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Long-term outcome after arterial ischemic stroke in children and young adults

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ABSTRACT

Objective: To compare long-term outcome of children and young adults with arterial ischemic stroke (AIS) from 2 large registries.

Methods: Prospective cohort study comparing functional and psychosocial long-term outcome (≥2 years after AIS) in patients who had AIS during childhood (1 month–16 years) or young adulthood (16.1–45 years) between January 2000 and December 2008, who consented to follow-up. Data of children were collected prospectively in the Swiss Neuropediatric Stroke Registry, young adults in the Bernese stroke database.

Results: Follow-up information was available in 95/116 children and 154/187 young adults. Median follow-up of survivors was 6.9 years (interquartile range 4.7–9.4) and did not differ between the groups ($p = 0.122$). Long-term functional outcome was similar ($p = 0.896$): 53 (56%) children and 84 (55%) young adults had a favorable outcome (modified Rankin Scale 0–1). Mortality in children was 14% (13/95) and in young adults 7% (11/154) ($p = 0.121$) and recurrence rate did not differ ($p = 0.759$). Overall psychosocial impairment and quality of life did not differ, except for more behavioral problems among children (13% vs 5%, $p = 0.040$) and more frequent reports of an impact of AIS on everyday life among adults (27% vs 64%, $p < 0.001$). In a multivariate regression analysis, low Pediatric NIH Stroke Scale/NIH Stroke Scale score was the most important predictor of favorable outcome ($p < 0.001$).

Conclusion: There were no major differences in long-term outcome after AIS in children and young adults for mortality, disability, quality of life, psychological, or social variables. ***Neurology*®** **2015;84:1–7**

GLOSSARY

AIS = arterial ischemic stroke; **CI** = confidence interval; **IQR** = interquartile range; **mRS** = modified Rankin Scale; **OR** = odds ratio; **QoL** = quality of life; **SNPSR** = Swiss Neuropediatric Stroke Registry.

Outcome of arterial ischemic stroke (AIS) in children is considered more favorable than in adults due to the better brain plasticity in children. However, several studies showed that more than half of survivors of childhood AIS have long-term physical disabilities and cognitive impairment.[1–4] We previously compared short-term outcomes in children and young adults after AIS: although stroke etiology and risk factors were different, stroke severity and clinical outcomes were similar.[5]

Due to the ongoing maturation of the brain throughout childhood, only long-term follow-up captures the full extent of a brain injury. Studies of long-term outcome in children with AIS are mostly based on small single-center cohorts.[6,7] One study analyzed the long-term impact of childhood AIS on outcome in young adults: 63% of patients had mild to moderate deficits.[8] Studies comparing long-term outcome after AIS in children and young adults are lacking.

The aim of this study was to compare functional and psychosocial outcomes and quality of life (QoL) in children and young adults with AIS during long-term follow-up.

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Supplemental data at Neurology.org

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METHODS This prospective cohort study is based on 2 registries: the Swiss Neuropediatric Stroke Registry (SNPSR) and the Bernese stroke registry. Methods of both registries and study populations were described previously.[5] In the following description, child refers to the age at AIS occurrence, not the age at follow-up. Likewise, young adult refers to the age at AIS occurrence. In brief, the SNPSR is a prospective multicenter pediatric cohort of all patients with AIS or intracerebral venous thrombosis in Switzerland. Research fellows contact all centers providing specialist care for children with AIS monthly and all neuropediatricians once a year to identify children with stroke. Children from the SNPSR aged 1 month to 16 years who experienced AIS between January 2000 and December 2008 were included in this study.

The Bernese stroke database is a large prospective registry including patients with AIS or intracerebral venous thrombosis. The University Hospital Bern (Inselspital) covers a catchment area of about 1.5 million inhabitants and young adults with AIS are usually referred to the Inselspital. All patients from the Bernese stroke registry aged 16–45 years with AIS between January 2000 and December 2008 were included in this study. All patients included in our previous short-term analysis who agreed to long-term follow-up assessment were eligible for this study.

