Late Emergence of Cognitive Deficits After Unilateral Neonatal Stroke

Robyn Westmacott, PhD; Daune MacGregor, MD; Rand Askalan, MD; Gabrielle deVeber, MD

Background and Purpose—Neonatal arterial ischemic stroke (AIS) affects a surprisingly large number of children each year, yet little is known about the long-term neuropsychological implications.

Methods—Using age-appropriate Wechsler scales of intellectual ability, this longitudinal study examined 26 children with a history of acutely diagnosed unilateral neonatal AIS as preschoolers (3 years 6 months to 5 years 11 months) and again as grade-school students (6 years 1 month to 12 years 5 months), and contrasted performance with the normative sample of the test.

Results—As preschoolers, patients’ performance did not differ from the normative sample for Full Scale IQ, Verbal IQ, or Performance IQ, and there were no significant differences associated with infarct laterality. As school-age children, performance was significantly lower than the normative sample for Full Scale IQ Working Memory and Processing Speed, but not for Verbal IQ or Performance IQ. Contrasts between Time 1 and Time 2 revealed a significant decline in Full Scale IQ, which reflected emerging deficits in nonverbal reasoning, working memory, and processing speed. Individual subject analyses revealed that 69% of the children showed significant declines in 1 or more IQ index measures. We found no significant differences in cognitive performance associated with lesion laterality, though males performed more poorly than females on several cognitive measures at Time 2.

Conclusions—These findings suggest that children with unilateral neonatal stroke, particularly males, are at increased risk for emerging deficits in higher-level cognitive skills during the school years. Continued follow-up of these children is needed, even those with no apparent deficits as toddlers or preschoolers. (Stroke. 2009;40:2012-2019.)

Key Words: cognition ■ cognitive impairment ■ neonatal ischemia ■ neuropsychology ■ outcome ■ pediatric stroke ■ psychology and behavior ■ stroke in children

The incidence of neonatal arterial ischemic stroke (AIS) is much higher than previously thought, affecting one in 4000 live births.1 Survival rate after neonatal stroke is very high, but many of these children live with significant neurological deficits, including hemiparesis and hemi-sensory impairments.2 Speech is often delayed after neonatal stroke to either hemisphere, but most children develop age-appropriate spoken language by the time they enter school.3–5 With respect to overall cognitive development, some studies suggest that, when tested as toddlers and preschoolers, most children with neonatal stroke fall broadly within the normal range6–8 though other studies have revealed evidence of early cognitive weakness.9,10 Little is known about longer-term cognitive outcome after neonatal stroke, however, as no studies have followed a group of these children into the later school years.

Studies of longer-term cognitive outcome after neonatal stroke are needed to determine whether early deficits resolve, remain stable, or become more pronounced over time, and whether apparently normal infants grow into deficits with maturation. Research in pediatric populations with other insults to the central nervous system (eg, head injury, congenital hydrocephalus, cranial irradiation) has revealed that cognitive deficits often emerge later in childhood as children are expected to process information in a more complex and efficient manner.11–13 It has been speculated that children with early focal brain lesions are less vulnerable to emerging cognitive deficits, but this hypothesis is largely based on reports of good motor and language outcome.3,14 In fact, early focal brain injury of mixed etiology is also associated with more pronounced cognitive deficits as the age at assessment increases.15

Longitudinal studies are best suited to address questions regarding long-term outcome. A few studies have used a longitudinal design to investigate long-term cognitive outcome after early focal brain injury, but none have been exclusive to neonatal stroke. Aram and Eisele16 reported overall stability in the intellectual performance of children with focal vascular lesions, but age at brain injury ranged from prenatal to 16 years. Muter and colleagues17 also

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documented intellectual stability for the majority of their subjects with unilateral focal brain lesions, but some of these subjects sustained the injury after the neonatal period (up to 6 months of age). Because postnatal brain development is so rapid in the first few months of life, the impact of focal brain injury may vary considerably depending on the time of onset within the first 6 months. Other studies have combined children with acutely diagnosed neonatal AIS and those with retrospectively diagnosed presumed perinatal stroke (PPERI), which is problematic from a methodological standpoint because children with PPERI are typically only diagnosed when neurological deficits are very severe and the exact timing of the lesion cannot be confirmed. To date, no longitudinal studies have focused on long-term cognitive outcome after neonatal stroke (ie, diagnosis confirmed between birth and 28 days of life).

