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ABSTRACT

Objective: We examined cognitive performance in children after stroke to study the influence of age at stroke, seizures, lesion characteristics, neurologic impairment (NI), and functional outcome on cognitive outcome.

Methods: This was a prospectively designed study conducted in 99 children who sustained an arterial ischemic stroke (AIS) between the age of 1 month and 16 years. All children underwent cognitive and neurologic follow-up examination sessions 2 years after the insult. Cognitive development was assessed with age-appropriate instruments.

Results: Although mean cognitive performance was in the lower normative range, we found poorer results in subtests measuring visuoconstructive skills, short-term memory, and processing speed. Risk factors for negative cognitive outcome were young age at stroke, seizures, combined lesion location (cortical and subcortical), as well as marked NI.

Conclusions: We recommend that all children with a history of AIS undergo regularly scheduled neuropsychological assessment to ensure implementation of appropriate interventions and environmental adjustments as early as possible. *Neurology*® 2014;82:1–9

GLOSSARY

AIS = arterial ischemic stroke; **ANOVA** = analysis of variance; **BG** = basal ganglia; **BSID** = Bayley Scales of Infant Development; **FDI** = freedom from distractibility; **FSIQ** = full-scale IQ; **K-ABC** = Kaufman Assessment Battery for Children; **mRS** = modified Rankin Scale; **NI** = neurologic impairment; **PIQ** = performance IQ; **POI** = perceptual organization index; **PSI** = processing speed index; **SES** = socioeconomic status; **VCI** = verbal comprehension index; **VIQ** = verbal IQ; **WAIS-R** = Wechsler Adult Intelligence Scale–Revised; **WISC** = Wechsler Intelligence Scale for Children; **WM** = white matter; **WMI** = working memory index.

Arterial ischemic stroke (AIS) in childhood has a reported incidence of 2–13:100,000.[1,2] Neurologic outcome after AIS is similar in young adults and children,[3] with lasting neurologic impairment (NI) in more than half of childhood stroke survivors.[4–6] Based on animal and human studies and according to the "early plasticity thesis," the developing brain is plastic and thus more capable of reorganization after an insult than the adult brain.[7–10] However, younger age at stroke is associated with poorer intellectual outcome and a broader spectrum of dysfunctions across multiple neuropsychological domains.[6,11–17] Further, children with combined cortical and subcortical lesions have overall poorer cognitive outcome,[16,18] and larger lesion size negatively influences cognitive and functional outcome,[4,19,20] possibly due to disruption of more neural network connections, adversely affecting functional brain organization.[21] Regarding lesion laterality, controversial reports exist concerning the effect of lesion laterality on neuropsychological outcome.[11–13,15,16,22] In addition, persistent seizures[10,22] and persistent NI such as hemiplegia/paresis or visual field deficits also negatively influence neuropsychological and functional outcome.[5,11,19]

The main goal of this study was to examine the influence of age, lesion characteristics, seizures, NI, and functional outcome on cognitive outcome in a population-based group of children 2 years after an AIS occurrence. We hypothesized the following: 1) cognitive outcome would be in the low

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Table 1 Demographic and neurologic characteristics of the participants