Long-term follow-up data were obtained by a telephone interview with the patients or their proxies. For 1 child and 1 young adult, follow-up was assessed during a clinical visit. In case of outdated contact details, we applied every legally and ethically possible way to trace these patients. The interview was performed by neurologists, neuropediatricians in training, or research fellows using a structured questionnaire (appendix e-1 on the *Neurology*® Web site at Neurology.org). In brief, the questionnaire covers the following domains: functional outcome (modified Rankin Scale [mRS] score); recurrent cerebrovascular events; comorbidities; neurologic and psychosocial sequelae such as seizures, fatigue, behavioral problems, general state of health; treatment; occupational status; and impact on everyday life. Overall QoL was assessed by a continuous scale and on 5-point Likert scales. Additional complaints of patients not covered by the questionnaire were also recorded. Favorable outcome was defined as mRS score 0–1, unfavorable as mRS score 2–6.

Statistical analysis. Quantitative data are expressed as median and interquartile range (IQR). Data are reported in frequency tables. Because some patients were lost during long-term follow-up, we compared baseline characteristics in patients included in the short-term study with those in the long-term study in order to detect any selection bias. Missing data are indicated in the tables and figures. Kolmogorov-Smirnov test was used to check for normal distribution. 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). The Wilcoxon Paired Ranks Test was used to compare short- and long-term outcome as expressed by the mRS. The survival distribution of the 2 groups was compared with a log-rank (Mantel-Cox) test. Possible predictors of outcome (dependent variable = unfavorable outcome) with a regression coefficient $p < 0.2$ in the binary logistic regression analysis were included in the multivariate logistic regression analysis. A 2-sided p value <0.05 was considered statistically significant.

Standard protocol approvals, registrations, and patient consents. The registries and long-term follow-up assessments were approved by the local ethical committees and conducted according to the Swiss law on research. Consent was obtained from all participants.

Table 1 Baseline characteristics in children and young adults with arterial ischemic stroke

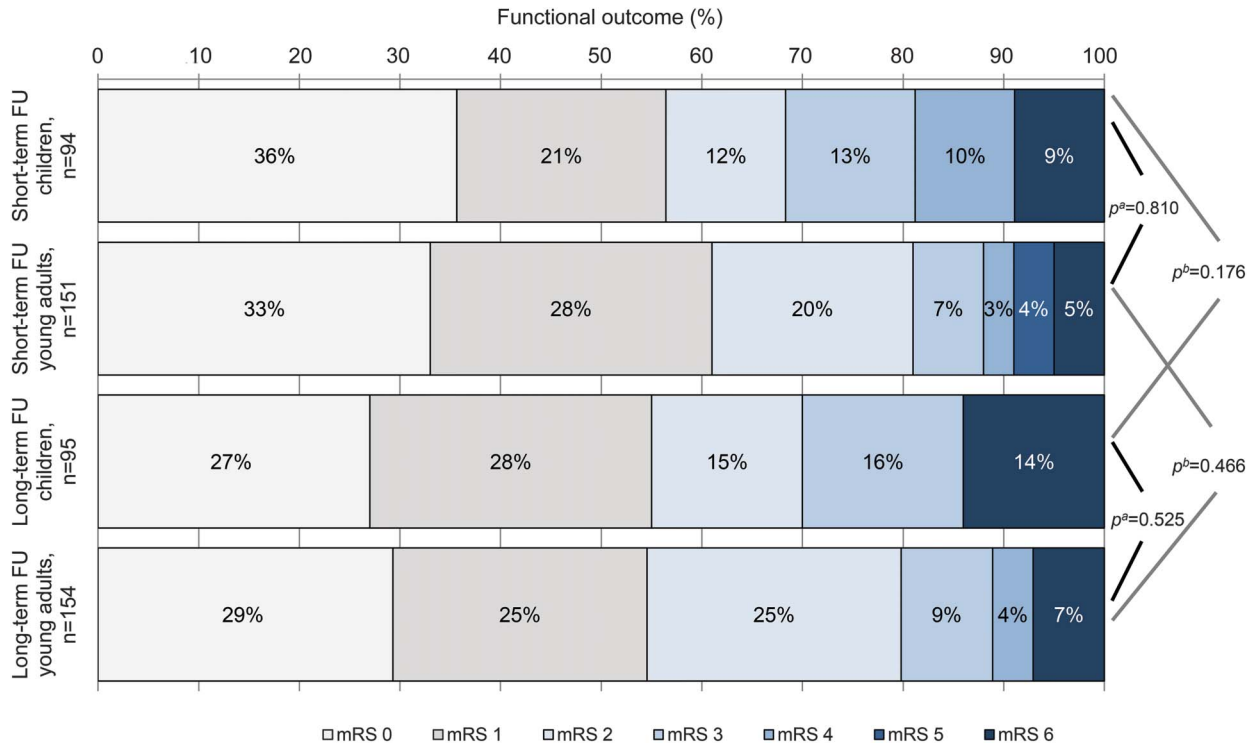
Characteristics	Children (n = 95)	Young adults (n = 154)	p
Female sex, n (%)	40/95 (42)	76/154 (49)	0.297
Traditional vascular risk factors, n with condition/valid n (%)			
Hypertension	3/63 (5)	31/152 (20)	0.004
Diabetes mellitus	0/94	3/153 (2)	0.290
Hyperlipidemia	9/56 (16)	45/149 (30)	0.050
Previous TIA	3/95 (3)	10/153 (7)	0.380
Previous stroke	0/95	4/153 (3)	0.301
Family history of stroke	9/87 (10)	23/133 (17)	0.175
Family history of CHD	11/87 (13)	15/132 (11)	0.832
PedNIHSS/NIHSS score on admission, median (range)	5 (0–27)	6 (1–38)	0.350
Stroke etiology (TOAST), n (%)			<0.001
Large artery disease	0/95	5/154 (3)	
Cardioembolic	16/95 (17)	57/154 (37)	
Small artery disease	0/95	4/154 (3)	
Other determined etiology	46/95 (48)	45/154 (29)	
No cause identified	13/95 (14)	34/154 (22)	
Incomplete investigations	3/95 (3)	7/154 (5)	
More than one cause	17/95 (18)	2/154 (1)	