We sought to establish cognitive outcome in a large group of children with unilateral acutely diagnosed neonatal AIS followed longitudinally through the preschool and grade-school years. Through prospective serial cognitive testing, we tracked the emergence of cognitive deficits to determine their frequency, characteristics, and predictors. We hypothesized that children with neonatal AIS would show evidence of later-emerging cognitive deficits in the school years.

### Methods

#### Patient Population

Participants were identified on enrollment in the Children’s Stroke Outcome Study at The Hospital for Sick Children in Toronto. Children were considered for participation if they had a history of AIS diagnosed acutely in the neonatal period (between birth and 28 days of life) from 1992 to 2001, and a single unilateral arterial ischemic stroke conforming to established arterial territories documented on MRI or CT. In all cases, the clinical indications for performing imaging, and subsequently making the diagnosis of stroke, was the observation of seizures within the neonatal period. Exclusion criteria were: bilateral lesions, cerebral sinovenous thrombosis, hypoxie-ischemic encephalopathy, premature birth (<36 weeks gestation), presumed perinatal stroke diagnosed later in infancy, epilepsy or seizures outside of the neonatal period, and other neurological comorbidities. Children who were not fluent in English were excluded.

Children born after 2001 were excluded as they had not yet reached school-age by study completion. Eligible participants were invited to participate in an initial neuropsychological assessment between the ages of 3 to 5 years and a follow-up assessment after 6 years of age. To ensure unbiased enrollment in the study, we implemented a telephone recruitment procedure for all neonates with AIS from our institution.

#### Clinical Data

Demographic and neurological characteristics were obtained from a review of health records. Chronic neurological status was evaluated using the Pediatric Stroke Outcome Measure (PSOM), obtained within 1 year of the school-age neuropsychological assessment (see Table 1 for details about the PSOM scoring). Hemiparesis was rated as severe in 5 subjects, moderate in 5 subjects, and mild in 13 subjects. The remaining 3 subjects had no detectable hemiparesis. Maternal education level was used as an indicator of socioeconomic status and rated on a 5-point scale (1 = did not complete high school; 2 = completed high school; 3 = some post-secondary training but not a diploma or degree; 4 = completed a university or college program; 5 = professional or graduate school).

#### Radiographic Data

MRI/CT scans were obtained acutely in the neonatal period. The study neurologists reviewed MRI/CT films at clinic visits and coded stroke lesion characteristics (including size and location) referring to clinically generated neuroimaging reports, in a similar fashion to previous studies of early focal brain injury. All patients had focal porencephaly involving 1 or more lobes. See Table 2 for the details of this coding system. Lesion size and location for individual patients are presented in Table 3.

#### Neuropsychological Assessment

As preschoolers, children completed the Wechsler Preschool and Primary Scale of Intelligence-Revised Edition (WPPSI-R) or the WPPSI - Third Edition (WPPSI-III). Both versions provide index scores for overall intellectual ability (Full Scale IQ), verbal ability (Verbal IQ), and nonverbal ability (Performance IQ), with a mean score of 100 and a standard deviation of 15. Scores between 90 and 110 fall within the “average range.” As school-age students, children completed either the Wechsler Intelligence Scale for Children - Third Edition (WISC-III) or the WISC – Fourth Edition (WISC-IV). Both versions provide index scores for overall intellectual ability (Full Scale IQ), verbal ability (Verbal Comprehension Index), nonverbal ability (Perceptual Reasoning Index), auditory attention and mental
Statistical Analysis

The preschool and school-age group scores were first examined separately. One-tailed $z$ tests with an alpha of 0.05 were used to compare the patient group’s WPPSI and WISC Index scores with the theoretical mean of the normative sample (i.e., $M = 110$, $SD = 15$). Two-tailed independent-samples $t$ tests were used to explore whether or not there were any significant differences based on sex (male versus female) or lesion laterality (right versus left). Because of the predominance of children with left hemisphere lesions in our sample (69%), the laterality analysis was underpowered.