	Early childhood 1 mo–2 y 11 mo (n = 24)	Preschool 3 y–5 y 11 mo (n = 22)	Middle childhood 6 y–9 y 11 mo (n = 22)	Late childhood ≥10 y (n = 31)	Total (n = 99)
Sex, n (%) male	14 (58.3)	21 (95.5)	16 (72.7)	20 (64.5)	71 (71.7)
Age at insult, y, mean (SD)	1.2 (0.81)	4.49 (1.01)	7.86 (1.24)	13.51 (1.54)	7.27 (4.96)
Age at testing, y, mean (SD)	3.57 (1.25)	6.53 (1.05)	9.94 (1.30)	15.45 (1.50)	9.45 (4.87)
Months between insult and testing, mean (SD)	25 (5.38)	23.81 (4.74)	23.33 (4.45)	22.74 (4.46)	24.46 (6.42)
Lesion location, n (%)					
Cortical	8 (33.3)	6 (27.3)	6 (27.3)	5 (16.1)	25 (25.3)
Subcortical	11 (45.8)	4 (18.2)	7 (31.8)	8 (25.8)	30 (30.3)
Cortical and subcortical	5 (20.8)	9 (40.9)	5 (22.7)	14 (45.2)	33 (33.3)
Infratentorial	0	3 (13.6)	4 (18.2)	4 (12.9)	11 (11.1)
Laterality, n (%)					
Left	9 (37.5)	10 (45.5)	11 (50)	20 (64.5)	50 (50.5)
Right	13 (54.2)	9 (40.9)	8 (36.4)	6 (19.4)	36 (36.4)
Bilateral	2 (8.3)	3 (13.6)	3 (13.6)	5 (16.1)	13 (13.1)
Neurologic outcome, n (%)[a]					
No NI	6 (26.1)	8 (36.4)	8 (36.4)	17 (54.8)	39 (39.8)
Minimal NI	6 (26.1)	6 (27.3)	8 (36.4)	8 (25.8)	28 (28.6)
Marked NI	11 (47.8)	8 (36.4)	6 (27.3)	6 (19.4)	31 (31.6)
Functional outcome, mRS score, n (%)[a]					
0	6 (26.1)	8 (36.4)	8 (36.4)	16 (51.6)	38 (38.8)
1	4 (17.4)	2 (9.1)	3 (13.6)	7 (22.6)	16 (16.3)
2	4 (17.4)	4 (18.2)	6 (27.3)	3 (9.7)	17 (17.3)
3	9 (39.1)	7 (31.8)	2 (22.7)	5 (16.1)	26 (26.5)
4	0	1 (4.5)	0	0	1 (1)
Seizures, n (%)					
Acute seizures	8 (33.3)	1 (4.5)	1 (4.5)	3 (9.7)	13 (13.1)
Persistent seizures	2 (8.3)	0	1 (4.5)	1 (3.2)	4 (4)
SES, n (%)[b]					
High school	0	3 (13.6)	1 (4.5)	3 (9.7)	7 (7.1)
College/job training	8 (33.3)	10 (45.5)	13 (59.1)	21 (67.7)	52 (52.5)
Graduate school	12 (50)	4 (18.2)	5 (22.7)	4 (12.9)	25 (25.3)
No information	4 (16.7)	5 (22.7)	3 (13.6)	3 (9.7)	15 (15.2)

Abbreviations: NI = neurologic impairment; mRS = modified Rankin Scale; SES = socioeconomic status.
[a] Neurologic/functional outcome data are missing in 1 patient.
[b] Due to the retrospective collection of the SES variable, SES is missing in 15 patients.

average range; 2) younger age at stroke negatively influences cognitive outcome; 3) combined cortical and subcortical lesions are more detrimental to cognitive outcome than isolated cortical or subcortical lesions; and 4) NI negatively affects cognitive outcome.

METHODS

Participant population. The Swiss Neuropediatrics Stroke Registry, a population-based multicenter registry, contains information about all children residing in Switzerland who have been diagnosed with an AIS since January 2000. For registry purposes, AIS is defined as focal neurologic deficit of acute onset confirmed by cranial CT or MRI showing an infarction in a corresponding location. Cognitive and neurologic examination was performed by a trained pediatric neurologist or trained neuropsychologist who visited the different centers in Switzerland.

All registrants recorded between January 2000 and December 2010 (159 children, aged 1 month to 16 years) were considered for this study. Previous studies by our group[13,15] included 10 and 22 AIS children, respectively. Children were excluded from this analysis for the following reasons: death (n = 12), did not report for follow-up (n = 39), preexisting conditions that influence cognition such as trisomy 21 (n = 6), and use of a test that was not part of the predefined assessment battery (n = 3). Thus, 99 children

Table 2 Modified Rankin Scale for children

Score	Description
0	No symptoms
1	No significant disabilities despite symptoms, behavior appropriate to age, and normal further development
2	Slight disability; unable to carry out all previous activities, but same independence as other age- and sex-matched children
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance
5	Severe disability; bedridden, requiring constant nursing care and attention
6	Dead

were included in this study. Severity of stroke acutely (average ped-NIHSS, a pediatric adaptation of the NIH Stroke Scale for adults) was comparable between participating and nonparticipating children. With the exception of a slightly younger age at stroke of the nonparticipating children (mean 5.58 years, SD 5.19, $t[157] = 2.04$, $p = 0.043$), the demographics sex and socioeconomic status (SES) as well as neurologic outcome 6 months after the incidence were comparable between participating and nonparticipating children. SES was recorded retrospectively and was defined as the parents' highest level of education (high school, college/on-the-job training, graduate school).

