의학석사 학위논문

Stroke in children: clinical analysis of 185 patients

소아 뇌졸중 환자 185 명의 임상 양상 분석

2014 년 2 월

서울대학교 대학원

의학과 뇌신경과학 전공

정 고 운

소아 뇌졸중 환자 185 명의 임상 양상 분석

지도 교수 채종희

이 논문을 의학석사 학위논문으로 제출함

2013 년 10 월

서울대학교 대학원

의학과 뇌신경과학 전공

정 고 운

정고운의 의학석사 학위논문을 인준함

2013 년 12 월

위 원 장 (인)

부위원장 (인)

위 원 (인)

Stroke in children: clinical analysis of 185 patients

by

Goun Jeong

A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Master of Science in Medicine (Neuroscience) at Seoul National University College of Medicine

December 2013

Approved by Thesis Committee:

Professor_____Chairman

Professor_____Vice chairman

Professor_____

Abstract

Introduction: Childhood stroke is an important cause of long-term disability. Understanding its risk factors is crucial for the choice of treatment and the development of prevention strategies for recurrent stroke. This study aimed to investigate the etiology or risk factors of childhood stroke according to age, and to identify the etiology that predicts outcome and recurrence.

Methods: Data were collected retrospectively for patients aged 1 month to 18 years who had been diagnosed with stroke at the Seoul National University Children's Hospital between January 2002 and June 2013. Patients were classified into four age groups: (1) infancy, 1 month to 1 year; (2) early childhood, 1–5 years; (3) late childhood, 6–11 years; and (4) adolescence, ≥12 years. Stroke types were classified into arterial ischemic stroke (AIS), cerebral sinovenous thrombosis (CSVT), metabolic stroke (MS), and hemorrhagic stroke (HS). Overall outcome was classified into favorable outcome (Glasgow Outcome Scale score, 1–2) and poor outcome (Glasgow Outcome Scale score, 3–5). Gender, initial signs, time to diagnosis, stroke types, and etiologies/risk factors were analyzed according to age group. Analysis of predictors of overall outcome and recurrence was done. Chi-squared tests (or Fisher's exact

test, when appropriate) and logistic regression models were used for statistical analysis.

Results: One hundred eighty-five children were enrolled in the study (100 boys and 85 girls). The mean age at diagnosis was 6.5 years, and the peak frequency was observed during the first year of life. Hemiparesis was the most common presenting sign. There were 156 patients (84%) with AIS, nine patients (5%) with CSVT, nine patients (5%) with MS, and 11 patients (6%) with HS. Etiologies were identified in 154 (83%) patients, with different distributions according to age group (P = 0.001). The most common single etiology was moyamoya disease (MMD) (n = 54, 29%), whereas the second most common etiology was methylenetetrahydrofolate reductase (*MTHFR*) gene mutation (n = 21, 11%). The most common etiologies according to age group were (1) infection, cardiac disease, and prothrombotic conditions in infancy; (2) MMD, cardiac disease, and inflammatory vasculopathy in early childhood; (3) MMD, prothrombotic condition, and metabolic disease in late childhood; and (4) cardiac disease, prothrombotic condition, and metabolic disease in adolescence. Most patients had a favorable outcome (82%). According to stroke type, AIS had a more favorable outcome (OR = 0.404, P = 0.048), whereas MS had a poorer outcome (OR = 6.607, P = 0.007). Among the etiologies/risk factors of AIS, inflammatory/postinfectious vasculopathy

and MMD had a relatively more favorable outcome, although the difference was not statistically significant. The etiologies or risk factors associated with poor outcome were metabolic disease (OR = 6.607, $P = 0.007$), mixed signs at onset (OR = 4.072, $P = 0.001$), presence of recurrent stroke (OR = 3.237, $P = 0.010$), and association of post-stroke epilepsy (OR = 6.950, $P < 0.001$). Although multiple etiologies/risk factors were not associated with poor outcome overall ($P = 0.199$), the MMD-plus group had a poorer outcome compared with the MMD-only group ($P = 0.014$) in AIS. The median follow-up duration was 3.2 years (range: 0.1-10.9 years). The recurrence rate was low in AIS (OR = 0.308, $P = 0.012$), whereas it was high in MS (OR = 25.333, $P < 0.001$). In AIS, the most common etiologies/risk factors for recurrence were systemic vasculitis (OR = 7.941, $P = 0.045$) and MMD (OR = 3.220, $P = 0.020$). Time to diagnosis and the presence of multiple etiologies were not associated with clinical outcome. Nearly all children survived stroke ($n = 172$, 93%); however, neurological sequelae remained in 2/3 of them. Twenty-six patients (14%) suffered from epilepsy.

Conclusions: The etiology and risk factors of childhood stroke in our center were different from those reported in Western countries, in which the most common single etiology was MMD. The most common etiologies, such as infection in early infancy, MMD and cardiac disease in early childhood,

MMD and prothrombotic condition in late childhood, and prothrombotic condition in adolescence, varied according to age group. Age should be considered when establishing a strategy to evaluate risk factors in childhood stroke. MS showed a poorer outcome and high recurrence rate. Among the etiologies/risk factors of AIS, inflammatory/postinfectious vasculopathy and MMD had a relatively more favorable outcome, and systemic vasculitis and MMD showed high recurrence rate.

Keywords: Childhood stroke, age, etiology, outcome, moyamoya disease

Student number: 2012 – 21755

Contents

Abstract i

Contents v

List of tables vi

List of figures vii

Introduction 1

Materials and Methods 3

Results 6

Discussion 31

References 37

초록 (국문) 42

List of tables

Table 1. Glasgow Outcome Scale 14

Table 2. Clinical characteristics of patients 15

Table 3. Comparison of the demographics of the below 1 year group versus the 1 year and over group 17

Table 4. Initial presentation of the 185 patients 18

Table 5. Most common etiologies/risk factors 19

Table 6. Most common etiologies/risk factors according to age group 20

Table 7. Etiologies/risk factors according to stroke type 21

Table 8. Patients who had two or more etiologies 22

Table 9. Predictors of poor outcome 23

Table 10. Etiologies/risk factors and poor outcome in AIS 24

Table 11. Comparison of clinical characteristics between the group with MMD only and the group with MMD plus other etiologies in AIS 25

Table 12. Predictors of recurrence 26

Table 13. Etiologies/risk factors and recurrence in AIS 27

Table 14. Clinical characteristics of mortality cases 28

Table 15. Morbidities after stroke 29

Table 16. Comparison with previous studies 36

List of figures

Figure 1. Distribution of age at diagnosis of stroke 30

Introduction

Stroke is defined as the sudden occlusion or rupture of cerebral arteries or veins, resulting in focal cerebral damage and clinical neurological deficits [1]. Childhood stroke is defined as a cerebrovascular event occurring between 28 days and 18 years of age [2]. Perinatal and neonatal strokes have different etiologies and are not included in childhood stroke. Stroke classification begins with the distinction of ischemia from hemorrhage. Ischemic varieties are arterial ischemic stroke (AIS), cerebral sinovenous thrombosis (CSVT), and metabolic stroke (MS). In AIS, arterial occlusion is usually due to thromboembolism and results in focal infarction within an arterial territory. In CSVT, symptomatic thrombosis of the cerebral veins and/or dural venous sinuses may result in parenchymal venous infarction. Metabolic stroke results from energy failure caused by metabolic conditions such as mitochondrial disease, organic acidemias, and single-gene diseases [3]. Strokes due to vascular rupture are termed hemorrhagic stroke (HS) and are classified into primarily by their intracranial location. Overlap between ischemic and hemorrhagic stroke can occur in certain circumstances such as the hemorrhagic transformation of initially bland ischemic infarct.

Great efforts have been made to increase public recognition of adult stroke, yet there is a lack of awareness of childhood stroke, despite it being an important cause of long-term morbidity and mortality. The combined annual incidence rates of childhood ischemic and hemorrhagic stroke are 1.8–13 per 100,000 children per year in the United States and Europe [4-7].