Change in cognitive test performance over time was evaluated using 2-tailed paired $t$ tests contrasting group means in overall intellectual ability (Full Scale IQ), verbal ability (Verbal IQ from the WPPSI or Verbal Comprehension Index from the WISC), and nonverbal ability (Performance IQ from the WPPSI or Perceptual Reasoning Index from the WISC) across the 2 assessments. Within-subject change over time was evaluated on an individual patient basis by examining whether or not the discrepancy between scores at Time 1 and Time 2 ($T_2 - T_1$) was greater than expected based on the standard error of the mean (SEM) for each Index measure and an alpha of 0.05. These SEM values are published in the Examiner’s Manual for each test and reflect the test-retest reliability of that particular Index measure. The SEM values provide a cut-off for...
examining whether or not a discrepancy is greater than expected simply because of test-retest variability. We multiplied the SEM values for each Index measure by 1.64 to obtain the cut-off value with a 0.05 probably of Type 1 Error. This method for evaluating within-subject change over time has been used extensively in neuropsychological research.\textsuperscript{18,26,27} Of note, because there are no measures of working memory and processing speed before 6 years of age, we could not evaluate longitudinal changes in these skills.

Results

Patient Population

Two hundred twenty-five children with neonatal AIS born after 2001 were enrolled in the Children’s Stroke Outcome Study. One hundred five children were excluded based on inclusion/exclusion criteria: 49 had bilateral or diffuse lesions, 32 had seizures outside the neonatal period or other neurological comorbidities, and 24 did not speak English. Of the 120 children who met the inclusion/exclusion criteria, 30 were excluded because they participated in 1 assessment only. There were no differences in PSOM scores, sex ratio, or etiology distribution between those subjects who participated and those who did not. We were not able to compare the groups on maternal education or socioeconomic status, as this information is not routinely collected outside of the neuropsychological assessment. A total of 26 children who met our strict inclusion and exclusion criteria participated in both assessments. At initial assessment, age ranged from 3 years 6 months to 5 years 11 months (M=4.9 years, median=4.8 years, SD=1.2 years). At follow-up assessment, age ranged from 6 years 1 month to 12 years 5 months (M=8.8 years, Median=9.4 years, SD=2.1 years). A minimum interval from time 1 to time 2 of 18 months was required. Excluded patients and patients who declined participation were similar to the study sample in terms of gender ratio, laterality ratio, and PSOM scores.

Clinical and Radiographic Characteristics

Demographic, neurological, and radiographic characteristics for the patient group are presented in Table 1. All 26 children presented with seizures, but limited to the neonatal period. For most children (77%), stroke etiology was unknown, and the remainder had either cardiac defects or perinatal distress. None had coagulation disorders. The right and left hemisphere lesion groups were matched on PSOM scores, maternal education, lesion size, and age at assessment. Similarly, there were no significant differences between males and females on any of these variables.

Preschool Assessment

As preschoolers, the patient group’s performance did not differ from the normative sample of the WPPSI for Full Scale IQ (M=99.50, SD=12.46), Verbal IQ (M=97.85, SD=12.52), or Performance IQ (M=99.81, SD=13.24). Examination of individual subject data (Table 3) indicated that performance fell below the average range (ie, <90) for 6 children (23.1%) on Full Scale IQ, 5 children (19.2%) on Verbal IQ, and 6 children (23.1%) on Performance IQ, which is not significantly different from the general population (25%). There were no significant differences associated with lesion laterality on any of the Index measures. However, there was a nonsignificant trend (t[24]=1.28, P=0.21) toward weaker Verbal IQ in children with left hemisphere lesions (M=95.8, SD=13.4) compared to those with right hemisphere lesions (M=102.5, SD=9.52). Similarly, there were no significant differences associated with patient sex on any of the Index measures, but there was a noteworthy trend (t[24]=1.88, P=0.07) toward poorer Verbal IQ in males (M=93.1, SD=11.5) than females (M=101.9, SD=12.3). Finally, there were no significant correlations between PSOM motor score and any of the IQ scores.