For purposes of analysis, similar to previous studies,[15,16,23] we stratified patients by age at stroke into 4 groups, based on cerebral and cognitive development[24]: 1) early childhood group (1 mo–2 y 11 mo), 2) preschool group (3 y–5 y 11 mo), 3) middle childhood group (6 y–9 y 11 m), 4) late childhood group (≥10 y). The assignment of lesion location was based upon a previous article[25] and was classified as one of the following: cortical (white matter [WM] or cortical infarct without subcortical involvement); subcortical (basal ganglia [BG] or thalamus or capsula interna); combined (WM/cortex, BG or thalamus or capsula interna); or infratentorial (brainstem or cerebellum). Finally, we coded laterality as left, right, or bilateral. Demographic variables and neurologic status of study participants are summarized in table 1.

Standard protocol approvals, registrations, and patient consents. The Research Ethics Committee of Berne, Switzerland, and the Swiss Ministry of Health approved the registry and this study. All parents or legal guardians provided written consent, according to the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Cognitive outcome. Cognitive development assessment included the following instruments administered according to the patient's age: the Bayley Scales of Infant Development (BSID-II[26]) for children under the age of 3 years, the Kaufman Assessment Battery for Children (K-ABC[27]) for children between ages 3 and 6 years, and the German Wechsler Intelligence Scale (Wechsler Intelligence Scale for Children [WISC]-III,[28] WISC-IV,[29] Wechsler Adult Intelligence Scale–Revised [WAIS-R][30]) for children aged 6 years and older. Due to our prospective design, we had to include the use of the developmental test BSID-II to measure and determine the status of cognitive development before age 3. We tested 54 children (54.6%) using the WISC-III/IV,[28,29] 7 adolescents (7.1%) with the WAIS-R,[30] 26 children (26.3%) with the K-ABC,[27] and 12 children (12%) with the BSID-II.[26] For primary intellectual outcome measures, we used full-scale IQ scores (FSIQ) from the WISC,[28,29] WAIS,[30] and K-ABC[27] and Mental Development Index from the BSID-II.[26] In addition, we used subtests and indices of the K-ABC[27] (Simultaneous Processing Scale and Sequential Processing Scale) and Wechsler tests[28–30] (verbal IQ/verbal comprehension index [VIQ/VCI], performance IQ/perceptual organization index [PIQ/POI], freedom from distractibility/working memory index [FDI/WMI], and processing speed index [PSI]) in some analyses. For several reasons (e.g., limited endurance or compliance), not all subtests of the Wechsler tests could be conducted, resulting in varying sample sizes in the analyses of the Wechsler subtests.

Neurologic outcome. Patients also underwent detailed neurologic examination and outcome was coded as follows: no NI (no neurologic signs or symptoms), minimal NI (neurologic signs at examination not interfering with daily life activities), or marked NI (NI associated with functional impairment). Furthermore, we scored functional outcome retrospectively (chart review and review of study data) using the modified Rankin Scale (mRS) with age-specific modification[3] (table 2). Neurologic outcome data are missing for 1 patient.

Statistical analysis. We used the Statistical Package for Social Sciences software for Windows, version 17 (SPSS, Chicago, IL) for statistical analyses and performed a distribution check for lesion location, laterality, SES, NI, and mRS score across the 4 age groups using a nonparametric χ^2 test. Subsequent to checking data for normal distribution and homogeneity of variance, we conducted 1-sample *t*-tests to compare cognitive outcome with that of the normative sample and independent sample *t* tests to assess differences in cognitive outcome due to sex, laterality (right vs left), or acute and persistent seizures. We performed univariate analyses of variance (ANOVA) with post hoc Bonferroni corrections to examine effects of age at stroke, lesion location, NI, and mRS scores on cognitive outcome and used several ANOVAs with post hoc Bonferroni corrections to study the influence of lesion location, NI, and mRS scores (due to the small number of children with an mRS score of 2, mRS scores 2 and 3 were concatenated for this analysis) on the Wechsler indices (patients older than 6 years). In a second step, we used 2-way ANOVA to search for an interaction between age at stroke and NI. To avoid small and unequal group sizes in 2-factor analysis, we dichotomized age at stroke in early (1 mo–5 y 11 mo, early childhood and preschool concatenated) and late childhood (6 y–16 y 11 mo, middle and late childhood concatenated). We set significance at $p < 0.05$.