Abbreviations: CHD = coronary heart disease; PedNIHSS = Pediatric NIH Stroke Scale; NIHSS = NIH Stroke Scale; TOAST = Trial of Org 10172 in Acute Stroke Treatment. A 2-sided probability (p) value <0.05 was considered statistically significant.

RESULTS Information on long-term follow-up was available for 95 of 116 children and for 154 of 187 young adults. Median follow-up of survivors was 6.9 years (IQR 4.7–9.4) and did not differ between children and young adults ($p = 0.122$). Follow-up data in children were more often based on interviews with proxies (51/62%) than in young adults (11/8%, $p < 0.001$). Baseline characteristics and stroke etiology are shown in table 1. There were no significant differences in baseline characteristics, stroke workup, and acute phase treatment in patients included in the short-term study as compared to those in the long-term study (table e-1). Median age of survivors at follow-up was 15 years (IQR 9.3–19) in children and 45 years (IQR 37.4–48.8) in adults. Five of 95 (6%) children and 7/154 (5%) young adults had a recurrent cerebrovascular event ($p = 0.759$), with one fatality in a young adult.

Long-term functional outcome according to mRS was similar in both groups ($p = 0.896$): 53 (56%) children and 84 (55%) young adults had a favorable outcome. Outcome from short-term (3–6 months) to long-term follow-up did not differ among children ($p = 0.176$) or young adults ($p = 0.466$) (figure 1).

Figure 1 Short-term and long-term outcome in children and young adults, assessed with the modified Rankin Scale



One child (1%) and 3 young adults (2%) had long-term follow-up (FU) only. mRS = modified Rankin Scale. p^a = Mann-Whitney *U* test, 2-sided significance; p^b = Wilcoxon paired rank test, 2-sided significance.