Etiologies/risk factors in childhood stroke differ from those in adult stroke [8]. The etiologies/risk factors identified in adult cases are primarily related to arrhythmias and obstructive atherosclerotic arteriopathies; in contrast, these are rarely thought to be related to childhood stroke. The International

Pediatric Stroke Study (IPSS) and other studies of childhood stroke reported various underlying systemic factors [8-11]. The most common etiologies/risk factors in childhood stroke include cerebral arteriopathies which are believed to be present in 50-80% of childhood AIS cases, cardiac disease, sickle cell disease, thrombophilias, and significant infections such as varicella, sepsis or meningitis [10, 12-14]. The typical clinical manifestations reported are hemiparesis, seizure, aphasia, or altered mentality.

However most studies on childhood stroke are reported from Europe or North America, and reports about childhood stroke among Korean children are limited [15, 16].

Therefore, this study aimed to investigate the etiologies/risk factors of childhood stroke according to age group, and to identify which etiologies/risk factors are associated with the clinical outcome.

Methods and Materials

1. Patients and clinical characteristics

This study included all patients aged 1 month to 18 years who had been diagnosed with stroke at the Seoul National University Children's Hospital, Seoul, Korea, between January 2002 and June 2013. The diagnosis of stroke was confirmed in all patients by brain computed tomography (CT) or magnetic resonance imaging (MRI). I reviewed retrospectively the medical history, etiologies/risk factors, laboratory data, and therapeutic regimens of the patients.

Cases of neonatal (occurring in the first 28 days of life) stroke were excluded. Data on children who, after the perinatal period, presented with infarctions that were presumed to have occurred during that period were also excluded from this analysis, because the exact time of infarction could not be confirmed. Other childhood cerebrovascular disorders that were excluded included transient ischemic attack (TIA) without infarction, hypotensive watershed injury, reversible hypertensive leukoencephalopathy, diffuse hypoxic encephalopathies, and asymptomatic infarction.

Patients were classified into four age groups: (1) infancy, 1 month to 1 year; (2) early childhood, 1–5 years; (3) late childhood, 6–11 years; and (4) adolescence, ≥12 years.

As accurate estimates of the timing of clinical events cannot be ascertained from clinical records, time to diagnosis (the time between first symptoms and final diagnosis) was classified into 3 categories: 6 hours and less, 6 to 24 hours, and more than 24 hours. These categories were chosen for the following reasons: first, 6 hours is the outer limit of the time for administration of thrombolysis in adults and current treatment trials being proposed in children include trials of acute thrombolysis; second, it is likely

that any acute treatment aimed at limiting brain injury would need to be administered within 24 hours of the injury [17, 18]. In this study, "early diagnosis" was defined as a diagnosis that was established within 24 hours after the onset of symptoms, and "late diagnosis" was defined when diagnosis was established after 24 hours.

The modes of initial presentation were defined in terms of (1) focal signs, such as focal neurological signs, speech impairment, and seizures; (2) diffuse signs, such as mental alteration, headache, and sleeping tendency; and (3) mixed signs.

2. Investigation protocol

The routine diagnostic evaluation of stroke included brain MRI and/or magnetic resonance angiography (MRA), cardiac assessment (echocardiography, electrocardiogram), prothrombotic profile (complete differential blood count, lipid profile, coagulation profile, protein C, protein S, antithrombin III, homocysteine, lupus anticoagulant, anticardiolipin antibodies, anti-b2-glycoprotein, *MTHFR* 1298A>C mutation, *MTHFR* 677C>T mutation, factor V Leiden, and prothrombin G20210A), immunologic profile (rheumatoid factor, antinuclear antibody, antineutrophil cytoplasmic antibodies, C3, C4, and anti-dsDNA), and metabolic evaluation (lactate, pyruvate, plasma amino acid, urine organic acid, ammonia, and genetic assessment of mitochondrial disease). Additional investigations included microbiological examination by culture, polymerase chain reaction, and viral antibody test. Magnetic resonance venography (MRV) was performed in patients in whom CSVT was suspected. Magnetic resonance spectroscopy (MRS) was performed for the differential diagnosis of mitochondrial disease.

3. Stroke types and etiologies/risk factors

Stroke was classified as AIS, CSVT, MS, and HS according to etiology. Etiologies are also frequently referred to as "risk factors", reflecting the variable strength of evidence for causality [19]. Etiologies/risk factors for AIS were subdivided into four groups: arteriopathy, cardiac disease, prothrombotic condition, and hematologic disease [1].

4. Clinical outcomes

The Glasgow Outcome Scale (GOS) was used to measure the overall outcome after stroke at the time of the last follow-up visit [20]. The scale presented here was a modified version that places the scores in reverse order (Table 1). The measured outcomes were dichotomized into favorable outcome (GOS score, 1–2) and poor outcome (GOS score, 3–5). Survival and recurrence after stroke were also recorded. Morbidity was evaluated as persistent motor deficit, epilepsy, focal neurological deficit, and other disabilities. Gender, time to diagnosis, initial signs, stroke types, and etiologies/risk factors were analyzed according to age group. In addition, I analyzed whether those variables are associated with overall outcome, recurrence, and survival.

5. Statistical analysis

To compare simple proportions, χ^2 tests (or Fisher's exact test, when appropriate) were used. P values < 0.05 were considered statistically significant. Logistic regression models were used to determine whether etiologies/risk factors were associated with particular modes of presentation or clinical outcomes compared with not having those etiologies/risk factors. Results are reported as odds ratio (OR) and 95% confidence interval (CI). All statistical analyses were performed using SPSS version 21 software.

Results

1. Patients and clinical characteristics

From January 2002 to June 2013, 185 patients with stroke were identified. The clinical characteristics of the patients are shown in Table 2. All patients were Korean.

There were 100 boys and 85 girls. The male:female ratio was 1.2:1. Gender ratio varied according to age group ($P = 0.009$). Male dominance was more prominent in adolescence (gender ratio, 3.5:1) than it was in preadolescence ($P = 0.001$).

The mean age at diagnosis was 6.5 years (range, 1 month to 18.9 years). Figure 1 illustrates the distribution of age at diagnosis. The peak frequency was observed during the first year of life. In infancy, infection ($P = 0.001$) and severe dehydration ($P = 0.006$) were more common, and moyamoya disease (MMD) was less common ($P = 0.003$). Table 3 demonstrates the comparison of the demographics of the below 1 year group versus the 1 year and over group. The categorization of patients into four groups according to their age at diagnosis revealed that 34 patients (18%) were 1-11 months, 61 patients (33%) were 1–5 years, 54 patients (29%) were 6–11 years, and 36 patients (19%) were older than 12 years of age at diagnosis.

Similar to what is observed in adults, the diagnosis of stroke was often delayed in this study. Sixty-six patients (21%) were diagnosed with a stroke within 6 hours and 19 of them (29%) were being hospitalized. Early diagnosis was established in 94 patients (51%) and late diagnosis was in 91 patients (49%). Time to diagnosis was different according to stroke type ($P =0.028$). Patients with HS were diagnosed earlier than those with other stroke types. In contrast, the diagnoses of MS were delayed than other stroke types. Among

AIS, patients with vasculitis, arterial dissection, and cardiac disease showed early diagnosis, and those with inflammatory vasculopathy, other vasculopathy, and MMD had late diagnosis relatively although the difference was not statistically significant.

Table 4 lists the initial presentation of the disease. Most patients (n = 149, 81%) had two or more symptoms. Hemiparesis was the most common presenting sign (n = 111, 60%). One hundred seventy-four patients (94%) presented with focal neurological signs: paresis was noted in 132 patients (72%), seizure in 71 patients (38%), speech impairment in 46 patients, facial palsy in 44 patients, visual disturbance in 15 patients, paresthesia in 11 patients, involuntary movements in 11 patients, and other focal neurological deficits in three patients.