RESULTS

Sample characteristics. Lesion location variability (not including infratentorial lesion due to small numbers, $\chi^2[6] = 7.76$, $p = 0.256$), lesion laterality (not including bilateral lesions due to small numbers, $\chi^2[3] = 6.69$, $p = 0.082$), SES ($\chi^2[9] = 16.67$, $p = 0.054$), NI ($\chi^2[6] = 7.26$, $p = 0.297$), and mRS (not including mRS score 4 due to only 1 patient [$\chi^2(9) = 9.12$, $p = 0.426$]) were evenly distributed across the different age groups. NI was evenly distributed across lesion location (not including infratentorial lesions due

Table 3 Mean cognitive outcome, stratified by independent variables

Independent variable	N	Mean cognitive outcome (SD)	F_{df}	p[a]
Age at stroke group			$3.32_{3,95}$	0.023[b]
Early childhood	24	88 (17.74)		
Preschool	22	92.68 (14.50)		
Middle childhood	22	99.45 (18.41)		
Late childhood	31	100.65 (15.14)		
Lesion location[c]			$2.52_{2,85}$	0.087
Cortical	25	94.92 (19.35)		
Subcortical	30	100.60 (18.81)		
Cortical and subcortical	33	90.73 (14.47)		
Neurologic outcome[d]			$6.89_{2,95}$	0.002[e]
No NI	39	102.08 (16.68)		
Minimal NI	28	94.82 (14.36)		
Marked NI	31	87.71 (16.89)		
Functional outcome, mRS score[d,f]			$7.34_{3,93}$	0.000[g,h]
0	38	102.74 (16.38)		
1	16	98.00 (12.83)		
2	17	94.61 (15.81)		
3	26	84.23 (15.92)		
Independent variable	**N**	**Mean cognitive outcome (SD)**	t_{df}	**p**
Sex			-1.28_{97}	0.203
M	71	96.92 (17.2)		
F	28	92.07 (16.3)		
Laterality[i]			1.11_{84}	0.269
Left	50	97.28 (16.54)		
Right	36	93.11 (17.93)		
Acute seizures			-2.18_{97}	0.032
Acute seizures	13	86.15 (21.72)		
No acute seizures	86	96.97 (15.85)		
Persistent seizures			-3.49_{97}	0.001
Persistent seizures	4	68.00 (13.49)		
Seizure-free	95	96.71 (16.19)		

Abbreviations: mRS = modified Rankin Scale; NI = neurologic impairment.
[a] Post hoc comparisons.
[b] Post hoc comparisons difference in cognitive outcome between the early and late childhood group ($p < 0.05$).
[c] Due to a small number of children with infratentorial lesions (n = 11), this subgroup was not included in the analysis.
[d] Neurologic/functional outcome is missing in 1 patient.
[e] Post hoc comparisons difference in cognitive outcome between children with marked NI and no NI ($p < 0.01$).
[f] Due to only 1 patient with an mRS score 4, this subgroup was not included in the analysis.
[g] Post hoc comparisons difference in cognitive outcome between children with an mRS score 3 and an mRS score 0 ($p < 0.000$).
[h] Post hoc comparisons difference in cognitive outcome between children with an mRS score 3 and an mRS score 1 ($p < 0.05$).
[i] Due to a small number of children with bilateral lesions (n = 13), this subgroup was not included in the analysis.

to small numbers [$\chi^2(4) = 3.63$, $p = 0.458$]). In accordance with the well-documented sex imbalance in pediatric stroke (male > female),[31] age group differences were found for sex ($\chi^2[3] = 8.84$, $p = 0.03$), with a very imbalanced ratio of male to female patients in the preschool age group (95.5% male). In the acute phase of AIS, 13 children (13.1%) had seizures and 4 (4.4%) of them had persistent seizures requiring ongoing antiepileptic treatment (table 1). Although acute and persisting seizures had a negative effect on cognitive outcome (table 3), those children were included in all analyses to avoid selective exclusion. Furthermore, there were no differences in the early childhood group in cognitive outcome ($t[9.59] = 0.081$, $p = 0.937$) when comparing children with acute seizures (mean = 88.5, SD = 24.18) to children without acute seizures (mean = 87.75, SD = 14.48).

Stroke patients' cognitive outcome compared to the normative sample. We compared cognitive outcome to published normative results (mean = 100, SD = 15 for indices, mean = 10, SD = 3 for subtests; summarized in table 4). Although all indices and subtest values fell within the average range, AIS children achieved lower scores in subtests measuring visuoconstructive skills (Triangles [K-ABC] or Object Assembly [Wechsler]), short-term memory (Digit Span [K-ABC and Wechsler], Hand Movements and Word Order [K-ABC]), and processing speed (Digit Symbol Code or Symbol Search [Wechsler]). In contrast, AIS children performed better in the verbal subtest on Similarities (Wechsler).