Mortality in children was 14% (13/95) vs 7% in young adults (11/154) ($p = 0.121$). Median survival time in children was 5 months (IQR 14 days–3 years), in adults 4 days (IQR 4 d–3 years) ($p = 0.072$). The survival distribution of the 2 groups did not differ ($p = 0.178$). Among patients who died before short-term follow-up, the cause was stroke in 3/8 (38%) children and 6/8 (75%) young adults.[5] Five children and 3 young adults died between short-term and long-term follow-up. Causes of death in these children were infection, leukemia, cardiac disease (1 each), and unknown (2). Causes of death in young adults who died between short-term and long-term follow-up were cardiac disease, hepatorenal syndrome, and metabolic disorder (1 each).

Functional outcome in survivors is shown in table 2. Fifty-one of 82 (62%) children and 91/143 (64%) young adults had at least one residual complaint ($p = 0.886$). Although overall language problems between children and young adults did not differ significantly, the language impairment was severe in just 6% of children vs 27% of young adults. The severity of residual symptoms did not change significantly within the year prior to the interview in the majority of patients. However, 23% of children and 14% of young adults reported ongoing improvements. Median follow-up duration was shorter in patients reporting ongoing improvement (5 years) compared with those reporting stable (7.2 years) or worsening (7.5 years) residual symptoms ($p = 0.008$).

The only difference in psychological and social outcome was increased behavioral disturbances in children ($p = 0.040$, table 3). Adults more commonly reported an impact of AIS on everyday life ($p < 0.001$).

Quality of life did not differ between children and young adults ($p = 0.204$; figure 2). A majority in both groups reported that they had enjoyed life in the week prior to the interview (figure e-1A). More than two thirds of children and young adults estimated their QoL as equal to or better than their peers (figure e-1B).

Therapy at long-term follow-up in stroke survivors is shown in table e-1. Adults were more likely to receive pharmacologic treatment, particularly aspirin, clopidogrel, antihypertensive agents, or statins. However, there were no differences in oral anticoagulants, antidiabetics, or antidepressants. Children more often had rehabilitation therapies such as physiotherapy, occupational therapy, or speech and language therapy.

In a multivariate logistic regression analysis, a low pediatric NIH Stroke Scale/NIH Stroke Scale score on admission was an independent predictor of favorable outcome in both children ($p = 0.003$, odds ratio

Table 2 Functional outcome in stroke survivors

Characteristics	Children (n = 82), n with condition/ valid n (%)	Young adults (n = 143), n with condition/valid n (%)	p
Paresis	45/82 (55)	66/139 (48)	0.330
Mild	22 (49)	23 (35)	
Moderate	16 (35)	30 (45)	
Severe	7 (16)	13 (20)	
Impaired balance	8/82 (10)	15/139 (11)	1.000
Visual disturbances	4/82 (5)	11/139 (8)	0.581
Language difficulties	17/82 (21)	37/143 (26)	0.421
Mild	10 (59)	21 (57)	
Moderate	6 (35)	6 (16)	
Severe	1 (6)	10 (27)	
Seizures	12/82 (15)	15/139 (11)	0.403
Active seizures	1 (8)	1 (7)	1.000
Headache	3/82 (4)	10/139 (7)	0.381
Evolution of residual symptoms within the last 12 months			0.114
Better	19/82 (23)	20/139 (14)	
Same	61/82 (75)	115/139 (83)	
Worse	2/82 (2)	4/139 (3)	

A 2-sided *p* value <0.05 was considered statistically significant.

[OR] 0.846, 95% confidence interval [CI] 0.757–0.945) and young adults ($p < 0.001$, OR 0.817, 95% CI 0.748–0.893). Other independent variables, namely age, sex, stroke etiology, risk factors such as hypertension, hypercholesterolemia, diabetes, previous TIA, or stroke, and most acute phase and secondary preventive treatment did not predict outcome. However, the absence of acute phase treatment with heparin in children ($p = 0.025$, OR 0.317, 95% CI 0.116–0.863) and with clopidogrel in adults ($p = 0.004$, OR 0.039, 95% CI 0.004–0.348) were additional predictors of favorable outcome.