Diffuse signs were documented in 102 patients (55%): 50 patients (27%) had headache, 34 (18%) showed altered mentality, 24 showed lethargy, 18 had nausea or vomiting, 15 had dizziness, eight showed irritability, and two had other diffuse signs. Eleven patients (11%) showed only diffuse signs, seven of whom had only nonspecific signs (headache, vomiting, lethargy, and respiratory difficulty). Ninety-one patients (49%) had mixed signs, which were associated with poor outcome (P = 0.001).

2. Stroke type

There were 156 patients (84%) with AIS, nine patients (5%) with CSVT, nine patients (5%) with MS, and 11 patients (6%) with HS type of stroke. Eleven patients with AIS had hemorrhagic components. AIS accounted for the overwhelming majority of stroke cases in all age groups.

3. Etiologies and risk factors according to stroke type

Etiologies/risk factors were identified in 154 patients (83%). Table 5 lists

the etiologies/risk factors according to their frequency. The distribution of etiologies/risk factors varied according to age group (P = 0.001). The most common etiologies/risk factors according to age group are shown in Table 6. The most common single etiology was MMD (n = 54, 29%). Table 7 summarizes the etiologies/risk factors according to stroke type and frequency.

(1) Arterial ischemic stroke

Etiologies/risk factors were identified in 126 patients (81%) and undetermined in 30 patients. The most common category was arteriopathy, followed by cardiac disease, prothrombotic condition, and hematologic disorder.

Arteriopathy. Arteriopathy includes (1) MMD; (2) infection; (3) inflammatory/postinfectious arteriopathy, such as focal cerebral arteriopathy, postvaricellar angiopathy, and childhood primary angiitis of the central nervous system (cPACNS); (4) systemic vasculitis, such as systemic lupus erythematosus (SLE), juvenile rheumatoid arthritis (JRA), polyarteritis nodosa (PAN), and Kimura disease; (5) arterial dissection; (6) other noninflammatory vasculopathies, such as incontinentia pigmenti and fibromuscular dysplasia.

CNS infection (n = 11), including meningitis, meningoencephalitis, and septic embolism, and specific pathogens were identified in seven patients. The pathogens included *Streptococcus pneumonia*, *Pseudomonas aeruginosa*, Group B Streptococcus, *Aspergillus* species, and *Mycobacterium tuberculosis*.

Cardiac disease. Twenty-three patients had underlying cardiac diseases. Fifteen patients had congenital heart disease, which had been identified before stroke in 13 patients, and cardiac surgery was performed in nine patients before stroke. Through the evaluation of risk factors, a large atrial septal defect was newly found in two patients who were asymptomatic before the stroke. Echocardiography revealed infective endocarditis with thrombosis in

four patients, suggesting the presence of embolic infarctions in those patients. Three of them had a natural valve and one of them had a mechanical valve. Arrhythmia was noted in three patients. One patient was treated with extracorporeal membrane oxygenation (ECMO) for the management of myocarditis-induced dilated cardiomyopathy. One patient had cardiomyopathy and one had myocarditis. One patient had left atrial myxoma, which was detected after the diagnosis of stroke. None of the patients had obstructive atherosclerotic arteriopathy.

Prothrombotic condition. Not all patients underwent complete analyses for thrombophilia markers. Methylenetetrahydrofolate reductase (*MTHFR*) gene mutation was found in 11 patients: six patients exhibited compound heterozygosity (CT/AC) at positions 677 and 1298, and five patients exhibited homozygosity at position 677 (TT). Antiphospholipid syndrome was reported in one patient. In two patients, strokes occurred during chemotherapy for acute lymphoblastic leukemia (ALL): one was an L-asparaginase-associated stroke and the other was associated with methotrexate.

Hematologic disorder. Hematological disorders were detected on a single case basis in six patients; leukemia, iron-deficiency anemia, hemophagocytic lymphohistiocytosis (HLH), hemolytic uremic syndrome (HUS), thrombotic thrombocytopenic purpura (TTP) associated with HUS, and total occlusion of the left internal carotid artery caused by a mass effect of suprasellar craniopharyngioma.

(2) Cerebral sinovenous thrombosis

CSVT was identified in nine patients. MRV was performed in seven patients, to confirm sinovenous thrombosis. Severe dehydration preceded stroke in three patients. Three patients had acute infection, such as septic embolism, enterovirus meningitis, or acute mastoiditis (in three patients). Prothrombotic conditions were found on a single-case basis in three patients;

antiphospholipid syndrome (APS), *MTHFR* gene mutation (677 TT homozygosity), and L-asparaginase for chemotherapy of leukemia.

(3) Metabolic stroke

Nine patients were newly diagnosed as having mitochondrial disease: eight patients had mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), and were confirmed to have the mitochondrial DNA (mtDNA) 3243 point mutation.

(4) Hemorrhagic stroke

Hemorrhagic stroke affected 11 patients. The hemorrhage was intracerebral in seven, intraventricular in two, and subarachnoidal in two cases. Three patients had arteriovenous malformation (AVM), and two patients had MMD. Other underlying diseases included ruptured arterial aneurysm, arterial dissection, mycotic embolism, *MTHFR* gene mutation (677 TT homozygosity), and Evans syndrome. One patient was failed to identify the etiology/risk factors.

4. Multiple etiologies

Seventeen patients (9%) had two or more etiologies (Table 8). MMD was the most common single disease with multiple etiologies (n = 11); eight patients had prothrombotic condition (*MTHFR* gene mutation or anticardiolipin antibody (ACA), and both), two patients had hematologic disease (aplastic anemia), and one patient had systemic vasculitis (SLE). Inflammatory vasculopathy had additional risk factors, such as *MTHFR* gene mutation, ACA, lupus anticoagulant, and infection. Among patients with cardiac disease, there was one case with *MTHFR* gene mutation and one with protein C deficiency.

5. Clinical outcomes

(1) Overall outcome

Table 9 lists the predictors of poor outcome. The overall outcome was favorable in 152 patients (83%) and poor in 33 patients (18%). A late diagnosis did not lead to a poor outcome (P = 0.929). The patients who presented mixed signs showed a poorer outcome than did the patients with focal signs only or diffuse signs only (P = 0.001). The overall outcome varied according to stroke type (P = 0.009). AIS had a more favorable outcome (OR = 0.404, P = 0.048), whereas MS had a poorer outcome (OR = 6.607, P = 0.007). Epilepsy after stroke was associated with poor outcome (P < 0.001). The presence of recurrent stroke was associated with a poorer outcome (OR = 3.237, P = 0.010).

Among the etiologies/risk factors of AIS, inflammatory/postinfectious vasculopathy and MMD had a relatively more favorable outcome, although the difference was not statistically significant (Table 10).

Although multiple etiologies/risk factors were not associated with poor outcome overall (P = 0.199), the MMD-plus group had a poorer outcome compared with the MMD-only group (P = 0.014) in AIS (Table 11). However, the recurrence rate was not different between the MMD-only and MMD-plus groups (P = 0.681).

(2) Recurrence

The median follow-up duration was 3.2 years (range: 0.1-10.9 years). Recurrent stroke occurred in 28 patients (15%). The mean time to 2nd stroke was 8.8 months (range, 5 days to 6.4 years), and the number of recurrences after the 1st stroke was 2–5 times (mean, 1.6 times).

Table 12 lists the predictors of recurrence. Mixed signs at initial

presentation and multiple etiologies were not associated with recurrence. Epilepsy after stroke did not predict recurrence. The recurrence rate varied according to stroke type. The recurrence rate was low in AIS (OR = 0.308, P = 0.012), whereas it was high in MS (OR = 25.333, $P < 0.001$). Multiple etiologies/risk factors did not increase the recurrence rate (P =0.469).

In AIS, the most common etiologies/risk factors for recurrence were systemic vasculitis (OR = 7.941, P = 0.045) and MMD (OR = 3.220, P = 0.020) (Table 13).

Among the patients who had been followed up for more than 1 year, recurrent stroke occurred in 26 patients (19%). Anticoagulation with warfarin or aspirin was used for the secondary prevention of stroke was used in 29 patients. However prophylaxis did not affect overall outcome (P = 1.000).

(3) Survival

Most of the patients had survived up to the last follow-up visit. The overall mortality rate was 7% (13 of 185 patients. Table 14 lists the characteristics of the cases with mortality.

