Acute Ischemic Stroke in Children versus Young Adults

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Objective: The aim of this study was to compare children and young adults with acute ischemic stroke (AIS) in 2 large registries.
Methods: We compared clinical characteristics, stroke etiology, workup, and outcome (modified Rankin scale score [mRS] at 3–6 months) in children (1 month–16 years) and young adults (16.1–45 years) with AIS. Data of children were collected prospectively in the nationwide Swiss NeuroPediatric Stroke Registry, young adults in the Bernese stroke database. Outcome (mRS) and stroke severity (pediatric adaptation of the National Institutes of Health stroke scale [PedNIHSS]) in children were calculated retrospectively.
Results: From January 2000 to December 2008, 128 children and 199 young adults suffered from an AIS. Children were more likely to be male than young adults (62%/49%, p = 0.023) and less frequently had hypertension ($p = 0.001$), hypercholesterolemia ($p = 0.003$), and a family history of stroke ($p = 0.048$). Stroke severity was similar in children and young adults (median PedNIHSS/NIHSS 5/6; $p = 0.102$). Stroke etiology (original TOAST classification) was more likely to be "other determined cause" in children than in young adults (51%/29%; $p < .001$). Cervicocerebral artery dissections were less frequent in children than in young adults (10%/23%; $p = 0.005$). Outcome at 3 to 6 months did not differ between children and young adults ($p = 0.907$); 59% of children and 60% of young adults had a favorable outcome (mRS 0–1). Mortality was similar among children and young adults (4%/6%; $p = 0.436$). In multivariate analysis, low PedNIHSS/NIHSS was the most important predictor of favorable outcome ($p < 0.001$).
Interpretation: Although stroke etiology and risk factors in children and young adults are different, stroke severity and clinical outcome were similar in both groups.

ANN NEUROL 2011;70:245–254

Childhood acute ischemic stroke (AIS) is increasingly recognized as an important cause of morbidity and is among the top 10 causes of death in children.[1] Previous studies showed that AIS in children and young adults has different etiologies. Unlike stroke in adults, which is mainly caused by atherosclerosis and thromboembolism, pathogenesis of AIS in childhood is poorly understood, and many disorders have been associated with childhood AIS, although there is increasing evidence that nonatherosclerotic arteriopathies (in the majority, focal transient arteriopathies) are the most common risk factor for childhood stroke.[2]

In addition, outcome of AIS in children is generally considered more favorable than in adults, given the better plasticity of the brain in children. However, this assumption is challenged by several studies showing that more than half of survivors of childhood AIS have long-term physical disabilities and cognitive impairment.[3–5]

Studies comparing children and young adults with AIS are limited. Two previous comparisons showed

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.22427

Received Sep 17, 2010, and in revised form Feb 7, 2011. Accepted for publication Mar 14, 2011.

The ethics committee approved both registries.

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conflicting results, and large comparisons are lacking.[6,7] The aim of this prospective study with retrospect aspects was therefore to compare clinical presentation, stroke etiology, workup, and outcome of children with AIS in a nationwide registry with young adults of a hospital-based registry.

Patients and Methods

The 2 Populations

SWISS NEUROPEDIATRIC STROKE REGISTRY. The Swiss NeuroPediatric Stroke Registry (SNPSR) is a prospective multicenter pediatric cohort of all patients with AIS or intracerebral venous thromboses in Switzerland and was started in January 2000. On December 31, 2007, 7.6 million people were living in Switzerland. Swiss children with an acute neurological deficit are immediately referred to hospitals providing specialist care for stroke patients (5 university and 9 nonuniversity hospitals). All centers recruit patients for the SNPSR. Research fellows contact the centers monthly, and all neuropediatricians in Switzerland are contacted once per year to identify children with stroke.

THE BERNESE STROKE REGISTRY. The canton of Bern is the second largest canton of Switzerland both by surface and population (Supplementary Fig). On December 31, 2007, 962,982 people were living in the canton. According to the federal statistical office, the canton of Bern is demographically and socioeconomically similar to the rest of Switzerland: 51.2% of the population are women (50.8% in Switzerland), 22.0% are younger than 20 years (22.9% in Switzerland), the unemployment rate (16–65 years) in Bern is 2.0% (2.8% in Switzerland), 80.8% are working (78.9% in Switzerland), and 19.9% have higher degrees (21.5% in Switzerland).