Effects of age at stroke, lesion characteristics, seizures, sex, NI, and mRS scores on cognitive performance. Age at stroke linearly influenced cognitive outcome (table 3). Post hoc comparisons showed that cognitive outcome in the early childhood group was worse than in the late childhood group, while cognitive outcomes in the other age groups were not different. Neither sex nor lesion location (cortical, subcortical, or combined) nor lesion laterality (left or right) influenced cognitive outcome. In contrast, the severity of NI as well as the outcome on the mRS influenced cognitive outcome. In post hoc comparisons, children with marked NI showed a worse cognitive performance compared to children with no NI, while cognitive outcome in the other NI groups were not different. Furthermore, post hoc comparisons revealed that children with an mRS score of 3 showed poorer cognitive outcome than children with an mRS score of 0 or 1, while cognitive outcomes in the other mRS groups were not different. To analyze the interaction between age at stroke and NI, we used a 2-factor ANOVA and could again show effects of age at stroke ($F_{1,92} = 5.41$, $p = 0.022$ [early: 90.66 < late: 98.34]) and NI ($F_{2,92} = 4.6$, $p = 0.013$ [no NI: 100.43 > minimal NI: 94.53 > marked NI:

Table 4 Cognitive assessment results at 2 years post AIS

Measure	N	Variable	Test mean	Sample mean	SD	t	*df*	*p*	Mean difference
BSID-II	12	MDI	100	90.5	20	−1.64	11	0.128	−9.5
K-ABC	26	FSIQ	100	89.42	17.58	−3.10	25	0.005	−10.58
	26	Simultaneous PS	100	90.5	20.04	−2.42	25	0.023	−9.5
	26	Sequential PS	100	88.96	16.9	−3.33	25	0.003	−11.04
K-ABC subtests	8	Sequential shapes	10	8.63	3.78	−1.03	7	0.337	−1.38
	8	Face recognition	10	8.88	3.4	−0.936	7	0.38	−1.13
	26	Hand movements	10	8.04	2.95	−3.4	25	0.002	−1.96
	26	Gestalt closure	10	9.31	3.62	−0.975	25	0.339	−0.69
	26	Digit span	10	7.85	2.91	−3.78	25	0.001	−2.15
	23	Triangles	10	7.35	3.34	−3.81	22	0.001	−2.65
	23	Word order	10	8.43	3.33	−2.26	22	0.034	−1.56
	18	Analogy	10	9.61	3.52	−0.47	17	0.65	−0.39
	17	Spatial memory	10	9.47	3.43	−0.64	16	0.54	−0.53
	8	Foto series	10	9.38	4.44	−0.4	7	0.70	−0.63
Wechsler	61	FSIQ	100	99.15	15.35	−0.43	60	0.666	−0.852
	61	PIQ/POI	100	96.39	15.72	−1.79	60	0.078	−3.61
	61	VIQ/VCI	100	103.18	15.87	1.57	60	0.123	3.18
	49	FDI/WMI	100	95.86	15.84	−1.83	48	0.073	−4.14
	48	PSI	100	93.42	14.85	−3.07	47	0.004	−6.58
Wechsler subtests	57	Picture completion	10	10.14	3.12	0.340	56	0.735	0.14
	55	Information	10	9.44	3.01	−1.39	54	0.170	−0.56
	58	Digit symbol code	10	9.02	3.32	−2.25	57	0.028	−0.983
	59	Similarities	10	11.63	2.98	4.19	58	0.000	1.63
	56	Picture arrangement	10	9.39	3.29	−1.38	55	0.172	−0.61
	58	Arithmetic	10	9.76	3.43	−0.54	57	0.594	−0.24
	59	Block design	10	9.54	3.15	−1.12	58	0.269	−0.46
	59	Vocabulary	10	10.69	3.23	1.65	58	0.104	0.7
	50	Object assembly	10	8.06	2.94	−4.66	49	0.000	−1.94
	58	Comprehension	10	10.55	2.93	1.44	57	0.157	0.55
	48	Symbol search	10	8.62	2.69	−3.52	47	0.001	−1.38
	55	Digit span	10	8.2	3.19	−4.19	54	0.000	−1.8
	35	Labyrinth	10	10.17	4.03	0.251	34	0.803	0.171

Abbreviations: AIS = arterial ischemic stroke; BSID-II = Bayley Scales of Infant Development; FDI/WMI = freedom from distractibility/working memory index; FSIQ = full-scale IQ; K-ABC = Kaufman Assessment Battery for Children; MDI = Mental Developmental Index; PIQ/POI = performance IQ/perceptual organization index; PS = processing scale; PSI = processing speed index; VIQ/VCI = verbal IQ/verbal comprehension index.

88.53]) on cognitive outcome, but we found no interaction effect ($F_{2,92} = 0.47$, $p = 0.628$).