(4) Morbidity

Table 15 lists the morbidities after stroke in the 185 patients. About 1/3 of the patients recovered fully without neurological deficits. Most morbidities were tolerable and did not affect daily activity: fine motor dysfunction, mild motor weakness, intermittent headache/dizziness, involuntary movements, speech impairment, visual-field defect, and facial asymmetry. Severe morbidities were also reported: 13 patients (7%) had spastic monoplegia/hemiplegia and required special care and assistance, one patient was wheelchair bound, and two patients were bedridden. Other severe neurological deficits included blindness, hearing loss, and hallucination.

Epilepsy after stroke occurred in 26 patients (14%): one patient was

seizure free without antiepileptic drugs (AEDs), 10 patients were seizure free with AEDs, five patients had less-frequent seizures with AEDs, and 10 patients were intractable to AED. Patients with epilepsy had a worse outcome than did the nonepileptic group (OR = 6.950, $P < 0.001$).

Table 1. Glasgow Outcome Scale

Score	Description
1	**Good recovery** Resumption of normal activities, even though there may be minor neurological or psychological deficits
2	**Moderate disability (disabled but independent)** Patient is independent as far as daily life is concerned. The disabilities found included varying degrees of dysphasia, hemiparesis, or ataxia, as well as intellectual and memory deficits and personality changes
3	**Severe disability (conscious but disabled)** Patient depends upon others for daily support because of mental or physical disability, or both
4	**Persistent vegetative state** Patient exhibits no obvious cortical function
5	**Death**

Table 2. Clinical characteristics of patients (n = 185)

	n (%)	P value
Gender (male:female)	100:85	
Gender ratio by age group		0.009
1–11 months	15:19	
1–5 years	33:28	
6–11 years	24:30	
≥12 years	28:8	
Age		
Age at diagnosis	6.5 ± 5.1 years	
Age by stroke type		0.014
AIS	6.3 ± 4.9 years	
CSVT	7.5 ± 6.4 years	
MS	11.1 ± 4.0 years	
HS	8.5 ± 5.7 years	
Age group		
1–11 months	34 (18)	
1–5 years	61 (33)	
6–11 years	54 (29)	
≥12 years	36 (19)	
Time to diagnosis		
0–6 hours	66 (36)	
7–24 hours	28 (15)	
>24 hours	91 (49)	
Early diagnosis by stroke type		0.028
AIS	82/156 (53)	
CSVT	3/9 (33)	
MS	1/9 (11)	
HS	8/11 (73)	
Early diagnosis by etiology in AIS		
MMD	24/52 (46)	
Inflammatory	4/10 (40)	
Vasculitis	3/4 (75)	
Infection	6/11 (54)	
Other vasculopathy	0/3 (0)	
Dissection	2/3 (67)	
Cardiac disease	15/23 (65)	
Prothrombotic	9/14 (64)	
Hematologic	3/6 (50)	

Initial presentation	
Focal only	83 (45)
Diffuse only	11 (6)
Mixed sign	91 (49)
Stroke type	
AIS	156 (84)
CSVT	9 (5)
MS	9 (5)
HS	11 (6)

AIS, arterial ischemic stroke; CSVT, cerebral sinovenous thrombosis; MS, metabolic stroke; HS, hemorrhagic stroke

Table 3. Comparison of the demographics of the below 1 year group versus the 1 year and over group

	<1 year (n = 34)	≥1 year (n = 151)	P value
Gender (male:female)	15:19	85:66	0.253
Time to diagnosis			0.572
≤24 hours	19	75	
>24 hours	15	76	
Initial sign			0.483
Focal or diffuse	18	65	
Diffuse	1	10	
Mixed	15	76	
Stroke type			0.253
AIS	30	126	
CSVT	3	6	
MS	0	9	
HS	1	10	
Etiology/risk factor			
MMD	3	51	0.003*
Inflammatory vasculopathy	0	10	0.212
Systemic vasculitis	0	4	1.000
Infection	8	7	0.001*
Other vasculopathies	2	1	0.087
Dissection	0	4	1.000
Cardiac disease	7	16	0.146
Prothrombotic condition	3	15	1.000
Hematologic disease	2	4	0.304
Metabolic disease	0	9	0.215
Dehydration	3	0	0.006*
AVM	0	3	1.000
Aneurysm	0	1	1.000
Poor outcome	8	25	0.330
Survival	31	140	0.710
Recurrence	2	26	0.116
Epilepsy	7	19	0.273

AIS, arterial ischemic stroke; CSVT, cerebral sinovenous thrombosis; MS, metabolic stroke; HS, hemorrhagic stroke; MMD, moyamoya disease; AVM, arteriovenous malformation

*Statistically significant (P < 0.005)

Table 4. Initial presentation of the 185 patients

	n (%)
Focal sign	174 (94)
Paresis	132
Seizure	71
Speech impairment	46
Facial palsy	44
Visual disturbance	15
Paresthesia	11
Involuntary movement	11
Others	3
Diffuse sign	102 (55)
Headache	50
Altered mentality	34
Lethargy	24
Nausea/vomiting	18
Dizziness/vertigo	15
Irritability	8
Others	2
Mixed sign	91 (49)

Table 5. Most common etiologies/risk factors

Etiology	*n* (%)
MMD	54 (29)
Cardiac disease	23 (12)
Prothrombotic condition	18 (10)
Infection	15 (8)
Inflammatory vasculopathy	10 (5)
Metabolic disease	9 (5)
Hematologic disease	7 (4)
Systemic vasculitis	4 (2)
Arterial dissection	4 (2)
Other vasculopathy	3 (2)
Dehydration	3 (2)
AVM	3 (2)
Aneurysm	1 (1)

MMD, moyamoya disease; AVM, arteriovenous malformation

Table 6. Most common etiologies/risk factors according to age group

Age group	Most common etiologies/risk factors	*P* (%)
1–11 months (Infancy)	Infection	8 (24)
	Cardiac disease	7 (21)
	Prothrombotic condition	3 (9)
1–5 years (Early childhood)	MMD	31 (51)
	Cardiac disease	5 (8)
	Inflammatory vasculopathy	6 (11)
6–11 years (Late childhood)	MMD	18 (33)
	Prothrombotic condition	6 (11)
	Metabolic disease	5 (8)
≥12 years (Adolescence)	Cardiac disease	46 (18)
	Prothrombotic condition	6 (18)

MMD, moyamoya disease

Table 7. Etiologies/risk factors according to stroke type (n = 185)

	n (%)
AIS	156 (84)
Arteriopathy	83
MMD	52
Infection	11
Inflammatory vasculopathy	10
Systemic vasculitis	4
Arterial dissection	3
Other vasculopathy	3
Cardiac disease	23
Prothrombotic condition	14
Hematologic disease	6
Undetermined	30
CSVT	9 (5)
Severe dehydration	3
Infection	3
Prothrombotic condition	3
MS	9 (5)
MELAS	8
Mitochondrial disease	1
HS	11 (6)
AVM	3
MMD	2
Aneurysm	1
Arterial dissection	1
Infection	1
Hematologic disease	1
Prothrombotic condition	1
Undetermined	1

AIS, arterial ischemic stroke; CSVT, cerebral sinovenous thrombosis; MS, metabolic stroke; HS, hemorrhagic stroke; MMD, moyamoya disease; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; AVM, arteriovenous malformation

Table 8. Patients who had two or more etiologies (n = 17)

	N
MMD	11
MMD + *MTHFR* gene mutation	5
MMD + ACA	2
MMD + *MTHFR* gene mutation+ ACA	1
MMD + AA	2
MMD + SLE	1
Inflammatory vasculopathy	4
FCA + *MTHFR* gene mutation	1
FCA + ACA	1
FCA + LA	1
FCA + Infection	1
Cardiac	2
CHD + *MTHFR* gene mutation	1
CHD + Protein C deficiency	1