School-Age Assessment

When these same 26 patients were tested as school-age children, new cognitive weaknesses became apparent in several areas. As a group, patients’ performance was significantly lower than the normative sample of the WISC for Full Scale IQ (M=92.81, SD=12.81, Z=−2.44, P<0.01), Perceptual Reasoning (M=95.15, SD=13.90, Z=−1.65, P<0.05), Working Memory (M=88.77, SD=14.21, Z=−3.81, P<0.01), and Processing Speed (M=90.50, SD=12.48, Z=−3.23, P<0.01). There was also a trend toward weaker Verbal Comprehension (M=95.35, SD=12.34, Z=−1.58, P=0.055), but this did not reach significance. Examination of individual subject data (Table 3) showed that performance fell below the average range for 10 children (38.5%) on Full Scale IQ, 6 children (23.1%) on Verbal Comprehension, 8 children (30.8%) on Perceptual Reasoning, 15 children (57.7%) on Working Memory, and 11 children (42.3%) on Processing Speed. There were no significant differences associated with lesion laterality, though there was a nonsignificant trend (t[24]=1.23, P=0.23) toward weaker Verbal Comprehension in children with left hemisphere lesions (M=93.39, SD=14.00) compared with right hemisphere lesions (M=99.75, SD=5.99).

With respect to sex differences, males performed more poorly than females on multiple Index measures including: Full Scale IQ (Males: M=87.6, SD=13.4; Females: M=97.3, SD=10.8; t[24]=2.04, P=0.05), Perceptual Reasoning (Males: M=89.3, SD=15.3; Females: M=100.1, SD=10.7; t[24]=2.11, P=0.05), and Processing Speed (Males: M=84.3, SD=12.4; Females: M=95.8, SD=10.2; t[24]=2.58, P=0.02). There was a nonsignificant trend (t[24]=1.58, P=0.13) toward poorer Verbal Comprehension in males (M=91.3, SD=14.0) than females (M=98.8, SD=10.0), and no group difference (t[24]=1.09, P=0.29) on the Working Memory Index (Males: M=85.5, SD=17.1; Females: M=91.6, SD=11.0). Finally, there were no significant correlations between PSOM motor score and any of the IQ scores.

Longitudinal Analysis

Paired t tests contrasting performance at Time 1 (preschool assessment) and Time 2 (school-age assessment) revealed
significantly lower scores at Time 2 on indices of overall intellectual ability (t(25)=3.48, P=0.002) and nonverbal ability (t(25)=2.81, P=0.01), but no change in verbal ability (t(25)=1.23, P=0.23). Examination of individual patient data indicated that 18 children (69.2%) showed a significant decline from Time 1 to Time 2 (ie, greater decline than expected based on the SEM for that measure) on one or more Index measures (Table 4). Specifically, 4 children showed significant declines on all 3 Index measures, 5 showed declines in Full Scale IQ and nonverbal ability, 2 showed declines in Full Scale IQ and verbal ability, 4 declined in Full Scale IQ alone, 2 declined in nonverbal ability alone, and 1 declined in verbal ability alone. Of note, these declines do not pertain to raw test scores but rather to standardized test scores. The children whose standardized test scores declined did not lose skills from Time 1 to Time 2. However, relative to healthy age-matched peers, these children made slower gains over time, gradually diverging from the norm. Five children did show significant gains on one or more Index measures from Time 1 to Time 2, however. One child showed significant improvement on all 3 Index measures, 2 children improved on Full Scale IQ and verbal ability, and 1 child improved on verbal ability alone. There was no correlation between follow-up interval (ie, length of time between assessments) or PSOM motor score and any of the index scores.

Table 4. Longitudinal Analysis of Individual Patient Data

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<th>Lesion Location</th>
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*Because Time 1 scores were subtracted from Time 2 scores, negative values indicate declines from Time 1 to Time 2.

Difference scores that were greater than the cut-off value (SEM × 1.64) are indicated. The cut-off values are as follows: FSIQ=4.4, Verbal=7.4, Nonverbal=7.9. These values were determined by multiplying the SEM for each index by 1.64 to obtain cut-offs with an alpha of 0.05.