The Bernese stroke database is a prospective registry including patients with AIS or intracerebral venous thrombosis that was started in January 2000. The University Hospital Bern (Inselspital) covers a catchment area of about 1.5 million inhabitants. The Inselspital is the single comprehensive stroke center within this area. Young adults with AIS in the catchment area are usually referred to the Inselspital.

Children

All children from the SNPSR aged 1 month to 16 years suffering from an AIS between January 2000 and December 2008 were included in this study. Children with intracranial hemorrhage and intracerebral venous thrombosis were excluded. Stroke was defined as an acute focal neurological deficit with corresponding ischemic lesions on computed tomography (CT) and/or magnetic resonance imaging (MRI).[8] Some data from the registry have been reported previously.[3,9–11] The investigation protocol in children with AIS, recommended by the SNPSR, is presented in Table 1. These and additional investigations were carried out at the discretion of the treating neuropediatrician. Stroke subtypes were categorized according to the TOAST criteria and the "proposed classification for subtypes of arterial ischemic stroke in children."[12,13] Steno-occlusive arteriopathy and moyamoya syndrome were defined according to the definition of Wraige and coworkers.[12] Cervical artery dissection was defined as MRI showing intramural hematoma or dissection flap, and/or catheter angiography showing string sign, pseudoaneurysm, or dissection flap.[12] The diagnosis was also established if color duplex sonography showed a stenosis or occlusion of the cervical internal carotid artery with a wall hematoma and patient history and clinical symptoms were compatible with a dissection.[14] Cardioembolic etiology was based on echocardiography or documented cardiac arrhythmias by electrocardiography (ECG) or 24-hour ECG. If the stroke occurred during or after cardiac intervention, etiology was classified as cardioembolic as well. Stroke severity was scored retrospectively using the pediatric version of the National Institutes of Health Stroke Scale (PedNIHSS) based on the clinical examination by neuropediatricians.[15] PedNIHSS is the National Institutes of Health Stroke Scale (NIHSS) modified for use in children. It is increasingly used by pediatric neurologists, although it is not yet broadly validated. A single study showed that PedNIHSS predicts neurological outcome following childhood AIS and that it can be used retrospectively.[16,17] Because international guidelines for treatment of AIS in children were lacking during the study period, antithrombotic therapy, thrombolysis, and secondary prevention were performed at the discretion of the treating neuropediatrician.

Neuropediatricians examined all patients 6 months after stroke onset. Disability was scored in retrospect using the modified Rankin scale score (mRS) with age-specific modification based on information from the clinical examination by the neuropediatrician.[18] Details on modifications are shown in Table 2. Two patients (2%) were lost for follow-up.

Young Adults

All patients from the Bernese stroke registry aged >16–45 years suffering from an AIS between January 2000 and December 2008 were included in this study. Patients with intracranial hemorrhages and intracerebral venous thrombosis were excluded. Stroke was defined as an acute focal neurological deficit with duration of the symptoms >24 hours with a corresponding ischemic lesion on CT and/or MRI scan.[19] Some aspects of these patients including standard investigation protocols have been published previously.[20,21] In brief, the severity of the neurological deficit was assessed on admission by a neurologist using the NIHSS.[17] The recommended institutional investigation protocol in all patients with AIS is summarized in Table 1. The investigations were carried out at the discretion of the treating physician. Stroke etiology was classified according to the TOAST criteria.[13] We further searched for atrial fibrillation, cervical artery dissection, foramen ovale or atrial septal defects, atrial septal aneurysm, coagulopathy, and vasculitis. Definition of cervical artery dissection was based on findings from MRI and angiography as stated above. Thrombolysis, antithrombotic therapy, and secondary prevention were performed according to a standardized protocol similar to

