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Neuropsychological Problems after Paediatric Stroke: Two Year Follow-Up of Swiss Children

Abstract

Aim: The aim of this study was to obtain information about neurological and cognitive outcome for a population-based group of children after paediatric ischaemic stroke. **Methods:** Data from the Swiss neuropaediatric stroke registry (SNPSR), from 1.1.2000 to 1.7.2002, including children (AIS 1) and neonates (AIS 2). At 18 – 24 months after a stroke, a follow-up examination was performed including a history, neurological and neuropsychological assessment. **Results:** 33/48 children (22 AIS 1, 11 AIS 2) participated in the study. Neurological outcome was good in 16/33. After childhood stroke mean IQ levels were normal (94), but 6 children had IQ < 85 (50 – 82) and neuropsychological problems were present in 75%. Performance IQ (93) was reduced compared to verbal IQ (101, p = 0.121) due to problems in the domain of processing speed (89.5); auditory short-term memory was especially affected. Effects on school career were common. Outcome was worse in children after right-sided infarction. Children suffering from stroke in mid-childhood had the best prognosis. There was no clear relationship between outcome and localisation of the lesion. After neonatal stroke 7/11 children showed normal development and epilepsy indicated a worse prognosis in the remaining 4. **Conclusion:** After paediatric stroke neuropsychological problems are present in about 75% of children. Younger age at stroke as well as an emergence of epilepsy were predictors for worse prognosis.

Key words
Paediatric stroke · cognitive outcome

Abbreviations

AIS	arterial ischaemic infarction
AIS 1	childhood stroke
AIS 2	neonatal stroke
CT	computed tomography
DQ	development quotient
FIQ	full intelligence quotient
MRA	magnetic resonance angiography
MRI	magnetic resonance imaging
PalIQ	parallel intelligence quotient
PIQ	performance intelligence quotient
SIQ	sequential intelligence quotient
SNPSR	Swiss neuropaediatric stroke registry

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SS	scale score
VIQ	verbal intelligence quotient

Introduction

In the last decade paediatric stroke has attracted increased interest and several studies have been published on the different aspects of incidence, risk factors and outcome [6,7,9,31]. Motor impairment and life-long handicaps could be demonstrated in 30 – 50% of children in retrospective studies [5,8,9,14,32]. However, scarce data are available concerning prospective and population-based data on cognitive outcome and the prevalence of behavioural and psychological problems.

Although less pronounced than in adults after stroke, significant shifts to lower IQ levels and learning disabilities have been described in children by Ganesan et al. [9] and Max et al. [20]. The known sex difference in adults could not be confirmed in children [15]. In children with congenital lesions, Goodmann et al. [13] and Vargha Kadhem et al. [35] found a preservation of verbal capacity compared to performance, regardless of the site of lesion, whereas Hogan et al. [15] showed after acquired lesions in children a trend towards more affected verbal IQ after left hemispheric injury. The presence of epilepsy has a negative effect on neuropsychological outcome [5,32,35]. There are conflicting data within the paediatric literature concerning age at stroke: Ganesan et al. [9] reported poorer outcome in younger patients, which was not supported by data from McFie et al. [21] and Banich et al. [2]. Data on behavioural and emotional problems are controversial.

The aim of our prospective, population-based, multicentre study was to gain information on neurological and cognitive outcome, the influence of the afore-mentioned variables, and the effects on social life in children after neonatal and childhood stroke.

Patients and Methods

Subjects

In a prospective multicentre, population-based study, all children from birth up to 16 years living in Switzerland suffering from paediatric stroke (arterial ischaemic infarction and sinus venous thrombosis) were registered anonymously by the Swiss Neuropaediatric Stroke Registry (SNPSR) since January 2000. Methods of registration and data from this registry on incidence, manifestation, risk factors and short-term neurological outcome were published by Steinlin et al. [31]. Neurological and neuropsychological examination was done by a neuropaediatrician (J.P.) who visited the different centres in Switzerland. A comparison of neurological outcome after 6 months and after 24 months was done.