DISCUSSION This comparison of long-term clinical outcome after AIS in children and young adults describes 3 major findings: (1) There were no major differences in long-term functional outcomes, for mortality or disability, and recurrence rates were similar. (2) Overall psychosocial impairment did not differ between patients who experienced AIS during childhood vs early adulthood, although children had more behavioral problems and adults more commonly reported a negative impact of AIS on everyday life. (3) QoL was similar in patients who experienced AIS during childhood vs early adulthood.

Mortality in children (14%) and young adults (7%) did not reach a statistically significant difference at long-term follow-up. Long-term follow-up reports on mortality in children after AIS are scarce. Previous studies reported mortality rates of 2%–11.5% in children and 3%–27% in young adults.[7,9–15] However, there are no population-based studies with long-term follow-up in children. In our short-term study, median survival time in children was 5 months, vs a median of 4 days in young adults ($p = 0.072$).[5] This difference was mainly caused by the fact that 6 of 11 young adults died due to stroke, vs 3 of 13 children. An underlying disease that provoked the stroke usually caused deaths among children.

Five percent of children and 6% of young adults had a recurrent ischemic cerebrovascular event. Recurrence rates in children were lower than in most previous reports on childhood AIS, ranging from 6.6% to 38% after follow-up periods from 5 months to 5 years.[8,16–19] Low recurrence rates in our child cohort can be explained by few patients with underlying diseases that carry a high risk of recurrence, such as moyamoya and sickle-cell disease.

In our previous study on short-term outcome in children and young adults, we found no differences in functional outcome. There is a general assumption that long-term outcome in children after acquired brain disease is better than in adults due to the increased plasticity of the immature brain. However, long-term functional outcome in our study was similar: 56% of children and 55% of young adults had a good outcome after a median follow-up duration of 6.9 years. There were no differences in outcome from short-term to long-term follow-up among children or young adults.

The mRS is a crude estimate of functional outcome and was not designed for use in children. Therefore, we assessed additional items to capture slight deficits that were not detected by the mRS. There were no significant differences regarding motor deficits, balance problems, visual disturbances, seizures, or headache. One fifth of children and one fourth of young adults had language impairments, with no significant difference overall. However, among patients with language impairment, only 6% of children had a severe deficit, vs 27% of young adults. The ongoing lateralization process in children might explain this: cognitive functions in the language domain emerge from an initially bilateral pattern towards more specialized unilateral networks.[20–22] In contrast to young adults, children have wider networks to reactivate for compensation after damage of the areas responsible for language. Lateralization during maturation and reactivation of networks are not only observed in language domains, but also in other functions such as visuospatial tasks; however, these domains were not tested in our study.[22,23] In contrast to language and cognition, motor function lateralizes

Table 3 Psychological and social outcome in stroke survivors

Characteristics	Children (n = 82), n with condition/ valid n (%)	Young adults (n = 143), n with condition/valid n (%)	p
Psychological outcome			
Any psychological/psychiatric disorders	12/82 (15)	27/143 (19)	0.466
Behavioral disturbances	11/82 (13)	7/139 (5)	0.040
Fatigue	11/82 (13)	25/143 (18)	0.452
Difficulty concentrating or memory problems	8/82 (10)	15/139 (11)	1.00
Residence			0.584
At home, no special care	75/82 (92)	127/142 (89)	
At home, needs more care than expected	7/82 (8)	11/142 (8)	
Nursing home	0/82	4/142 (3)	
Schooling/occupation			0.348
Regular school/back to prior work	63/82 (77)	93/137 (68)	
Special needs school/part-time, retraining	16/82 (19)	29/137 (21)	
Unable to read or work	3/82 (4)	15/137 (11)	
Stroke impact on everyday life			
Everyday life impaired in general	22/82 (27)	88/137 (64)	<0.001
Social life impaired	27/82 (33)	64/138 (46)	0.072
Dependent in social activities	12/82 (15)	10/139 (7)	0.104
Estimation of general state of health			0.418
Poor	0/82	3/136 (2)	
Fair	3/82 (4)	14/136 (10)	
Average	32/82 (39)	43/136 (32)	
Good	32/82 (39)	54/136 (40)	
Excellent	15/82 (18)	22/136 (16)	

A 2-sided p value <0.05 was considered statistically significant.

earlier, and therefore reorganization processes might be similar in adults and children.