TABLE 1: Investigation Protocol in Children and Young Adults

Children	Young Adults
Laboratory Investigations	
Red/white blood cell and platelet counts	Red/white blood cell and platelet counts
C reactive protein	Glucose, cholesterol, electrolytes, transaminases, creatinine, and urea
Blood sedimentation rate	Prothrombin time, activated partial thromboplastin time
Serologies (if suspicion of specific infection)	Vasculitis screening, if indicated (including C reactive protein, blood sedimentation rate, antinuclear antibodies, and antiphospholipid antibodies)
Activated partial thromboplastin time	
Protein C and S	
Antithrombin III	
Homocysteine	
APC resistance	
Factor V Leiden	
Mutation analysis for MTHFR (folate metabolism) and factor II (prothrombin G20210A)	
Antinuclear antibodies	
Cardiolipin antibodies	
Antiphospholipid antibodies	
Lupus anticoagulant	
Lipid profile including lipoprotein(a)	
Neuroimaging	
CT or MRI	CT or MRI
CTA or MRA	Neurovascular ultrasound
Neurovascular ultrasound	CTA or MRA
DSA as deemed necessary	DSA as deemed necessary
Cervical MRI with fat suppression technique if indicated	Cervical MRI with fat suppression technique if indicated
Cardiac Investigations	
12-lead electrocardiography	12-lead electrocardiography
TTE	24-hour electrocardiography
TEE if there is a special indication	TTE
24-hour electrocardiography and bubble examination only if there is a special indication.	TEE
Risk Factor Assessment	
Sex	Sex
Hypertension (defined by values $\geq$95th percentile according to age, sex, and height at discharge or preadmission history of hypertension)	Hypertension (preadmission history and medical records)

TABLE 1 (Continued)

Children	Young Adults
Hyperlipidemia (total venous plasma cholesterol concentration >5.2mmol/l or lipoprotein(a), >30mg/dl	Diabetes mellitus (fasting venous plasma glucose values of ≥7.0mmol/l, and/or ≥11.1mmol/l 2 hours after intake of 75g of oral glucose and on 1 other occasion during the 2-hour test or preadmission history of diabetes)
Previous infection (including varicella infection in the past 12 months)	Hypercholesterolemia (total venous plasma cholesterol concentration >5mmol/l)
Congenital heart disease	Coronary heart disease

APC = activated protein C; CT = computed tomography; CTA = computed tomographic angiography; DSA = digital subtraction angiography; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; MTHFR = methylenetetrahydrofolate reductase; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

international guidelines.[22,23] Outcome was assessed 3 to 6 months after stroke using the mRS[19]; 32.5% of patients returned to the hospital for clinical examination and 63.5% were interviewed by phone. Telephone interviews were performed by physicians and study nurses, who were experienced in the use of the mRS. Seven patients (4%) were lost for follow-up.

Statistical Analysis

Quantitative data are expressed as mean values ± 1 standard deviation. The PedNIHSS/NIHSS score on admission is given as median value. Data are reported in frequency tables. The following variables were analyzed and compared between children and young adults: baseline characteristics, conventional vascular risk factors, etiology, cervical artery dissection, workup, thrombolysis, acute therapy, and outcome. For comparison of stroke severity, NIHSS and PedNIHSS scores were used. Differences between children and young adults were assessed using Fisher exact test (for comparison of proportions), independent t test (for comparison of continuous variables), and Mann-Whitney U test (for comparison of ordinal variables). A 2-sided p value <0.05 was considered statistically significant. Favorable outcome was defined as mRS 0 to 1, unfavorable as mRS 2 to 6. Forward stepwise logistic regression analysis was performed to assess predictors of favorable outcome among children, among young adults, and in all patients.

Results

From January 1, 2000 to December 31, 2008, 128 children and 199 young adults with AIS were recorded in the 2 registries. Baseline characteristics, vascular risk

TABLE 2: Modified Rankin Scale for Children and Adults

Score	Children	Young Adults
0	No symptoms at all	No symptoms at all
1	No significant disabilities despite symptoms; behavior appropriate to age and normal further development	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but same independence as other age- and sex-matched children (no reduction of levels on the gross motor function scale)[28]	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance; in younger patients adequate motor development despite mild functional impairment (reduction of 1 level on the gross motor function scale)	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance; in younger patients reduction of at least 2 levels on the gross motor function scale	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, requiring constant nursing care and attention	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead	Dead

TABLE 3: Baseline Characteristics in Children and Young Adults With Acute Ischemic Stroke