Effects of lesion characteristics, NI, and mRS scores on the Wechsler indices. We found main effects of lesion location on the Wechsler indices FSIQ, VIQ/VOI, FDI/WMI, and PSI (table 5). Post hoc comparisons revealed that all these index measures were lower in the combined cortical and subcortical group than in either the cortical (VIQ/VCI, FDI/WMI, PSI) or subcortical (FSIQ, VIQ/VCI) group. There was no difference in performance between the cortical and the subcortical groups. No main effects were found for laterality on the Wechsler indices. Main effects of NI were found on the Wechsler indices FSIQ, PIQ/POI, FDI/WMI, and PSI. Post hoc comparisons revealed that children with marked NI showed poorer performance than children without NI on FSIQ, PIQ/POI, and PSI and that children with minimal

Table 5 Effects of lesion characteristics, NI, and mRS scores on the Wechsler indices, mean (SD)

	Wechsler FSIQ	F_{df}	p^a	Wechsler PIQ/POI	F_{df}	p^a	Wechsler VIQ/VOI	F_{df}	p^a	Wechsler FDI/WMI	F_{df}	p^a	Wechsler PSI	F_{df}	p^a
Lesion location[b]		$5.89_{2,50}$	0.005[c]		$1.78_{2,50}$	0.179		$7.35_{2,50}$	0.002[d,e]		$5.19_{2,38}$	0.010[f]		$3.75_{2,39}$	0.032[g]
Cortical (n = 12)	101.25 (14.36)			94.75 (16.22)			107.33 (13.11)			103.70 (13.17)			100.64 (14.38)		
Subcortical (n = 17)	107.59 (17.16)			102.59 (17.49)			111.18 (17.25)			100.08 (18.71)			96.75 (17.14)		
Cortical and subcortical (n = 24)	91.71 (13.21)			93.13 (15.35)			93.92 (14.25)			86.68 (13.55)			87.32 (10.68)		
Neurologic outcome[h]		$4.25_{2,58}$	0.019[i]		$4.46_{2,58}$	0.016[j]		$1.82_{2,58}$	0.172		$4.5_{2,46}$	0.016[k]		$5.95_{2,45}$	0.005[l,m]
No NI (n = 29)	104.52 (15.25)			102.1 (15.62)			106.86 (15.26)			102.48 (14.41)			99.92 (15.29)		
Minimal NI (n = 19)	96.42 (13)			93.16 (13.22)			101.58 (15.21)			91.11 (15.81)			88.63 (13.12)		
Marked NI (n = 13)	91.15 (15.23)			88.38 (15.48)			97.31 (17.17)			87.5 (13.42)			83.5 (5.93)		
Functional outcome, mRS score[n]		$5.97_{2,58}$	0.004[o]		$6.28_{2,58}$	0.003[p]		$2.62_{2,58}$	0.081		$6.25_{2,46}$	0.004[q]		$12.44_{2,17.91}$[r]	0.000[s]
0 (n = 28)	105.50 (14.56)			103.54 (14.94)			107.75 (14.75)			103.14 (14.39)			101.04 (14.57)		
1 (n = 12)	97.92 (14.38)			93.67 (14.39)			102.33 (15.17)			95.30 (11.74)			90.33 (17.51)		
≥2 (n = 21)	91.38 (13.66)			88.95 (14.27)			97.57 (16.51)			86.76 (15.59)			84.19 (5.52)		

	Wechsler FSIQ	t_{df}	p	Wechsler PIQ/POI	t_{df}	p	Wechsler VIQ/VOI	t_{df}	p	Wechsler FDI/WM	t_{df}	p	Wechsler PSI	t_{df}	p
Laterality[t]		1.31_{50}	0.197		1.88_{50}	0.066		0.47_{50}	0.638		0.68_{39}	0.503		1.3_{39}	0.203
Left (n = 35)	100.83 (14.81)			98.34 (14.50)			104.03 (14.53)			96.18 (13.37)			95.65 (14.95)		
Right (n = 17)	94.88 (16.49)			89.94 (16.41)			101.76 (19.17)			92.69 (19.06)			89.53 (13.89)		

Abbreviations: FDI/WMI = freedom from distractibility/working memory index; FSIQ = full-scale IQ; mRS = modified Rankin Scale; NI = neurologic impairment; PIQ/POI = performance IQ/perceptual organization index; PSI = processing speed index; VIQ/VCI = verbal IQ/verbal comprehension index.

[a] Post hoc comparisons.

[b] Due to a small number of children with infratentorial lesions (n = 8), this subgroup was not included in the analysis.

[c] Post hoc comparisons difference in FSIQ between combined cortical and subcortical and subcortical location ($p < 0.01$).