Lesion Location: S, subcortical (basal ganglia and/or thalamus); F, frontal cortex; P, parietal cortex; T, temporal cortex; O, occipital cortex.
No statistically significant effect of lesion laterality was found. Examination of group means indicates a trend toward greater decline in nonverbal ability for the left hemisphere group (M = −6.83, SD = 6.52) compared to those with right hemisphere lesions (M = −1.75, SD = 10.18, t[24] = 1.54, P = 0.14). Sex comparisons showed that males had a significantly greater decline in nonverbal ability (M = −9.50, SD = 5.25) than females (M = −1.64, SD = 8.27, t[24] = 2.83, P = 0.01), and there was a nonsignificant trend toward greater decline in Full Scale IQ for males (M = −9.42, SD = 8.50) versus females (M = −4.36, SD = 10.56, t[24] = 1.33, P = 0.19). Performance changes in verbal ability did not differ for males (M = −1.75, SD = 7.84) and females (M = −3.14, SD = 12.39, t[24] = 0.34, P = 0.74).

Discussion

This is the first longitudinal study to examine long-term cognitive outcome exclusively in children with acutely diagnosed unilateral neonatal AIS. This is an ideal population for studying the impact of early brain injury on development because the lesions are focal and singular, the time of onset can be pinpointed within several days by acute findings on initial CT/MRI, and it is possible to select a group with no neurological comorbidities. Moreover, lesion location can also be easily classified based on affected vascular territory, as these represent arterial vaso-occlusive infarcts in standardized brain territories. Studying a carefully selected and matched subject group such as this increases the statistical power, making it more likely that significant deficits will be detected.

As preschoolers, we found that our subject group did not differ from the normative sample of the WPPSI on measures of overall intellectual ability, verbal ability, or nonverbal ability. In contrast, when these same children were tested again as school-age students, we found evidence of emerging cognitive weaknesses in nonverbal reasoning skills, working memory, and processing speed. We also found a nonsignificant trend toward an emerging weakness in verbal ability. Of note, when we examined the working memory and processing speed performance for the 8 children who were excluded from this study because they had only completed the school-age assessment, we found similarly weak scores to the participant group on these 2 measures. It is also noteworthy that the PSOM motor scores were not significantly correlated with any of the IQ measures for preschool or school-aged children, suggesting that motor function is not linearly related to cognitive outcome.

Longitudinal analyses revealed significantly lower scores at Time 2 on measures of overall intellectual ability and nonverbal ability, but no significant change in verbal ability. In addition to emerging deficits in information processing skills (ie, working memory and visuomotor speed), children with unilateral neonatal AIS made slower gains than age-matched peers with respect to overall intellectual ability and nonverbal reasoning. Although the comparison of performance across time was complicated by the necessary use of different cognitive tests as preschoolers and as school-age children, the likelihood of this creating a significant confound in the results is greatly reduced by the fact that these 2 tests are designed to be used track development longitudinally and are highly comparable in structure and administration.

It is important to note that, although we found statistically significant declines, the cognitive weaknesses were relatively mild for most children in our sample (Full Scale IQ median = 94.5). Thus, children with unilateral neonatal AIS appear to be at risk for emerging cognitive difficulties in the school years, but not to the extent that they would be classified by standard IQ tests as “intellectually impaired.” Rather, the weaknesses tend to be more subtle, often affecting complex cognitive skills such as working memory, processing speed, and abstract reasoning. Moreover, it is important to note that not all children exhibited cognitive weaknesses and a few actually showed improvement from Time 1 to Time 2. Other studies suggest that children with bilateral lesions or an active seizure disorder are at risk for more severe cognitive impairments.

A recent study of neonatal AIS suggested normal cognitive outcome in children with no other neurological comorbidities, but the majority of the subjects were preschoolers at the time of assessment. Thus, the follow-up interval in the Ricci et al study may have been too short to detect later-emerging cognitive morbidity. Our study illustrates the importance of continuing to follow this population of children well into school years, when difficulties with higher-level cognitive abilities are more likely to emerge.