Characteristics	Children, n = 128	Young Adults, n = 199	*p*
Age, yr (SD)	6.7 (5.1)	35.5 (7.9)	<0.001
Female sex, No. (%)	49 (38.3)	102 (51.3)	0.023
Traditional vascular risk factors, No. (%)			
Hypertension	4 (5)	37 (19)	0.003
Diabetes mellitus	0	6 (3)	0.085
Hyperlipidemia	11 (15)	54 (28)	0.037
Hypercholesterolemia	7	54	0.003
Elevated lipoprotein(a)	4		
Previous TIA	3 (2)	11 (6)	0.263
Previous stroke	2 (2)	5 (3)	0.709
Family history of stroke	12 (11)	34 (20)	0.048
Family history of MI	12 (11)	20 (12)	0.849
NIHSS score on admission, median (range)[a]	5 (0–27)	6 (1–38)	0.102

A 2-sided *p* value <0.05 was considered statistically significant.
[a]Children were scored with the pediatric version of the NIHSS.
MI = myocardial infarction; mRS = modified Rankin Scale; NIHSS = National Institute of Health Stroke Scale; SD = standard deviation; TIA = transient ischemic attack.

factors, and stroke severity are shown in Table 3. Children were more likely to be male ($p = 0.023$) and had fewer risk factors such as hypertension ($p = 0.001$), hypercholesterolemia ($p = 0.003$), and a family history of stroke ($p = 0.048$). Stroke severity was similar in children and young adults (median PedNIHSS/NIHSS score 5 vs 6, $p = 0.102$). Detailed information on stroke etiology is shown in Table 4. According to the original TOAST classification,[13] causes of stroke were more likely to be "other determined cause" and multifactorial in children than in young adults, whereas young adults were more likely to suffer from cardioembolic strokes ($p < 0.001$). Cervical artery dissection was less often detected in children than in young adults ($p = 0.005$), and children were more likely to suffer from moyamoya syndrome ($p = 0.007$) or steno-occlusive arteriopathy ($p < 0.001$). Information on stroke workup and therapy is shown in Table 5. Transthoracic echocardiography was more often performed in children, transesophageal echocardiography (TEE) and 24-hour ECG more often in adults ($p < 0.001$). The majority of both pediatric and adult patients underwent MRI scans, whereas CT scans were more often performed in children than young adults ($p < 0.001$). Imaging of intracranial vessels was performed in all young adults and in 120 of 128 (94%) children. Stroke etiology was determined in 6 of 8 children without intracranial vessel status; 5 patients had a cardioembolic stroke, 1 a hypertensive encephalopathy. Imaging of extracranial vessels was performed in all adults and in 109 of 128 (85%) children. Stroke etiology was determined in 17 of 19 children without extracranial vessel status; 10 children had a cardioembolic stroke, and 7 had strokes due to other determined etiologies (2 hypertensive encephalopathies, 2 metabolic strokes, 2 infectious diseases, and 1 intraoperative stroke). Investigations to establish stroke etiology according to the original TOAST classification were incomplete in 3 of 128 children (2%) and 7 of 199 young adults (3%).

Thrombolysis was performed in 5 children (4%) and 57 young adults (29%), ($p < 0.001$).

Children were less likely to be treated with antiplatelet agents within the first 48 hours ($p = 0.006$); however, the use of heparin/phenprocoumon was similar in both groups. Fifteen percent of children did not receive any treatment within 48 hours, mainly because of late presentation or contraindications.

Outcome did not differ between children and young adults ($p = 0.907$); 59% of children and 60% of young adults had a favorable outcome (mRS 0–1) (Table 6). However, no child was left very severely disabled (mRS 5) compared to 8 young adults (4%). Mortality was 6% (8 of 128) in children and 4% (8 of 199) in young adults ($p = 0.436$). Three of 8 children and 6 of 8 young adults died because of their stroke. Five children