This study focuses on data of neuropsychological outcome 18 – 24 months after the acute event of an arterial ischaemic infarction for children registered between January 2000 and July 2002.

Inclusion criteria for arterial ischaemic infarction (AIS) were: 1) childhood stroke (AIS 1) defined as a focal neurological deficit of acute onset lasting at least 20 minutes and CT or MRI showing infarction in a localisation consistent with neurological signs and symptoms; 2) neonatal stroke (AIS 2) defined as focal neurological symptoms, seizures or lethargy only, and CT, ultrasound or MRI showing focal ischaemic lesion during the neonatal period. Arterial stroke in the setting of generalised hypoxia was only included if there was a predominantly focal ischaemic lesion in an area of a recognisable vascular distribution. Preterm babies of < 37 weeks gestational age suffering a stroke during the neonatal period were excluded.

Assessment of outcome and cognitive testing

All registered patients between January 2000 and July 2002 were asked whether they would agree to participate in a follow-up examination including:

1. Careful history on problems since the acute event;
2. Questionnaire for the parents and/or children concerning neurological outcome, assistance in daily activities, school career and behavioural and emotional problems;
3. Detailed neurological examination. We defined:
   - complete neurological recovery if no neurological signs or symptoms were present,
   - mild neurological deficits if there were neurological signs at examination but without functional impairment,
   - moderate-severe neurological deficits if there were neurological signs, and symptoms which lead to functional impairment or loss of function.
4. Neuropsychological assessment. Depending on chronological and developmental age, children were evaluated with the Bayley Scales of Infant Development (BSID-II) (age range 0 – 42 months) [3], the Kaufman Assessment Battery for Children (K-ABC) (age range 2.6 – 12.5 years) [16], the Hamburg-Wechsler Intelligence Test for Children (HAWIK-III, German version of WISC) (age range 6.0 – 16.11 years) [34] and the Hamburg-Wechsler Intelligence Test for Adults (HAWIE-R, German version of WAIS) (age range 16 – 74 years) [33]. In children of 6 years and older HAWIK-III was preferred over K-ABC. Mental retardation was considered as severe with an IQ or a developmental quotient (DQ) < 50 and mild with an IQ/DQ of 50 – 70. A borderline intelligence was defined as IQ/DQ of 70 – 84 and normal IQ/DQ ≥ 85.

Neuropsychological problems were defined if results in a subtest were at least one standard deviation (SD) below the population mean (≤ 7 points).

Age groups were classified according to previous studies [21,31]: group 1: neonates, group 2: 2 months to 4.11 years, group 3: 5.0 to 9.11 years and group 4: ≥ 10 years. This provided comparable group sizes and is theoretically based on the fact that the most dynamic period of brain development is during early childhood [11,17] and after the first five years of life, no significant change in synaptic density is to be expected [27].

Statistical analysis

The χ^2 test was used to compare the proportion of patients with test scores more than one standard deviation below the population mean with the proportion to be expected in a normal population. Two-sided *t*-tests were used to compare group means with population means for data that fulfilled the requirements

of parametric tests. P values ≤ 0.05 were considered to be significant, those of ≤ 0.1 > 0.05 were considered to be a trend. Non-linear quadratic regression analyses was used for the U-shaped data of relation of age at time of stroke and outcome. Statistical analyses were performed using Excel statistic programs (Excel Version 2000) and SPSS version 12.0 (SPSS INC, Chicago, IL, USA).

The study was approved by the Research Ethics Committee from Bern, Switzerland.

Results

Patients

48 children (34 males) were registered for arterial ischaemic infarction by the SNPSR from January 2000 through July 2002. In 11 children participation was refused or the children were lost to follow-up. At the 6 months follow-up examination, these children did not differ from the study group. Four children died during the acute episode. Death was related to stroke or underlying disease, details were published in our previous paper [31]. 33 children were eligible for follow-up examination. Two children were excluded for further neuropsychological evaluation because of marked pre-existing cognitive problems (one child with trisomy 21, one attending a special school). Further details are summarised in Table **1**.