MMD, moyamoya disease; *MTHFR*, methylenetetrahydrofolate reductase; ACA, anticardiolipin antibody; AA, aplastic anemia; SLE, systemic lupus erythematosus; FCA, focal cerebral arteriopathy; LA, lupus anticoagulant; CHD, congenital heart disease

Table 9. Predictors of poor outcome (n = 33)

	Poor outcome n/total (%)	OR (95% CI)	P value
Male	12/100 (12)	2.407 (1.104–5.244)	0.027
Age group			
1–11 months	8/34 (24)	1.551 (0.630–3.819)	0.340
1–5 years	8/61 (13)	0.598 (0.252–1.417)	0.243
6–11 years	14/54 (26)	2.063 (0.947–4.496)	0.068
≥12 years	3/36 (8)	0.361 (0.104–1.256)	0.109
Delayed diagnosis	6/31	1.129 (0.422–3.017)	0.809
Mixed signs	25/91 (28)	4.072 (1.726–9.607)	0.001*
Stroke type			
AIS	24/156 (15)	0.404 (0.164–0.993)	0.048*
CSVT	1/9 (11)	0.563 (0.068–4.658)	0.594
MS	5/9 (56)	6.607 (1.670–26.143)	0.007*
HS	3/11 (27)	1.800 (0.451–7.183)	0.405
Multiple etiologies/risk factors	5/17 (29)	2.083 (0.680–6.381)	0.199
Epilepsy	13/26 (50)	6.950 (2.825–17.010)	<0.001*
Recurrence	10/28 (36)	3.237 (1.328–7.887)	0.010*

Univariate logistic regression was performed.

OR, odds ratio; CI, confidence interval; AIS, arterial ischemic stroke; CSVT, cerebral sinovenous thrombosis; MS, metabolic stroke; HS, hemorrhagic stroke

*Statistically significant (P < 0.005)

Table 10. Etiologies/risk factors and poor outcome in AIS

Etiology/risk factor	Poor outcome *n*/total (%)	OR (95% CI)	*P* value
MMD	6/52 (12)	0.623 (0.231–1.679)	0.350
Inflammatory	0/10 (0)		0.362†
Vasculitis	1/4 (25)	1.870 (0.186–18.764)	0.595
Infection	4/11 (36)	3.571 (0.958–13.316)	0.058
Other vasculopathy	0/3 (0)		1.000†
Dissection	1/3 (33)	2.826 (0.246–32.458)	0.404
Cardiac disease	5/23 (22)	1.667 (0.553–5.024)	0.364
Prothrombotic	3/14 (21)	1.571 (0.404–6.111)	0.514
Hematologic	3/6 (50)	4.967 (0.956-25.801)	0.057
Undetermined	1/30 (3)	0.154 (0.020–1.192)	0.154

Univariate logistic regression was performed, with the exception of the cases marked with †, which represent the results of Fisher's exact test.

AIS, arterial ischemic stroke; OR, odds ratio; CI, confidence interval; MMD, moyamoya disease

† Fisher's exact test

*Statistically significant ($P < 0.005$)

Table 11. Comparison of clinical characteristics between the group with MMD only and the group with MMD plus other etiologies in AIS

	MMD only (n = 41)	MMD plus (n = 11)	P value
Sex (male:female)	19:22	5:6	1.000
Mean age (years)	5.10 ± 3.51	5.50 ± 3.19	0.734
Delayed diagnosis	5 (12%)	0 (0%)	0.571
Mixed sign	16 (39%)	3 (27%)	0.726
Poor outcome	2 (5%)	4 (36%)	0.014*
Recurrence	8 (73%)	3 (27%)	0.681
Survival	40 (98%)	100 (100%)	1.000
Epilepsy	5 (12%)	2 (29%)	0.630

MMD, moyamoya disease; AIS, arterial ischemic stroke

*Statistically significant ($P < 0.005$)

Table 12. Predictors of recurrence (n = 28)

	Recurrence n/total (%)	OR (95% CI)	P value
Male	11/100 (11)	2.023 (0.890–4.599)	0.093
Age group			
1–11 months	2/34 (6)	0.300 (0.068–1.333)	0.114
1–5 years	11/61 (18)	1.385 (0.604–3.174)	0.442
6–11 years	10/54 (19)	1.427 (0.611–3.331)	0.411
≥12 years	5/36 (14)	0.884 (0.311–2.510)	0.816
Delayed diagnosis	7/31 (23)	1.036 (0.277–3.869)	0.958
Mixed signs	14/91 (15)	1.039 (0.465–2.322)	0.926
Stroke type			
AIS	19/156 (12)	0.308 (0.123–0.774)	0.012*
CSVT	0/9 (0)		0.359†
MS	7/9 (78)	25.333 (5.030–132.673)	<0.001*
HS	2/11 (18)	1.265 (0.259–6.190)	0.772
Multiple etiologies/risk factors	3/17 (18)	1.647 (0.426–6.363)	0.469
Epilepsy	7/26 (27)	2.421 (0.908–6.455)	0.077

Univariate logistic regression was performed, with the exception of the cases marked with †, which represent the results of Fisher's exact test.

OR, odds ratio; CI, confidence interval; AIS, arterial ischemic stroke; CSVT, cerebral sinovenous thrombosis; MS, metabolic stroke; HS, hemorrhagic stroke

† Fisher's exact test

*Statistically significant (P < 0.005)

Table 13. Etiologies/risk factors and recurrence in AIS

Etiology/risk factor	Recurrence *n*/total (%)	OR (95% CI)	*P* value
MMD	11/52 (21)	3.220 (1.207–8.590)	0.020*
Inflammatory	1/10 (10)	0.790 (0.094–6.610)	0.828
Vasculitis	2/4 (50)	7.941 (1.049–60.093)	0.045*
Infection	0/11 (0)		0.362†
Other vasculopathy	0/3 (0)		1.000†
Dissection	0/3 (0)		1.000†
Cardiac disease	0/23 (0)		0.078†
Prothrombotic	3/14 (21)	2.148 (0.541–8.524)	0.277
Hematologic	1/6 (17)	1.126 (0.127-10.017)	0.915
Undetermined	1/30 (3)	0.207 (0.027–1.615)	0.133

Univariate logistic regression was performed, with the exception of the cases marked with †, which represent the results of Fisher's exact test.

AIS, arterial ischemic stroke; OR, odds ratio; CI, confidence interval; MMD, moyamoya disease

† Fisher's exact test

*Statistically significant ($P < 0.005$)

Table 14. Clinical characteristics of mortality cases

Sex	Age (years)	Stroke type	Underlying disease	Cause of death
M	11.3	AIS	ALL, L-asparaginase	Pulmonary hemorrhage
F	2.2	AIS	ALL, systemic fungal infection, infective endocarditis	ICH
F	7.2	AIS	ALL, fungal infection	Sepsis
M	2.5	AIS	ALL, infective endocarditis	DIC
M	6.5	AIS	Craniopharyngioma, mass effect of brain tumor	CNS infection, septic shock
F	10.6	AIS	MMD	Uncontrolled brain edema due to massive infarct
F	0.3	AIS	Complex heart disease, protein C deficiency	Sepsis, DIC, pulmonary edema
F	6.6	AIS	DCMP	Heart failure
F	0.9	AIS	HUS with TTP	ESRD, peritonitis, septic shock
F	2.0	AIS	APS	Pulmonary infarct, arrhythmia
M	0.3	CSVT	Nephrogenic DI, RTA, congenital Morgagni hernia	Severe metabolic acidosis, arrhythmia
F	4.9	MS	MELAS, HCMP, WPW syndrome	Aspiration pneumonia, septic shock
M	5.3	HS	CGD, fungal infection	Sepsis, gastrointestinal bleeding

AIS, arterial ischemic stroke; ALL, acute lymphoblastic leukemia; ICH, intracerebral hemorrhage; DIC, disseminated intravascular coagulation; MMD, moyamoya disease; DCMP, dilated cardiomyopathy; HUS, hemolytic uremic syndrome; TTP, thrombotic thrombocytopenic purpura; ESRD, end stage renal disease; APS, antiphospholipid syndrome; CSVT, cerebral sinovenous thrombosis; DI, diabetes insipidus; RTA, renal tubular acidosis; MS, metabolic stroke; MELAS, mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; HCMP, hypertrophic cardiomyopathy; WPW syndrome, Wolff–Parkinson–White syndrome; HS, hemorrhagic stroke; CGD, chronic granulomatous disease