[d] Post hoc comparisons difference in VIQ/VCI between combined cortical and subcortical and cortical location ($p < 0.05$).

[e] Post hoc comparisons difference in VIQ/VCI between combined cortical and subcortical and subcortical location ($p < 0.01$).

[f] Post hoc comparisons difference in FDI/WMI between combined cortical and subcortical and cortical location ($p < 0.01$).

[g] Post hoc comparisons difference in PSI between combined cortical and subcortical and cortical location ($p < 0.05$).

[h] Neurologic outcome is missing in 1 patient.

[i] Post hoc comparisons difference in FSIQ between marked NI and no NI ($p < 0.05$).

[j] Post hoc comparisons difference in PIQ/POI between marked NI and no NI ($p < 0.05$).

[k] Post hoc comparisons no differences in FDI/WMI between the NI groups.

[l] Post hoc comparisons difference in PSI between marked NI and no NI ($p < 0.05$).

[m] Post hoc comparisons difference in PSI between minimal NI and no NI ($p < 0.05$).

[n] Due to a small number of children with an mRS score 2 (n = 8) and an mRS score 3 (n = 13), these subgroups were concatenated into the group mRS score ≥2. The only patient with an mRS score 4 was not included in the analysis.

[o] Post hoc comparisons difference in FSIQ between an mRS score ≥2 and an mRS score 0 ($p < 0.01$).

[p] Post hoc comparisons difference in PIQ/POI between an mRS score ≥2 and an mRS score 0 ($p < 0.01$).

[q] Post hoc comparisons difference in FDI/WMI between an mRS score ≥2 and an mRS score 0 ($p < 0.01$).

[r] The assumption of homogeneity of variance was violated; therefore we report the Welch F ratio.

[s] Post hoc comparisons difference in PSI between an mRS score ≥2 and an mRS score 0 ($p < 0.01$).

[t] Due a small number of children with bilateral lesions (n = 9), this subgroup was not included in the analysis.

NI performed poorer than children without NI on PSI. Between all other NI groups, no differences were found. Similarly, main effects for mRS scores were found on the Wechsler indices FSIQ, PIQ/POI, FDI/WMI, and PSI. All post hoc comparisons revealed that children with an mRS score ≥2 showed worse Wechsler outcomes than children with an mRS score of 0. Between all other mRS groups, no differences were found.

DISCUSSION As shown in previous studies[13,16] and supporting our first hypothesis, all indices and subtest results of the sample fell within the normative mean (table 4). However, scores in subtests measuring visuoconstructive skills, short-term memory, or processing speed, though still in the lower average range, were below the normative mean. In verbal subtests, in contrast, the sample's performance was at or slightly above the population norm. As shown in previous studies, verbal capacities seemed to be more resilient to brain insults than performance skills.[13,22] One possible explanation for these results stems from Teuber's[32] crowding hypothesis, which describes the functional superiority of language compared with visuospatial functions following a brain injury.[22] Moreover, impairments in fine motor abilities might also contribute to vulnerability of visuospatial function after brain injuries. Examination of the influence of NI on different Wechsler indices revealed that children with marked NI or with an mRS score ≥2 performed worse on the PIQ/POI and PSI, but not on the VIQ/VCI, compared to children without NI or without a functional impairment (mRS score 0, table 5). It is not surprising that motor problems such as hemiparesis negatively influenced fine motor– and speed-dependent tasks for PIQ/POI and PSI, which resulted in a reduced overall FSIQ in children with marked NI, confirming another of our hypotheses.

However, this approach does not explain why children with a slight/moderate functional disability (mRS score ≥2) performed worse on the fine motor–free FDI/WMI index. Working memory, vulnerable to insult in children with focal as well as generalized brain injuries,[33] is linked to a range of cognitive functions[34] and individual differences in working memory capacity have important consequences for the ability to acquire knowledge and new skills.[35] Because working memory impairments can be successfully remediated through neurocognitive training,[33] neuropsychological follow-up is especially important to detect and address working memory problems early on in the rehabilitative process.