TABLE 4: Stroke Etiology in Children and Young Adults With Acute Ischemic Stroke

Characteristics	Children, n = 128	Young Adults, n = 199	*p*
Stroke etiology (TOAST),13 No. (%)			<0.001
Large artery disease	0	6 (3)	
Cardioembolic	22 (17)	74 (37)	
Atrial fibrillation	0	2	
Atrial septum defect	1	1	
Patent foramen ovale	1	63	
Cardiac surgery	13	0	
Other	7	8	
Small artery disease	0	8 (4)	
Other determined etiology	66 (52)	57 (29)	
No cause identified	18 (14)	45 (23)	
Incomplete investigations	3 (2)	7 (3)	
>1 cause	19 (15)	2 (1)	
Other determined stroke etiologies, No. (%)			
Moyamoya syndrome	7 (5)	1 (0.2)	0.007
Cervical artery dissection	13 (10)	45 (23)	0.005
Steno-occlusive arteriopathy	23 (18)	0	<0.001
Isolated coagulopathy	2	3	
Antiphospholipid antibodies	0	2	
Afibrinogenemia	0	1	
Protein S deficiency	2	0	
Vasculitis	4	2	
Migrainous stroke	0	1	
CADASIL	0	1	
Drug abuse	1	3	
Arteriopathy of unknown origin	2	1	
Infectious disease	5	0	
Metabolic stroke (mitochondriopathy)	4	0	
Hypertensive encephalopathy	2	0	
Arteriopathy after radiotherapy	1	0	
Iatrogenic	2	0	
Sickle cell disease	0	0	

A 2-sided p value <0.05 was considered statistically significant.
CADASIL = Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy.

died because of liver, cardiac, or multiorgan failure, metabolic crisis, or leukemia.

In multivariate regression analysis, high PedNIHSS/NIHSS score on admission was an independent predictor of unfavorable outcome among children ($p < 0.001$), young adults ($p < 0.001$), and all patients ($p < 0.001$). Age, sex, stroke etiology, hypertension, hypercholesterolemia, diabetes, previous transient ischemic attack or stroke, thrombolysis, and therapy with antiplatelets or warfarin did not predict outcome.

TABLE 5: Stroke Workup and Therapy in Children and Young Adults With Acute Ischemic Stroke

Characteristics	Children, n = 128	Young Adults, n = 199	*p*
Imaging of the brain			
CT scan	84 (67)	45 (23)	<0.001
MRI scan	113 (88)	176 (88)	0.857
Imaging of extra- and intracranial vessels			
CT angiography	3 (2)	44 (22)	<0.001
MRA	92 (72)	166 (83)	0.009
Angiography	1	64 (32)	<0.001
Neurovascular ultrasound	60 (47)	162 (81)	<0.001
Imaging of intracranial vessels	120 (94)	199 (100)	<0.001
Imaging of extracranial vessels	109 (85)	199 (100)	<0.001
Echocardiography			
TTE	100 (78)	22 (11)	<0.001
TEE	0	142 (71)	<0.001
Holter ECG	9 (7)	164 (82)	<0.001
Thrombolysis	5 (4)	57 (29)	<0.001
IV thrombolysis	2 (2)	12 (6)	0.055
IA thrombolysis	3 (2)	38 (19)	<0.001
Mechanical thrombolysis	0	12 (6)	0.004
Acute therapy, within 48 hours			
Antiplatelets	76 (59)	151 (76)	0.006
Heparin/warfarin	33 (26)	48 (24)	0.693
No treatment	19 (15)	0	

A 2-sided *p* value <0.05 was considered statistically significant.
CT = computed tomography; ECG = echocardiography; IA = intra-arterial; IV = intravenous; MRA = magnetic resonance angiography; MRI = magnetic resonance imaging; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography.

Discussion

This is a prospective comparison of clinical stroke characteristics, etiology, workup, and outcome of children in a nationwide registry and young adults in a hospital-based registry. The 3 main findings are: (1) Stroke etiology (original TOAST classification) was more likely to be "other determined cause" and "multifactorial" in children than in young adults. Children less often suffered from cervical artery dissection and more often suffered from steno-occlusive arteriopathy or moyamoya syndrome. (2) Stroke severity in children and adults assessed with the NIHSS and PedNIHSS scores was similar. (3) Mortality and disability at 3 to 6 months were similar in both groups.

Stroke Etiology

Two previous studies comparing stroke etiology in children and young adults found more strokes due to "undetermined causes" in children than young adults, although with differing percentages.[6,7] Williams et al determined "other causes of stroke" in 49% of children and 44% of young adults, whereas Wraige et al established "other causes" in up to 80% of children and in only 16% of young adults.