The localisation of the lesions and involvement of the different structures are shown in Fig. **1**. After childhood stroke, brain damage was unilateral in 21 children und bilateral in one (affecting both sides of the brainstem), the left hemisphere was affected in nine and the right hemisphere in eight children, whereas after neonatal stroke all children had infarction in the territory of the left medial cerebral artery (two children had additional infarction of the right dorsal basal ganglia, in one there was right subarachnoidal haemorrhage and sinovenous thrombosis of the rectal and sagittal sinus). None of the children had diffuse brain damage on imaging.

Neurological outcome

Neurological outcome was good in 50% of patients after childhood stroke (seven without and four with mild neurological deficits) and poor in eleven children with moderate-severe neurological deficits. Ten children had hemiparesis and one child tetraparesis, additionally one child had an ataxia and one aphasia. So far none of the children has developed epilepsy. After neonatal infarction five of 11 children recovered fully, whereas six showed moderate-severe neurological deficits. Four children had hemi- and two tetraparesis. Four neonates developed epilepsy in the first days or months of life. Compared with our findings of neurological outcome after 6 months, children after childhood stroke showed no major difference in outcome after 18 – 24 months whereas in neonates there was either a trend to full recovery (45% at two years follow-up examination versus 30% at 6 months) or to deterioration of the neurological signs (54% with moderate-severe problems at two years follow-up examination versus 32% at 6 months); there were fewer children with minor neurological signs (0% versus 26%).

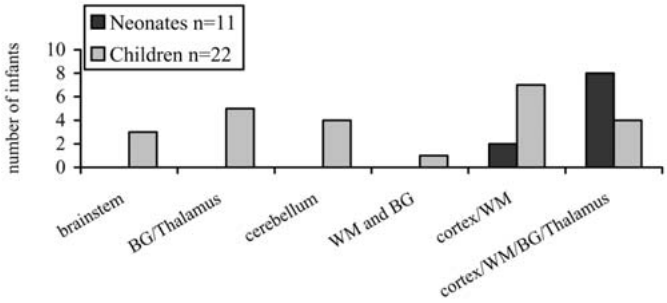

Fig. **1** Involvement of different structures after arterial ischaemic stroke; BG = basal ganglia, WM = white matter.

Table **1** Overview of children with childhood (AIS 1) and neonatal (AIS 2) infarction

	Childhood stroke (n = 22)	*Neonatal stroke (n = 11)*
Female (n)	4	4
Male (n)	18	7
Age at time of stroke, years (range)	8.5 (0.9 – 16.3)	0
Age at follow-up examination, years (range)	10.2 (2.1 – 18.2)	1.8 (1.0 – 3.7)

AIS = arterial ischaemic stroke, n = number

Neuropsychological outcome after childhood arterial ischaemic infarction (AIS 1)

Nine children were tested with age appropriate K-ABC, eight with WISC and three with WAIS. In two cases the BSID-II was used. Six children had a FIQ < 85 (range = 50 – 82), trisomy 21 and previous school problems were present in one of each and these two children were excluded from further neuropsychological analyses. Mean IQ for the remaining twenty children was 94.8 with a range of 66 – 120.

The results of WISC/WAIS and K-ABC are summarized in Table **2** demonstrating the number of children with abnormalities in each subtest.

The proportion of patients with subtest scores (in HAWIK/E or K-ABC) more than one standard deviation below the population mean (n = 14/19) differed significantly from the proportion to be expected in a normal population (expected: 3/19, $p < 0.001^{**}$). Only one child had one, eight children had two or three, and five more than three abnormal subtests.

These children differed significantly from the normal population in the performance of auditory short-term memory (digit span, word sequences) and in children tested with K-ABC in visuo-spatial skills (triangle design).