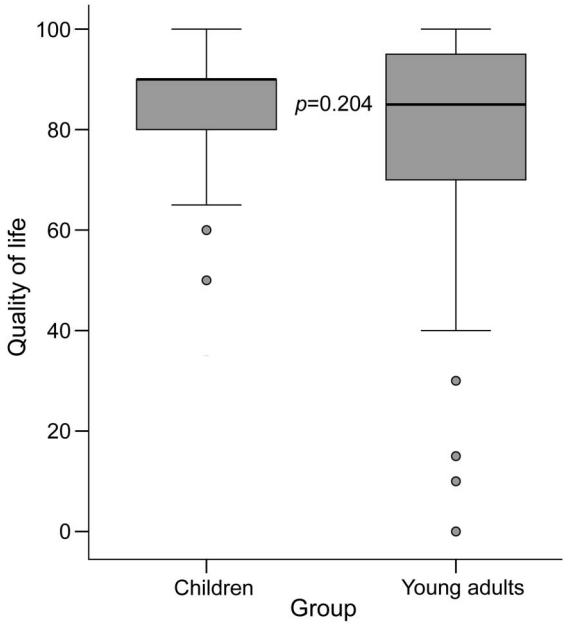
Initial stroke severity was the main predictor of outcome in both groups, which has not been previously described during long-term follow-up in children. Further predictors of outcome were the absence of heparin in children and the absence of clopidogrel in young adults. Both drugs are mainly given to severely affected patients or patients with multiple risk factors, and therefore probably reflect the underlying pathology.

Comparison of functional outcome after AIS, particularly in children, is hampered by the heterogeneity in study designs, populations, timing, and use of different outcome scales. In studies on outcome in childhood stroke, particularly the wide range of outcome scores, which are often not validated, hinders the comparison of results. In young adults, the definition of young ranges from 16 to 45 years, as in our study, to 18 to 55 years. Moreover, the few studies reporting long-term outcome in young adults are either based on a retrospective selection of patients,[24] which carries the risk of a selection bias, or use other outcome measures than the mRS.[11] In the prospective Follow-Up of Transient Ischemic Attack and Stroke Patients and Unelucidated Risk Factor Evaluation (FUTURE) study, the detailed comparison of the distribution of mRS scores reveals results that are similar to ours (mRS 0–1 in 46%, according to figure C in the cited article, compared to 55% in our study).[25]

Little is known about psychosocial disturbances after AIS in young patients, particularly in children.[26] However, for stroke survivors, psychosocial aspects may be more relevant than pure functional outcomes. Therefore we assessed items capturing the impact of stroke on everyday life. There were no differences in schooling or occupation, residence, or overall psychological outcome. However, children more often had behavioral problems and adults more commonly reported an impact of AIS on everyday life. The higher rate of behavioral disturbances in children was age-independent and was not specific for teenagers. Given the different life circumstances and expectations that define a normal life, young adults may be more likely to notice even slight impairments. Behavioral problems in children might reflect impairments in everyday life, whereas adults may have other means of coping, such as verbalizing their difficulties in discussions with relatives or health care providers. Despite these differences, general state of health was rated similarly.

Although no formal scales have been validated for both children and young adults, we tried to capture the impact of AIS on QoL in children and young adults. Median QoL on a continuous scale from 0 to 100 was 90 (IQR 80–90) in children and 85 (IQR 70–95) in young adults ($p = 0.204$). Ninety-four percent of children and 83% of young adults reported having enjoyed life in the week prior to the follow-up assessment. Given the functional impairment (mRS >1) in 44% of children and 45% of young adults, the overall good QoL is surprising. However, when asked to rate their QoL in comparison with presumed peers, almost one third of both children and young adults estimated their QoL as worse. These findings are in line with previous studies.[1,27,28] Compared with healthy controls, one study found that the well-being of pediatric stroke survivors was strongly affected, especially in patients with moderate to severe disability.[1] A further study showed that QoL in children after AIS assessed with a questionnaire adapted to their parents was excellent in 36%, adequate in 45%, and poor in 19%.[27] Another study revealed severe neurologic deficits, impaired executive function, low self-esteem, and poor family functioning, with resulting lower QoL in all domains.[28] Interestingly, in our study, 18% of