In our nationwide Swiss NeuroPediatric Stroke Registry with a recommended investigation protocol, 52% of children had a stroke due to "other determined causes" according to the original TOAST classification, compared to 29% of young adults. Main causes of stroke in children were steno-occlusive arteriopathies (18%) and cardioembolism (17%). In young adults, cardioembolism was the most frequent etiology (37%), followed by cervical artery dissections (23%). It is controversial whether a patent foramen ovale (PFO) is sufficient to assume a cardioembolic origin of a stroke. The prevalence of PFO in

TABLE 6: Outcome and Stroke Recurrence in Children and Young Adults

Characteristics	Children, n = 128	Young Adults, n = 199
Median (range) time to follow-up, mo	6 (3.5–6)	4 (3.3–6.5)
Outcome		
mRS 0	44 (34)	63 (32)
mRS 1	30 (23)	52 (26)
mRS 2	18 (14)	38 (19)
mRS 3	14 (11)	15 (8)
mRS 4	12 (9)	8 (4)
mRS 5	0 (0)	8 (4)
mRS 6	8 (6)	8 (4)
Lost for follow-up	2 (2)	7 (4)
Recurrent events		
Recurrent stroke	1	0
Recurrent TIA	0	1

mRS = modified Rankin scale; TIA = transient ischemic attack.

young adults was not much greater than the background prevalence, and potentially would be the same in children, if TEEs had been performed. If patients with PFOs but no other cardiac anomaly are excluded from the group of cardiogenic emboli, cardiogenic etiology is equally frequent in children and young adults.

Moyamoya syndrome and steno-occlusive arteriopathies were rarely seen in adults, whereas cervical artery dissections were more often detected in young adults than in children. Despite thorough investigations, stroke etiology remained undetermined in 23% of young adults and 14% of children.

Wraige et al proposed a pediatric TOAST classification that covers the main conditions leading to AIS in children in our study.[12] A similar classification for young adults is lacking. TOAST classification was developed as part of a trial in older adults. However, few young adults have atherosclerosis of large or small vessels, and 29% of our young adults had a stroke with a determined etiology, which was not captured by the original TOAST classification. Therefore, a revision of this classification for young adults would be desirable. Especially cervical artery dissection, the second most important cause of stroke in young adults, should be a separate item in a future classification. Based on Wraige's classification and our findings, we propose a modified TOAST classification for young adults in Table 7.

Stroke Severity

Stroke severity on admission has never been systematically assessed in childhood AIS, and comparisons in children and young adults have not been performed. We therefore used the PedNIHSS, which is a slight modification of the NIHSS for adults.[14] Items such as hemianopia and aphasia are difficult to test in very young children. Therefore, stroke severity in children might be underscored. In our study, stroke severity did not differ between children and young adults, and high PedNIHSS/NIHSS scores were the most powerful predictor of outcome in children, young adults, and the whole population.

Outcome and Mortality

Mortality did not differ; at 3 to 6 months, 6% of children with AIS and 4% of young adults were dead. Mortality rates in children were similar to those of the International Pediatric Stroke Study Group with a mortality rate of 3.4% at hospital discharge.[24] However, causes of death differed among children and young adults; 6 of 8 young adults died because of their stroke, in contrast to 3 of 8 children; children more often died because of the underlying disease, which provoked the stroke. Unlike in our series, in Lanthier and coworkers' series all deaths were attributable to complications of the stroke itself.[25] Differences in stroke etiology among children and young adults might account for the differences in cause of mortality; stroke in children is more often due to "other determined" or "multifactorial" causes. Potentially underlying fatal disorders such as severe infections and metabolic encephalopathies might be more often associated with stroke in children than in adults. Young adults conversely more often have traditional stroke etiologies such as cardioembolism and cervical artery dissections, which become life threatening if they lead to a massive brain infarction.

TABLE 7: Category Definitions for Proposed Stroke Classification in Young Adults

1	Cardioembolic
2	Cervical artery dissection
3	Small artery disease
4	Large artery disease
5	Other determined etiology
6	Multiple probable/possible etiologies
7	Undetermined etiologies
8	Unknown etiology

Thrombolysis has been shown to reduce handicap in adults. Randomized trials of thrombolysis in children have not yet been performed. Although in our study only few children underwent thrombolysis, outcomes in both groups were similar. Whether a broad use of thrombolysis would have improved outcome in childhood AIS cannot be derived from our study. However, in our study thrombolysis in many children was not possible because of late presentation or contraindications against thrombolysis.