The children tested using the WISC/WAIS *t*-test showed a higher VIQ than PIQ (p = 0.121). More detailed analyses revealed the difference to be due to a significantly higher IQ in the domain of verbal comprehension compared to IQ in the domains of percep-

Table **2** Neuropsychological data after childhood arterial ischaemic stroke (n = 21)

WISC/WAIS	*No.*	*Norm*	*Mean (range)*	*SD*	*No. below norm*	*P value* χ^2
Full scale IQ	10	100 ± 15	99.2 (82 – 120)	12.9	2	0.300
Verbal IQ	10	100 ± 15	103.3 (85 – 123)	13.9	1	0.612
Performance IQ	10	100 ± 15	94.5 (78 – 118)	14.7	4	0.037**
VC	6	100 ± 15	113.3 (84 – 122)	13.9	0	0.288
PO	6	100 ± 15	98.3 (88 – 122)	13.1	0	0.288
PS	6	100 ± 15	89.5 (79 – 97)	7.2	2	0.241
FD	6	100 ± 15	100.8 (95 – 115)	7.7	0	0.288
Picture completion	10	10 ± 3	11.2 (7 – 15)	3.1	2	0.720
Information	10	10 ± 3	8.8 (3 – 12)	3.1	3	0.221
Codes	10	10 ± 3	8.1 (4 – 14)	3.1	4	0.037**
Similarities	10	10 ± 3	11.1 (7 – 16)	3.1	1	0.612
Picture arrangement	10	10 ± 3	10.3 (6 – 17)	3.5	3	0.221
Arithmetic	10	10 ± 3	9.3 (1 – 14)	3.8	3	0.221
Bloc design	10	10 ± 3	8.5 (7 – 15)	3.8	3	0.221
Vocabulary	10	10 ± 3	10.3 (7 – 13)	1.9	1	0.612
Object assembly	10	10 ± 3	8.5 (5 – 13)	2.3	3	0.221
Comprehension	10	10 ± 3	12.3 (7 – 17)	3.1	1	0.612
*Code comparison**	6	10 ± 3	8.1 (8 – 9)	0.4	1	0.288
Digit span	10	10 ± 3	7.2 (1 – 11)	2.9	6	< 0.001**
*Maze**	6	10 ± 3	12 (9 – 17)	2.8	0	0.288
Full-scale IQ	9	100 ± 15	93.9 (78 – 120)	17.0	2	0.601
Sequential IQ	9	100 ± 15	91.8 (77 – 117)	14.2	4	0.019**
Parallel IQ	9	100 ± 15	96.1 (53 – 129)	21.8	2	0.601
Hand movements	9	10 ± 3	8.7 (6 – 13)	2	2	0.601
Perception of gestalt	9	10 ± 3	7.5 (0 – 15)	5.11	2	0.601
Digit span	9	10 ± 3	8.4 (4 – 15)	3.4	4	0.019**
Triangle design	8	10 ± 3	7.9 (2 – 12)	3.3	4	0.008**
Word sequences	8	10 ± 3	8.9 (5 – 14)	3.1	3	0.094*
Analogy	8	10 ± 3	11 (5 – 16)	3.4	1	0.795
Spatial memory	8	10 ± 3	10.6 (5 – 15)	3	1	0.795
Photo series	9	10 ± 3	10.7 (7 – 13)	1.9	1	0.697
Sequential shapes	1	10 ± 3	10		0	
Face recognition	1	10 ± 3	1		1	

* p = ≤ 0.1 > 0.05 (trend); ** p < 0.05 (significant); WISC = Wechsler intelligence scale for children; WAIS = Wechsler adult intelligence scale; VC = verbal comprehension; PO = perceptual organisation; PS = processing speed; FD = freedom from distractibility; K-ABC = Kaufman assessment battery of children; No. = number of children; SS = scale score; SD = standard deviation

tual organisation (p = 0.031**), processing speed (p = 0.003**) and freedom of distractibility (p = 0.0175**). These differences were not related to the hemispheric side of lesion.

The children tested using the K-ABC *t*-test showed no statistically significant difference between SIQ and Pal IQ.

Relation to side of infarction

Fig. **2** demonstrates that children after left-sided infarction showed better performance in different IQ values than children with right-sided infarction. However, statistical significance was only reached for the domain of processing speed (p = 0.016**). No statistically significant differences were found in verbal performance as well as in any of the subtests.