Table 15. Morbidities after stroke (*n* = 128)

	N (%)
Mild to moderate	
Fine motor dysfunction	44 (24)
Mild motor weakness	21 (11)
Headache/Dizziness	13 (7)
Involuntary movements	6 (3)
Speech impairment	4 (2)
Visual field defect	3 (2)
Facial asymmetry	2 (1)
Severe	
Epilepsy	26 (14)
Spastic hemiplegia/monoplegia	13 (7)
Blindness	2 (1)
Hearing loss	2 (1)
Hallucination	1 (0.5)
Wheelchair bound	1 (0.5)
Bedridden state	2 (1)
Brain death	1 (0.5)
Expired	13 (7)

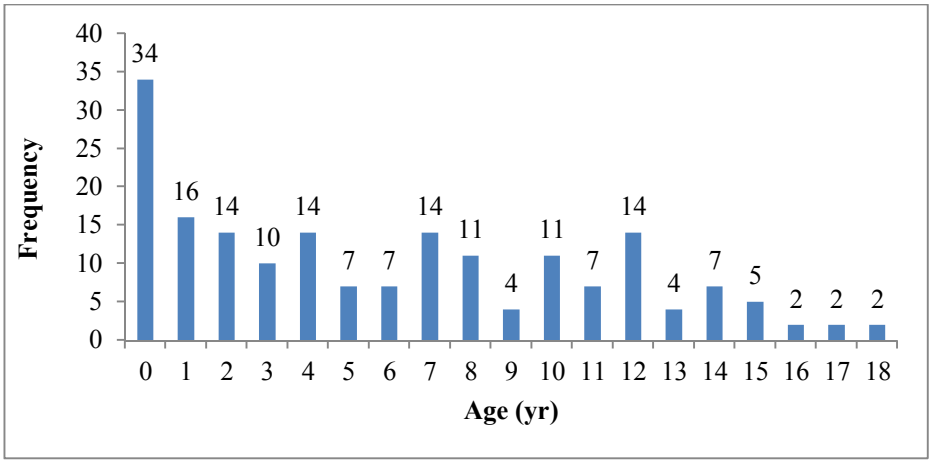

Figure 1. Distribution of age at diagnosis of stroke. The peak frequency was during the first year of life.

Discussion

Childhood stroke is an important cause of long-term morbidity and mortality in developing brain and is a complex condition that is associated with various etiologies and risk factors compared with stroke of adulthood. Advances in noninvasive diagnostic methods and laboratory tests have led to an increase in the recognition of etiologies of childhood stroke. Despite efforts to raise awareness regarding stroke in children, this condition is often overlooked as a cause of symptoms by primary physicians and caregivers [17, 21], and a delay in diagnosis occurs in many children, with the exception of those who are hospitalized. The current literature is insufficient to plan treatment strategies according to etiology. I reviewed a large series of 185 patients extensively, and investigated the etiologies/risk factors of childhood stroke according to age group and evaluated a correlation between etiologies/risk factors and clinical outcome.

Several studies have found that childhood stroke is more common in boys than it is in girls [22]. A similar male dominance (gender ratio, 1.2:1) was observed, and the condition was more prominent in adolescence than in preadolescence in this study. The gender disparity observed in adulthood stroke has been attributed to lifestyle differences such as increased levels of smoking and alcohol intake in men. These factors are unimportant in the pathogenesis of childhood stroke. Moreover, the overall male predominance in adults has been attributed to the neuroprotective effects of estrogen. It is possible that elevated testosterone levels also play a role in boys with childhood stroke, as reported previously [23].

Most of the patients (89%) included in the present study had identifiable etiologies/risk factors for stroke. The most common etiologies, such as infection in early infancy, MMD and cardiac disease in early childhood,

MMD and prothrombotic condition in late childhood, and prothrombotic condition in adolescence, varied according to age group. In addition, the peak age of stroke was early infancy, which is related to infection. The age distribution was similar to that of the IPSS, but the proportion of infection in early infancy was relatively low in that study [8]. A high prevalence of infection in early infancy was found in another single Korean tertiary center study [15]. Considering that our center is one of the largest tertiary referral children's hospitals in Korea, cases of early infantile stroke with severe infection were referred from all over the country, and CNS-infection-associated stroke can be considered as one of the most important risk factors in our hospital. The age-related variations in etiologies may suggest the need for different investigative strategies that will depend on the child's age.

The etiologies of stroke vary according to the population studied (Table 16). For example, sickle cell disease is most common in the African-American population, moyamoya disease is frequent in Japanese and Korean populations, and coagulation disorders are more frequent in European populations [1, 11, 24]. Etiologies/risk factors which are common in Europe or North America were rare in this study: none of the patients had sickle cell disease, and arterial dissection was found in only 2% of the patients. Instead, the most common single etiology was MMD (29% of the whole cohort). This proportion is much higher than that reported recently by the IPSS, which found 61 MMD patients (9%) [8]. In comparison, within East-Asian series, Japan showed a similar frequency, and China and Taiwan had fewer patients than did the present study [15, 25-28]. In addition, Kim et al. reported that infarction was a frequent clinical manifestation of MMD (initial presentation in 39% of cases) [24]. Thus, children with a sudden onset of focal neurological deficits, especially in East Asia, should be suspected of having MMD first.

Similar to Europe or North America, cardiac disease was the second most

common etiology/risk factor of childhood stroke [9, 10]. About 43% of the cases of stroke that were associated with cardiac disease occurred in association with cardiac surgery; thus, improvement of perioperative care may be another target for the prevention of this disease. In contrast to what is observed in adults with stroke, congenital heart diseases were more common than was acquired pathology. In this study, a large atrial septal defect was newly detected via risk-factor evaluation in two patients who were asymptomatic before the stroke. Thus, cardiac assessment may be included in the risk-factor evaluation, even for patients who do not have cardiac symptoms. Complex heart structural lesions associated with stroke should be repaired to improve cardiac function and prevent recurrent stroke.

MTHFR gene mutation was a notable prothrombotic condition in the present study (11%). It was identified in all stroke types: 19 patients with AIS, one patient with CSVT, and one patient with HS. None of them had hyperhomocysteinemia. Moreover, *MTHFR* mutation was frequently found among patients who had multiple etiologies/risk factors. Although *MTHFR* gene mutation is associated with childhood stroke, it is also common in the general population, and its significance in the absence of hyperhomocysteinemia is unclear. In the meta-analysis of 22 observational studies, the *MTHFR* gene mutation 677C>T was associated with AIS only, albeit weakly (OR = 1.58; 95% CI, 1.20–2.08) [29]. Moreover, although the prevalence of *MTHFR* gene mutation has been reported in populations with various ethnic backgrounds, few data concerning the Korean population are available [30, 31], rendering it more difficult to explain the role of *MTHFR* gene mutation in this condition. *MTHFR* gene mutation was not associated with overall outcome (P = 0.653) or recurrence (P = 0.596) in this study. However, not all patients underwent analyses for *MTHFR* gene mutation, because investigation of *MTHFR* gene mutation has been actively performed since 2009 in our center. To prove the role of *MTHFR* gene mutation in

childhood stroke, an additional study including a large number of patients would be needed.

In general, most patients had a favorable outcome; however, this depended mainly on the etiology/risk factor of stroke. Regarding stroke type, AIS had a more favorable outcome, whereas MS had a worse outcome. Among the etiologies/risk factors in AIS, inflammatory/postinfectious vasculopathy and MMD had a relatively more favorable outcome. Although the general outcome of MMD was favorable, some difference was present between the MMD-only and MMD-plus groups. The MMD-plus group exhibited a worse outcome. Therefore, preoperative evaluation should be performed carefully in MMD patients regarding the presence of coexisting risk factors, and close attention to management during the peri/postoperative periods is needed. Other variables associated with poor outcome were a mixed sign at initial presentation, epilepsy after stroke, and presence of recurrent stroke.