Except for sex, our age-at-stroke groups were comparable in all other demographic and neurologic characteristics (table 1). This strengthens our finding that young age at stroke has a significant negative influence on cognitive outcome and is in line with the early vulnerability thesis, replicating findings of previous studies[11,12,14–16] as well as confirming our second hypothesis. Although sex did not influence cognitive outcome, the distinctive sex imbalance in the preschool age group is of interest. While it is possibly a result by chance, it could also arise from the fact that boys in this age group have more infections that are known as a significant risk factor in the childhood stroke literature.[36]

Recent research concerning the effect of lesion location points to a combination of cortical and subcortical lesions as conferring higher risk of negative cognitive outcome than when lesions occur in only one of those locations.[18,16] Although we did not find such an effect on cognitive outcome in general, we could confirm that combined lesions had a negative impact on the Wechsler Indices FSIQ, VIQ/VCI, FDI/WMI, and PSI. However, this may be due to actual size of lesions rather than lesion location. Considering the contemporary view of the importance of networks,[37] larger lesions disrupt a wider network of neural connections, resulting in more negative cognitive outcomes.[4,19–21] Although speculative, the negative effect of young age at stroke might also be explained by the network theory. An insult during early childhood, an important period for synaptogenesis, may disrupt more extensive developing neural networks than a later insult to already existing networks.

Similar to previous reports,[12,13,16,22] we found no lateralization effect on cognitive outcome. Contrary to the nonexistent laterality effect on outcome, we confirmed a negative influence of acute and persisting seizures on cognitive outcome.[10,22] However, while poor cognitive outcome in the youngest age group is certainly influenced by the existence of seizures, it cannot solely be explained by this factor.

We note the following study limitations. First, K-ABC and Wechsler have distinct differences in their underlying theoretical concepts, limiting their comparability; therefore, we focused on general cognitive outcome and on the outcome of Wechsler indices. Moreover, due to our prospective study design and lack of intelligence measures for the youngest age group, it was necessary to include a developmental measure as an outcome measure. However, taking into account the result of a previous study,[38] which did not find any age at stroke effect, although their youngest age group was exclusively tested with the BSID-II, we argue that our finding that the early age group showed the worst cognitive outcome cannot solely be due to the use of the BSID-II. Moreover, the youngest children in our study with NI and a low cognitive outcome might be prone to a "growing into deficit" and therefore may have increasingly significant cognitive deficits with time. Second, this study did not include a demographically matched control group. As a consequence, we compared the cognitive outcome of our patient sample

with child-specific, psychometrically robust age-standardized norms. Third, a considerable number of patients refused follow-up examination. However, due to comparable demographics (SES and sex) as well as comparable neurologic outcome scores acutely and 6 months after the incidence, we do not expect possible biases. Fourth, due to missing lesion size analyses, we could not control this parameter in the examination of the influence of lesion location on cognitive outcome. Finally, although our sample size was sufficient to build similarly sized age groups, it was difficult to create comparable and appropriately large subgroups to analyze the relation of 2 or more factors, resulting in concatenation of the age subgroups in one analysis.

We investigated cognitive and neurologic outcome 2 years after the incidence in a population-based pediatric AIS sample. Although overall performance was within the lower range of the norm, our children showed poorer performance, especially in visuoconstructive skills, short-term memory, and processing speed. Our results suggest that young age at stroke, seizures, combined lesion location (subcortical and cortical), as well as persisting NI that led to a slight/moderate functional disability (mRS score $\geq$2) are risk factors for cognitive outcome in childhood stroke. Therefore, children with one or more of these risk factors have an obvious need for neuropsychological follow-up testing after stroke, because evidence-based intervention programs like working memory training exist to prevent further cognitive sequelae. Furthermore, testing should utilize motor-free and non-time-limited tasks to avoid the negative influence of residual motor impairments. Future research should take into account the considerable interaction between motor and neuropsychological impairments in stroke patients.[39]

AUTHOR CONTRIBUTIONS

Martina Studer: design of the study, analysis and interpretation of the data, drafting and revising the manuscript. Eugen Boltshauser: design and conceptualization of the study, registering patients, revising the manuscript. Andrea Capone Mori: registering patients, revising the manuscript. Alexandre Datta: registering patients, revising the manuscript. Joel Fluss: registering patients, revising the manuscript. Danielle Mercati: registering patients, revising the manuscript. Annette Hackenberg: registering patients, revising the manuscript. Elmar Keller: registering patients, revising the manuscript. Oliver Maier: registering patients, revising the manuscript. Jean-Pierre Marcoz: registering patients, revising the manuscript. Gian-Paolo Ramelli: registering patients, revising the manuscript. Claudia Poloni: registering patients, revising the manuscript. Regula Schmid: registering patients, revising the manuscript. Thomas Schmitt-Mechelke: registering patients, revising the manuscript. Edith Wehrli: revising the manuscript. Theda Heinks: interpretation of the data, revising the manuscript, supervision of neuropsychological aspects. Maja Steinlin: design and conceptualization of the study, registering patients, interpretation of the data, revising the manuscript, supervision of work.

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DISCLOSURE

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