset seizures occurred as initial presentation in most children (90%) and were associated with cortical involvement.^{3,7} Beside, early-onset seizures did not influence long-term mortality,² and mortality in AIS was found to be related to underlying diseases.^{1,5}

In our report, children with early-onset seizures are significantly associated with recurrent seizures and poststroke epilepsy after the acute stage. The cumulative incidence of developing subsequent late-onset seizures was 72.3% <4.5 years after discharge in children with previous AIS and early-onset seizures. Our study also reported that 60% of children with early-onset seizures would develop poststroke epilepsy. A recent retrospective study of children with strokes also pointed out that acute seizures at the time of stroke predicted the development of active epilepsy in children, and the cumulative risk of active epilepsy was only 25% by 5 years.⁸ Compared with our study, that study included children with hemorrhagic and ischemic stroke. It indicated that AIS may more likely lead to poststroke epilepsy. Among the adult population, the occurrence of early seizures did increase the risk of subsequent recurrent seizures, but recurrent seizures develop only in a minority, about one thirds,⁴ of cases with early-onset seizures. In a population-based study, the risk of subsequent unprovoked seizures was 33.0% among patients with early-onset seizures and stroke.⁹ According to this study, children with early-onset seizures have a much higher risk of subsequent recurrent seizures compared with adults.

We tried to identify the risk factors for recurrent seizures after early-onset seizures, but no significant difference was found in age, sex, stroke risk factors, or use of AEDs in the acute stage. Many previous studies showed that the use of AEDs in the early stage did not prevent the occurrence of late-onset seizures or epilepsy in the case of traumatic brain injury and intracerebral hemorrhage.¹⁰ A retrospective study also pointed out that early-onset seizures did not

require long-term antiepileptic therapy to prevent recurrence in adults.¹¹ However, children with early-onset seizures had a much higher risk of subsequent recurrent seizures. Therefore, the management of early-onset seizures might be different between adults and children, and further studies are needed.

Conclusions

In this study, we found that most children with early-onset seizures would experience recurrent seizures after the acute stage. Additional studies are needed to clarify the relationship between early-onset seizures, late-onset seizures, and poststroke epilepsy, and the ideal way to prevent the recurrence of seizures.

Disclosures

None.

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