Figure 2 Quality of life



Quality of life (QoL) rated on a continuous scale from 0 (very poor) to 100 (optimal) was assessed in 82 (100%) surviving children and 137 (96%) young adults at long-term follow-up. Median QoL was 90 (interquartile range [IQR] 80–90) in children and 85 (IQR 70–95) in young adults ($p = 0.204$). p = Mann-Whitney U test, 2-sided significance.

children and 25% of young adults reported a better QoL than their peers. Surviving a life-threating event such as an AIS may increase the appreciation of life in general, despite residual impairments.

The difference in long-term use of antithrombotic medication reflects the fact that antithrombotic agents are being used less often in children than in young adults already in the acute phase after AIS.[5] Moreover, while antithrombotic secondary preventive treatment is usually given lifelong to young adults after AIS, it is withdrawn in some children with AIS, particularly when associated with transient risk factors, such as acute infectious diseases, if the etiology remained undetermined and in absence of recurrent cerebrovascular events.

Our study has several limitations and some of these have been addressed in our article on short-term follow-up.[5] In the present study, 18% of children and young adults were lost to follow-up, for reasons displayed in figure e-2. However, we applied every possible way to trace our patients, but were notably not allowed to have insight into death registries to assess whether patients have died. Furthermore, the median follow-up period was 6.9 years, which makes complete follow-up less likely. We did not find any differences in baseline characteristics in patients with or without information on long-term follow-up and rates of lost patients were equal in both groups, which makes a selection bias unlikely.

Second, most follow-up interviews were performed via telephone, which makes a physical examination and standardized neuropsychological testing impossible. Thus, we were unable to detect subtle differences in cognitive outcome as noted by our neuropsychological colleagues who reported that children following AIS have a cognitive performance that is lower than population norms in selective subtests at 2 years after the event.[4] However, given the nationwide population-based registry, an additional clinical study visit for long-term follow-up was unfeasible.

Third, there is no scale validated for both children and young adults to assess the impact of AIS on QoL. We therefore had to assess QoL using nonvalidated tools. However, functional outcomes in our study were similar to other cohorts assessing outcome in children and young adult cohorts. Thus, the relation of outcomes in children to young adults in our study may be generalized to comparable populations despite the use of nonvalidated QoL measures.

Finally, follow-up interviews of children were often performed with proxies, which was rarely the case in young adults. This is a major shortcoming when assessing outcome in children, since proxies tend to overestimate sequelae. However, there were no differences in obvious outcome measures such as mortality, recurrence rates, and favorable outcome (mRS 0–1), which can easily be defined both in children and young adults.

This study shows no major differences in long-term outcome after AIS in children and young adults. AIS has a major impact not only in young adults but also in children and is therefore not a benign condition that can easily be overcome by brain plasticity.

AUTHOR CONTRIBUTIONS

Dr. Barbara Goeggel Simonetti helped collect the data, performed the analyses, and wrote the manuscript together with U.F. Ariane Cavelti collected the data and revised the manuscript. Prof. Marcel Arnold planned and supervised the study and revised the manuscript. Dr. Sandra Bigi helped plan the study and collect the data and revised the manuscript. Dr. Mária Regényi helped collect the data and revised the manuscript. Prof. Heinrich P. Mattle helped collect the data and revised the manuscript. Prof. Jan Gralla helped collect the data and revised the manuscript. Dr. Joël Fluss helped collect the data and revised the manuscript. Prof. Peter Weber helped collect the data and revised the manuscript. Dr Annette Hackenberg helped collect the data and revised the manuscript. Prof. Maja Steinlin planned and supervised the study, helped collect the data, analyzed the data, and revised the manuscript. Prof. Dr. Urs Fischer planned and supervised the study, helped collect the data, analyzed the data, and wrote the manuscript together with B.G.S.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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