Both groups were comparable in number of children (left-sided: n = 11, right-sided: n = 8) and age at time of stroke (left = 8.5 years, right = 8.6 years).

We did not find a significant difference in IQ values in relation to the localisation of the lesion, most probably due to the small numbers of children in each group.

Influence of gender

Fig. **3** demonstrates the different IQ values of boys compared to girls. FIQ was not significantly different in both groups (p = 0.54). However 2/3 girls had PIQ < 85 compared to 2/7 boys. Girls showed significantly reduced visuo-spatial skills compared to boys (block design: Scale Score: 7.3 versus 10.3, p = 0.032**)

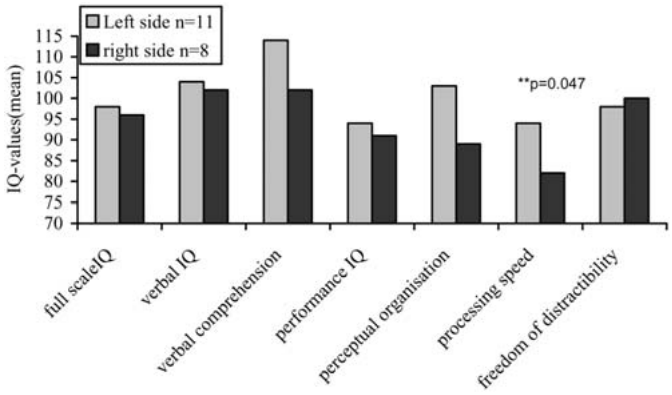

Fig. **2** Neuropsychological outcome in relation to side of infarction; IQ = intelligence quotient.

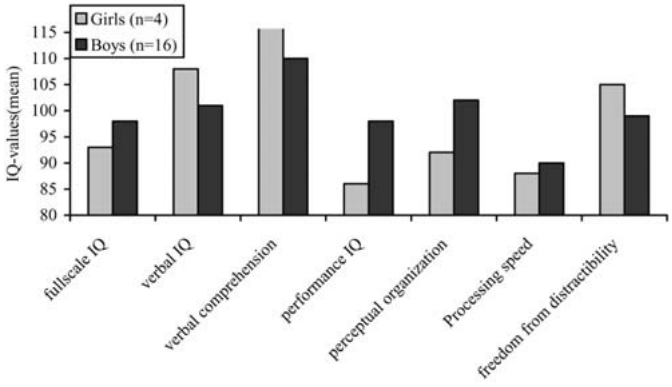

Fig. **3** Neuropsychological outcome in relation to gender (sex); IQ = intelligence quotient.

whereas comprehension was significantly better in females (comprehension: Scale Score: 15.3 versus 11.0, p = 0.040**).

There was a difference in group size (16 boys and 4 girls), and an insignificant difference of mean age at time of stroke of girls compared with boys (girls: 10.1 years, boys: 7.9 years, p = 0.55) which may have influenced the above results. Results have to be interpreted cautiously due to the small numbers.

Neuropsychological outcome in relation to age (childhood stroke)

The prognosis for cognitive performance of children in relation to age at the time of infarction is best after stroke in mid-childhood. Fig. **4** shows analyses by a quadratic regression model revealing that 23% of the variance is given by the two variables IQ and age at time of stroke (R square = 0.226). This corresponds to a (weak) relationship of the two variables.

Effects of childhood stroke on school and professional life

Of the group of children with childhood stroke (n = 22) three children were in an apprenticeship following school, one of them had problems with concentration and fatigue, another was unable to cope with the job of his choice and had to choose one at a lower level.