In contrast to our findings, Ballantyne et al recently reported stability of IQ in a group of children with perinatal stroke, though several differences in methodology appear to account for the contrasting results. Our study focused exclusively on children with unilateral acutely diagnosed neonatal stroke and no other neurological comorbidities, whereas the Ballantyne et al study included children with retrospectively diagnosed presumed perinatal stroke as well as children with seizure disorders. In addition, many subjects in the Ballantyne study were given outdated IQ tests and only a small number were actually tested longitudinally. Finally, the controls in the Ballantyne et al study performed within the gifted range on the IQ test, calling into question any comparisons between the patterns of performance for patients vs controls. For these reasons, we feel that our finding of emerging cognitive deficits in the school years more accurately reflects long-term outcome for children with unilateral neonatal stroke.

Another unique finding in our study is the sex difference in long-term cognitive outcome in neonatal AIS. Males performed significantly more poorly than a matched group of females on measures of overall intellectual ability, nonverbal reasoning, and processing speed. Of note, these sex differences were present only in the school-age assessment, suggesting that males with unilateral neonatal AIS may be at higher risk for emerging cognitive deficits. We also found a nonsignificant trend toward weaker verbal skills in males than females at both assessments, though both sexes were equally weak on measures of working memory. These findings were consistent with a large body of evidence from other early reports on brain injury populations (hypoxic-ischemic encephalopathy, intracranial hemorrhage, intraventricular...
hemorrhage) that males have poorer outcome than females with respect to mortality, physical morbidity, and cognitive outcome. One possible explanation for this sex difference is the relative immaturity of the male brain at birth, which may render it more vulnerable to the effects of early injury. Our study emphasizes the need to examine sex differences when studying cognitive outcome after early brain injury. Future research should explore how age at injury modulates the impact of sex on cognitive outcome. For example, are sex differences still apparent when stroke occurs later in childhood?

We found no significant differences in performance associated with lesion laterality, however, these comparisons were statistically underpowered because of the small size and large standard deviation of the right hemisphere group in our sample. There was a noteworthy trend toward poorer verbal skills in the left hemisphere group at both the preschool and school-age assessments. The cognitive difficulties in nonverbal reasoning, working memory, and visuomotor processing speed that emerged in the school-age assessment were equally pronounced for children with right and left hemisphere lesions. The issue of lateralized cognitive deficits after early focal brain lesion has generated a great deal of interest, largely because hemisphere differences are so pronounced after adult brain injury. However, pediatric studies examining lateralized cognitive deficits have yielded highly inconsistent results, suggesting that the relationship between lesion laterality and outcome is modulated by a variety of other factors including age at injury, lesion severity, and the specific cognitive skill in question. Because our study was underpowered, it will be necessary to study a larger group of children with right hemisphere neonatal AIS at similar long-term intervals to elucidate the impact of lesion laterality on long-term cognitive outcome. Larger samples would also permit examination of the impact of stroke location (e.g., anterior versus posterior) on cognitive outcome.

In summary, in our carefully selected sample of children with isolated unilateral acutely diagnosed neonatal AIS and no other neurological comorbidities, we found evidence of emerging cognitive deficits that were detected only when children were followed into the school years. In addition to emerging deficits in information processing skills, children with unilateral neonatal AIS made slower gains than age-matched peers with respect to overall intellectual ability and nonverbal reasoning. Moreover, we found that males were at greater risk than females for cognitive emerging difficulties. Our study highlights the importance of long-term follow-up in this population.

Further research is needed to explore issues regarding individual variability after neonatal AIS. As a group, the children in our sample exhibited emerging cognitive deficits in several areas, but there was considerable variability across subjects. Some children with unilateral neonatal AIS continue to show typical cognitive development, whereas others exhibit increasingly pronounced deficits as they grow older. As Stiles and colleagues note, when studying pediatric populations it is very difficult, if not impossible, to define the “typical” outcome associated with a particular type of brain injury because recovery occurs as part of a much broader and very complex developmental course. These authors argue that the focus of studying children with early brain lesions should, instead, be to explore the various alternate pathways that development can take, and to determine what factors influence the pathway of a given child. Greater understanding of alternate developmental pathways that may follow unilateral neonatal AIS will likely come from studies that explore interactions among stroke size/location and other neurological, demographic, and psychosocial factors.

Disclosures

None.

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