Most pediatric outcome studies use the Pediatric Stroke Outcome Measure (PSOM).[26] However, there is no modification of the PSOM for adults. We therefore adjusted the mRS considering the development steps in children. The mRS for children used in this study is presented in Table 2. Direct comparisons of disability among children and young adults might be difficult, especially in children not yet able to walk or to control urination and defecation. However, patients with no (mRS 0) or only minimal symptoms (mRS 1) can easily be defined in both children and young adults. Therefore, favorable outcome in this study was defined as mRS 0 to 1; 59% of children and 60% of young adults had a favorable outcome. The outcome in children is similar to the findings of the Canadian Pediatric Stroke Registry with 53% of childhood AIS having no or mild deficits. Whether long-term outcome in children is better than in young adults because of a greater plasticity of the brain in children cannot be derived from our study. However, previous studies showing that more than half of survivors of childhood AIS face a life with long-term physical disabilities and cognitive impairment challenge this assumption.[3]

We performed multivariate analyses to assess predictors of outcome among children, young adults, and all patients; in all 3 analyses, higher PedNIHSS/NIHSS scores were the most important predictor of unfavorable outcome. Age or being a child had no impact on outcome, which is different from a previous study with worse outcome in younger than older children.[27] However, this study by Simma et al did not take into account stroke severity in a multivariate analysis.

Limitations

Our study has several limitations: (1) We compared patients of a nationwide registry with young adults of a hospital-based registry. (2) Assessing stroke severity and disability is more difficult in children than in adults, and therefore comparisons between children and young adults might be limited to patients with extremes on both scales. PedNIHSS is not yet broadly validated, although it is already used by many physicians. The modified pediatric mRS and the proposed TOAST classification for young adults need further validation as well. (3) PedNIHSS and mRS in children were scored retrospectively based on the examination performed by a neuropediatrician. (4) In some children, vessel imaging has not been performed, which might account for some differences in stroke etiology among children and young adults. However, the most likely stroke etiology could be established in most children without the need for vessel imaging. Screening for coagulopathies in young adults were only performed if deemed necessary. Therefore, coagulopathies might be underdiagnosed in young adults. (5) Median time to follow-up was different in children and young adults. (6) TEE was not performed in children, and therefore PFO was not really excluded in the majority of children.

Conclusions

Stroke etiology and risk factors in children and young adults were different, but stroke severity and clinical outcome 3 to 6 months after AIS were similar. Further research is needed to determine long-term outcome and quality of life after AIS in children and young adults.

Acknowledgments

This research was supported by the Swiss Heart Foundation, Novartis Research Foundation, Foundation for Research in Clinical Neuropsychiatry, and Fondazione Ettore e Valeria Rossi.

None of the agencies that founded the Swiss NeuroPediatric Stroke Registry had any input into the design, performance, analysis, or reporting of either the registry or the present study, or saw the manuscript before submission. M.S., M.A., S.Bi., and U.F. had access to all data and they had final responsibility for the decision to submit the manuscript for publication.

We thank Dr P. Ballinari for statistical advice.

Authorship

S.Bi., U.F., M.S., and M.A. contributed equally to this work. S.Bi. collected the data, helped with the analyses, and codrafted the manuscript. U.F. collected the data, did the analyses, and wrote the paper; M.S. and M.A. planned and supervised the study, helped to collect the data, and revised the manuscript; K.N. collected data of young adults and planned the study together with M.S. and M.A; E.W., E.B., S.B̈, P.-Y.J., J.F., P.W., M.E.-K., and H.P.M. helped to collect the data, advised on analyses, and commented on drafts of the manuscript; S.Bi., U.F., M.S., and M.A. contributed equally to this work.

Potential Conflicts of Interest

K.N.: consultancy, Invatec Innovative Technologies, 2005–2006; grants/grants pending, Shire, for Swiss Young Stroke

Study; travel expenses, CongO GmbH, for meetings with the DEFINE group.

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