Fourteen children were at school age, eight of them performing well in normal school. Four of them had two and one three ab-

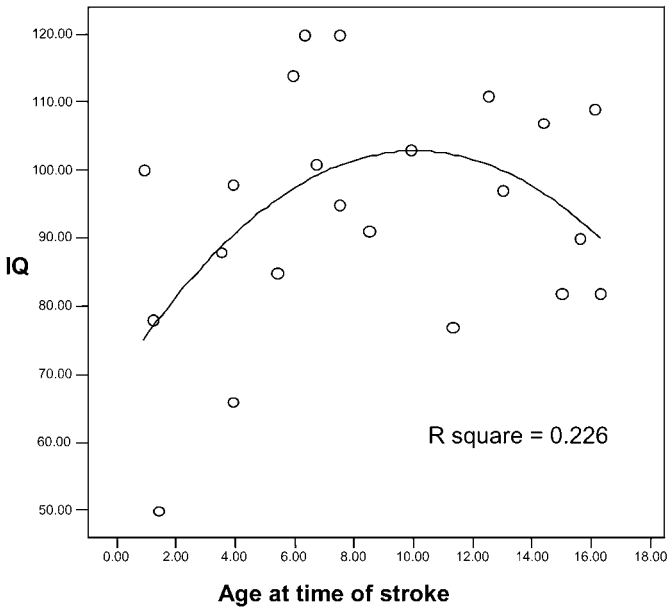

Fig. **4** Quadratic regression model for age at time of stroke (years) in relation to cognitive outcome after AIS (n = 19) (2 children were excluded, 1 child was too young for an intelligence test); IQ = intelligence quotient.

normal subtests. Two children were in regular school, but needed special assistance, one of them had two abnormal subtests. One girl was not able to return to normal school due to aphasia, and also neuropsychological problems (five abnormal subtests). One child was attending a school for mentally handicapped and two children a school for physically handicapped children, all of them had two or more abnormal subtests. Five children were preschoolers and three attended normal kindergarten, for two children it was already obvious that a normal school programme will not be possible.

Altogether 13/22 children after paediatric stroke suffered from additional problems, e.g., loss of self-esteem, aggression, anxiety, attention deficits, reduced tolerance of frustration, liability of affect and fatigue which is more than expected in the normal population (expectation: 1/22).

Cognitive outcome after neonatal stroke (AIS 2)

10 children were evaluated with the BSID-II and one with K-ABC. A summary of the results of cognitive outcome after neonatal stroke is listed in Table **3**. 2/3 children with a DQ < 50 had low APGAR scores followed by marked neurological impairment already present during the neonatal period (see Discussion).

Discussion

The strength of our study is the analysis of a population-based follow-up study of neuropsychological problems of Swiss children suffering arterial ischaemic stroke. As discussed in a previous paper [31] we believe the present study to be representative for children with childhood stroke, with some reservations for the group of neonates. A limiting factor of the study is the small number of patients enrolled. A long-term registry over sev-

Table **3** Outcome of children after neonatal stroke

Child	*DQ Motor*	*DQ Mental*	*Cerebral palsy*
*C1**	88	84	Hemiparesis
*C2**	< 50	< 50	Tetraparesis
*C3**	< 50	< 50	Hemiparesis
C4	120	110	none
C5	90	100	Hemiparesis
C6	100	100	none
C7	80	90	Hemiparesis
C8	100	100	none
C9	100	100	none
C10		110	none
*C11**	< 50	< 50	Tetraparesis
Mean (range), SD	**79.8 (40 – 120), 29.4**	**83.1 (40 – 110), 28.7**	**6/11**

* Epilepsy; DQ = developmental quotient; SD = standard deviation

eral years, combining registries from several centres/countries would increase numbers and would allow more detailed/specific statistical analyses, e.g., multiple comparisons. In addition, the wide range of age distribution required the use of different neuropsychological tests, therefore comparison of results was limited. However, the number of tests with statistically significant and trend results makes only chance results (type one error) unlikely.

Outcome after childhood stroke (AIS 1)

Neurological outcome of our children was similar to that reported in previous studies [6,8,9]. We would like to emphasise that, unlike neonatal stroke, neurological outcome after childhood stroke at 6 and 24 months follow-up examination, respectively, was not different [31], indicating that neurological recovery takes place within the first year after the acute event of a childhood stroke.

Similar to previous paediatric studies [5,9,20] but, unlike adults, cognitive outcome is favourable with mean low normal IQ. However, analysing the data in more detail reveals significant long-term problems and the increase in abnormal subtest results has to be assumed to be the reason for the marked school problems of these children.