As in previous studies, among children who suffer a first-ever stroke outside the neonatal period and go untreated, the risk of recurrence is about 10–25% [13, 32, 33], although this value may be as low as 6% in those with ≤1 risk factors [34] or as high as 90% in those with sickle cell disease [35]. In this study, the recurrence rate was 15%, which was similar to that reported by a previous study; however, multiple etiologies did not increase the recurrence rate. Previously reported common predictors of recurrent stroke were sickle cell disease, raised lipoprotein, and thrombophilias [11, 13, 33, 35], whereas the most common etiologies/risk factors for recurrence in AIS were systemic vasculitis and MMD in this study.

Most children survived stroke. The short-term mortality in this study was low. However, neurological sequelae were present in 2/3 of children after stroke. Mild-to-moderate motor disabilities were common. Compared with the low risk of epilepsy after stroke in adults, which has been estimated at 2–4%, the risk of epilepsy after childhood stroke has been documented as being high

[27, 36, 37]. In this study, 14% of patients suffered from epilepsy after stroke, which contributed to a poor outcome.

In summary, based on the results of our study, the distribution of risk factors of childhood stroke in Korea differed from that reported for Western countries. MMD was the most important etiology for childhood stroke in Korea. *MTHFR* gene mutation was an additional risk factor for childhood stroke, but its significance remains unclear. The most common etiologies/risk factors varied according to age group. Age should be considered when establishing a strategy to evaluate stroke risk. Clinical outcome and recurrence were associated with etiologies/risk factors; therefore, an active investigation aimed at identifying risk factor is important to plan the acute treatment and to prepare a prevention strategy for childhood stroke.

Table 16. Comparison with previous studies

Clinical study	IPSS [8]	Ganesan et al. [10]	Shi et al. [28]	Present study
Study design	Prospective, International multicenter study	Retrospective/prospective Single tertiary center	Retrospective Single tertiary center	Retrospective Single tertiary center
Stroke type included	AIS	AIS	AIS	AIS, CSVT, MS, HS
Exclusions	Neonatal stroke CSVT, MS, HS Watershed infarct	CSVT, MS, HS	Neonatal stroke HS	Neonatal stroke Watershed infarct Asymptomatic stroke
Age range (mean)	1 month to 18 years (5.7 years)	<20 years (5.0 years)	1 month to 16 years (2.7 years)	1 month to 18 years (6.5 years)
Number of patients	676	212	157	185
Gender ratio (male:female)	399:277 (1.4:1)	115:97 (1.2:1)	92:65 (1.4:1)	100:85 (1.2:1)
Most frequent etiologies/risk factors in AIS	Cardiac disease (31%) Infection (24%) FCA (13%) MMD (12%)	Large artery stenosis (31%) SCD (16%) Cardiac disease (12%) MMD (12%)	Infection (12%) MMD (12%) Head trauma (11%)	MMD (29%) *MTHFR* gene mutation (15%) Cardiac disease (12%)

IPSS, International Pediatric Stroke Study; AIS, arterial ischemic stroke; CSVT, cerebral sinovenous thrombosis; MS, metabolic stroke; HS, hemorrhagic stroke; MMD, moyamoya disease; FCA, focal cerebral arteriopathy; SCD, sickle cell disease; *MTHFR*, methylenetetrahydrofolate reductase

Reference

1. Adam Kirton, deVeber G. Cerebrovascular disease in children. In: Swaiman KF, editor. Pediatric neurology : principles & practice. 5th ed. Philadelphia: Elsevier/Saunders; 2012. p. 1395-436.
2. Lynch JK, Hirtz DG, DeVeber G, Nelson KB. Report of the National Institute of Neurological Disorders and Stroke workshop on perinatal and childhood stroke. Pediatrics. 2002 Jan;109(1):116-23.
3. Horvath R, Lochmüller H, Acsadi G. Metabolic stroke in childhood: Diagnostic approach and suggestions for therapy. Journal of Pediatric Neurology. 2010;8(3):321-32.
4. Agrawal N, Johnston SC, Wu YW, Sidney S, Fullerton HJ. Imaging data reveal a higher pediatric stroke incidence than prior US estimates. Stroke; a journal of cerebral circulation. 2009 Nov;40(11):3415-21.
5. Broderick J, Talbot GT, Prenger E, Leach A, Brott T. Stroke in children within a major metropolitan area: the surprising importance of intracerebral hemorrhage. Journal of child neurology. 1993 Jul;8(3):250-5.
6. Christerson S, Stromberg B. Childhood stroke in Sweden I: incidence, symptoms, risk factors and short-term outcome. Acta paediatrica. 2010 Nov;99(11):1641-9.
7. Giroud M, Lemesle M, Gouyon JB, Nivelon JL, Milan C, Dumas R. Cerebrovascular disease in children under 16 years of age in the city of Dijon, France: a study of incidence and clinical features from 1985 to 1993. Journal of clinical epidemiology. 1995 Nov;48(11):1343-8.
8. Mackay MT, Wiznitzer M, Benedict SL, Lee KJ, Deveber GA, Ganesan V, et al. Arterial ischemic stroke risk factors: the International Pediatric Stroke Study. Annals of neurology. 2011

Jan;69(1):130-40.

9. Lo W, Stephens J, Fernandez S. Pediatric stroke in the United States and the impact of risk factors. Journal of child neurology. 2009 Feb;24(2):194-203.

10. Ganesan V, Prengler M, McShane MA, Wade AM, Kirkham FJ. Investigation of risk factors in children with arterial ischemic stroke. Annals of neurology. 2003 Feb;53(2):167-73.

11. Strater R, Becker S, von Eckardstein A, Heinecke A, Gutsche S, Junker R, et al. Prospective assessment of risk factors for recurrent stroke during childhood--a 5-year follow-up study. Lancet. 2002 Nov 16;360(9345):1540-5.

12. Amlie-Lefond C, Bernard TJ, Sebire G, Friedman NR, Heyer GL, Lerner NB, et al. Predictors of cerebral arteriopathy in children with arterial ischemic stroke: results of the International Pediatric Stroke Study. Circulation. 2009 Mar 17;119(10):1417-23.

13. Fullerton HJ, Wu YW, Sidney S, Johnston SC. Risk of recurrent childhood arterial ischemic stroke in a population-based cohort: the importance of cerebrovascular imaging. Pediatrics. 2007 Mar;119(3):495-501.

14. Strater R, Vielhaber H, Kassenbohmer R, von Kries R, Gobel U, Nowak-Gottl U. Genetic risk factors of thrombophilia in ischaemic childhood stroke of cardiac origin. A prospective ESPED survey. European journal of pediatrics. 1999 Dec;158 Suppl 3:S122-5.

15. Lee EH, Yum MS, Ko TS. Risk factors and clinical outcomes of childhood ischemic stroke in a single Korean tertiary care center. Journal of child neurology. 2012 Apr;27(4):485-91.

16. Hwang YS, Yang MS. Clinical Characteristics of Childhood Cerebrovascular Disease and Analysis on the Prognostic Factors. J Korean Pediatr Soc. 1995 Mar;38(3):353-65.

17. Rafay MF, Pontigon AM, Chiang J, Adams M, Jarvis DA, Silver F, et al. Delay to diagnosis in acute pediatric arterial ischemic stroke. Stroke; a journal of cerebral circulation. 2009 Jan;40(1):58-64.

18. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. Stroke; a journal of cerebral circulation. 2008 Sep;39(9):2644-91.

19. Pappachan J, Kirkham FJ. Cerebrovascular disease and stroke. Archives of disease in childhood. 2008 Oct;93(10):890-8.

20. Jennett B, Bond M. Assessment of outcome after severe brain damage. Lancet. 1975 Mar 1;1(7905):480-4.

21. McGlennan C, Ganesan V. Delays in investigation and management of acute arterial ischaemic stroke in children. Developmental medicine and child neurology. 2008 Jul;50(7):537-40.