An interesting observation of this study is the superiority of the left hemispheric functions over right hemispheric functions. Similar to Aram et al. [1] we observed that the cognitive outcome of children after left-sided infarction was better than after right-sided infarction. In addition, irrespective of the side of infarction, VIQ was higher than PIQ and especially right-sided functions such as auditory short-term memory, abilities in the domain of processing speed and perceptual organisation and visuo-spatial skills were limited. These data suggest a dominance of language functions over right hemispheric functions, as also reported for congenital infarctions [13,35]. These findings differ from results in adults where left hemispheric infarction leads to reduced VIQ and right hemispheric infarction to reduced PIQ [36]. These differences in children might be a hint that right-sided functions are in evolution/development more restricted to one hemisphere with more limited potential for reorganisation than left hemispheric functions. An explanation for this superiority of reorganisation in left-sided functions has recently been reported by Staudt et al. [30] for congenital infarctions: after a left-sided lesion, the right hemisphere mediates speech as well as right hemispheric functions, left-sided functions might interfere and dominate over right-sided functions.

Sensorimotor impairment at the time of IQ testing might have influenced the results in the handicapped children (especially those with restricted hand motor control). However, PIQ was also reduced compared to VIQ in five of seven children without motor impairment.

When analysing outcome compared to age at time of acute event, children who suffered from stroke in the mid-childhood had the best prognosis (5 – 10 years), whereas in children who suffered from stroke before the age of five years as well as those with the acute event after the tenth year of life, cognitive outcome was less favourable (Fig. **4**). In neonates poor outcome was also influenced by the presence of epilepsy. Another confounder might be the fact that comparison of developmental quotients with intelligence quotients is limited. However the second age group up to five years (group 2) had similar poor outcome, suggesting that age at time of stroke seems to be of greater prognostic significance. Therefore, the growing evidence from the literature, that outcome is less favourable in children after early brain lesions [4,28] is supported by our study. We presume that lesions during the first years of life, the most dynamic period of brain development [11,17], lead to severe impairment. This early damage also interferes with later development of networks for higher cognitive functions. We have to assume that reorganisation for higher cognitive functions is easier once the basic networks have been established. Thus, the extent of neural network developed and the level of abilities present at time of stroke influence reorganisation and outcome. Still, our results suggest that in adolescence reorganisation capacities and functional flexibility are again reduced, which might be explained by the fact that grey matter volume (especially in the frontal and parietal lobe) already declines in post-adolescence [12].

Gender-related differences

Our study did not reveal an overall gender difference for outcome. Our observation that girls were weaker in visuo-spatial skills and processing speed and better in comprehension tasks than boys might just reflect the known gender difference in a healthy population [18,23]. Additional confounders for this observation might be the different size of groups and age at time of stroke.

Neonatal stroke

For neonates data of neurological outcome are comparable with the literature [19,22,25,29]. There were still changes of neurological findings between the ages of 6 to 24 months: children with mild neurological signs at 6 months had either recovered fully or showed marked neurological problems. This reflects the

well known fact that neurological problems are difficult to verify in infancy. Prognostic factors influencing outcome were the presence of epilepsy and perinatal signs of marked neurological impairment. These observations are consistent with those of Vargha-Khadem et al. [35], Muter et al. [24] and Ramaswamy et al. [26]. In our cohort it remained unclear whether neonatal problems were the result or cause of the ischaemic event.

The good psychomotor development in half of the children after neonatal stroke has to be interpreted cautiously. These children are too young to detect minor neuropsychological problems as described in our group of childhood stroke. For this reason we are planning a re-evaluation of this cohort at the age of 7 – 8 years.

Conclusion

Cognitive outcome after childhood stroke is marked by significant dysfunctions in school and professional life. Neonates and preschool children have less reorganisational capacities than elder children. In addition, there is an interesting predominance of left over right hemispheric functions, leading to better outcome after left hemispheric infarction. An increase in numbers of enrolled children seems mandatory to confirm our data and also to analyse these data in more detail.

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