22. Golomb MR, Fullerton HJ, Nowak-Gottl U, Deveber G, International Pediatric Stroke Study G. Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study. Stroke; a journal of cerebral circulation. 2009 Jan;40(1):52-7.

23. Normann S, de Veber G, Fobker M, Langer C, Kenet G, Bernard TJ, et al. Role of endogenous testosterone concentration in pediatric stroke. Annals of neurology. 2009 Dec;66(6):754-8.

24. Kim SK, Cho BK, Phi JH, Lee JY, Chae JH, Kim KJ, et al. Pediatric moyamoya disease: An analysis of 410 consecutive cases. Annals of neurology. 2010 Jul;68(1):92-101.

25. Wanifuchi H, Kagawa M, Takeshita M, Izawa M, Kitamura K. Ischemic stroke in infancy, childhood, and adolescence. Child's nervous system : ChNS : official journal of the International Society

for Pediatric Neurosurgery. 1988 Dec;4(6):361-4.

26. Chung B, Wong V. Pediatric stroke among Hong Kong Chinese subjects. Pediatrics. 2004 Aug;114(2):e206-12.

27. Lee YY, Lin KL, Wang HS, Chou ML, Hung PC, Hsieh MY, et al. Risk factors and outcomes of childhood ischemic stroke in Taiwan. Brain & development. 2008 Jan;30(1):14-9.

28. Shi KL, Wang JJ, Li JW, Jiang LQ, Mix E, Fang F, et al. Arterial ischemic stroke: experience in Chinese children. Pediatric neurology. 2008 Mar;38(3):186-90.

29. Kenet G, Lutkhoff LK, Albisetti M, Bernard T, Bonduel M, Brandao L, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. Circulation. 2010 Apr 27;121(16):1838-47.

30. Sadewa AH, Sunarti, Sutomo R, Hayashi C, Lee MJ, Ayaki H, et al. The C677T mutation in the methylenetetrahydrofolate reductase gene among the Indonesian Javanese population. The Kobe journal of medical sciences. 2002 Dec;48(5-6):137-44.

31. Zuo M, Lee MJ, Kim MH, Wu Y, Ayaki H, Nishio H, et al. C677T mutation of the methylenetetrahydrofolate reductase gene among the Korean infants in Seoul city. The Kobe journal of medical sciences. 1999 Dec;45(6):271-9.

32. De Schryver EL, Kappelle LJ, Jennekens-Schinkel A, Boudewyn Peters AC. Prognosis of ischemic stroke in childhood: a long-term follow-up study. Developmental medicine and child neurology. 2000 May;42(5):313-8.

33. Ganesan V, Prengler M, Wade A, Kirkham FJ. Clinical and radiological recurrence after childhood arterial ischemic stroke. Circulation. 2006 Nov 14;114(20):2170-7.

34. Lanthier S, Carmant L, David M, Larbrisseau A, de Veber G. Stroke in children: the coexistence of multiple risk factors predicts poor outcome. Neurology. 2000 Jan 25;54(2):371-8.

35. Russell MO, Goldberg HI, Hodson A, Kim HC, Halus J, Reivich M, et al. Effect of transfusion therapy on arteriographic abnormalities and on recurrence of stroke in sickle cell disease. Blood. 1984 Jan;63(1):162-9.

36. Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. Stroke; a journal of cerebral circulation. 2004 Jul;35(7):1769-75.

37. Golomb MR, Garg BP, Carvalho KS, Johnson CS, Williams LS. Perinatal stroke and the risk of developing childhood epilepsy. J Pediatr. 2007 Oct;151(4):409-13, 13 e1-2.

초 록

서론: 소아뇌졸중은 장기적인 신경계 후유증을 남기는 중요한 질환이다. 적절한 치료방법 정하고 재발을 막기 위해 원인 질환과 위험 인자를 규명하는 것이 필요하다. 본 연구에서는 소아뇌졸중의 임상 양상을 조사하고 연령에 따른 원인질환을 규명하고, 예후와 재발에 영향을 미치는 원인 질환이 무엇인지를 밝히고자 하였다.

방법: 2002년 1월부터 2013년 6월까지 서울대학교 어린이병원에서 소아뇌졸중으로 진단받은 생후 1개월에서 18세 사이의 환자들의 임상 양상, 뇌졸중 분류, 위험인자와 예후를 조사하였다. 뇌졸중은 동맥성 허혈성 뇌졸중, 뇌정맥 혈전증, 대사성 뇌졸중, 출혈성 뇌졸중으로 분류하였다. 전반적인 예후는 Glasgow outcome scale (GOS)에 따라 양호 (GOS 1-2)와 불량 (GOS 3-5)으로 구분하였다. 진단 시 연령, 성별, 초기 증상, 진단까지 걸린 시간, 뇌졸중의 분류, 원인질환 등을 연령군에 따라 분석하였고, 후유증, 생존여부, 재발에 영향을 미치는 요인을 조사하였다.

결과: 185명의 환자들의 남녀비는 100:85 (약 1.2:1)이었다. 진단 시 평균연령은 6.5세로 1세 미만이 가장 많은 비중을 차지하였다. 대부분의 환자가 2개 이상의 증상을 보였고 편마비가 가장 흔하였다 (60%). 뇌졸중의 종류에 따라 분류하면 동맥성 허혈성 뇌졸중 환자가 165명 (84%), 뇌정맥 혈전증이 9명 (5%), 대사성 뇌졸중이 9명 (5%), 출혈성 뇌졸중이 11명 (6%)이었다. 대부분의 환자들에서 원인 질환이 규명되었다. 단일 질환 중에서는 모야모야병이 가장 흔하였고 Methylenetetrahydrofolate reductase (MTHFR) 유전자 변이가 두번째였다. 연령대에 따라 흔한 원인 질환에 차이가 있었는데 1세 미만의 영아에서는 감염성 질환, 심장질환이 흔하였고, 유아기에는 모야모야병과 심장 질환이,

학령기에는 모야모야병과 혈전성 질환이, 사춘기에는 심장질환, 혈전성 질환, 대사성 질환이 주요 원인이었다. 대부분의 환자들은 예후가 양호하였다. 뇌졸중 분류에 따라서는 동맥성 허혈성 뇌졸중의 예후가 양호하였고 대사성 뇌졸중의 예후가 불량하였다. 동맥성 허혈성 뇌졸중 내에서는 염증성 혈관질환과 모야모야병이 비교적 양호한 예후를 보였다. 불량한 예후와 관련된 인자는 대사성 질환, 발병 시 국소증상과 미만성 증상을 동시에 보인 경우, 뇌졸중 후에 발생한 뇌전증, 그리고 뇌졸중의 재발이었다. 전체 환자군에서 2개 이상의 원인요인은 예후에 영향을 미치지 않았지만, 동맥성 허혈성 뇌졸중을 보였던 모야모야병 내에서 분석했을 때 모야모야병외에 다른 위험인자를 가진 경우가 모야모야병만을 가진 경우에 비해 상대적으로 예후가 불량하였다. 재발율은 동맥성 허혈성 뇌졸중에서 낮았고 대사성 뇌졸중에서는 높았다. 원인질환 중에서는 혈관염과 모야모야병의 재발율이 높았다. 진단에 걸린 시간과 2개 이상의 위험인자는 재발율에 영향을 미치지 않았다. 대부분 뇌줄중 후에 생존하였지만 환자의 2/3가 신경학적 후유증을 보였고 어른에 비해 상대적으로 뇌전증 발생 비율이 높았다.

결론: 한국의 소아 뇌졸중의 위험 인자는 서양과 다른 분포를 보였고 모야모야병은 가장 중요한 원인 질환이었다. 예후와 재발에 관여하는 것은 원인질환이었고 이는 연령에 따라 다른 분포를 보인다. 따라서 원인 인자를 조사하는데 있어서는 반드시 연령대를 고려해야 한다.

주요어: 소아 뇌졸중, 원인 질환, 모야모야병, MTHFR 유전자, 예후
학 번: 2012 – 21755