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Original Article

Clinical Predictors of Attention and Executive Functioning Outcomes in Children After Perinatal Arterial Ischemic Stroke

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ABSTRACT

BACKGROUND: Children with perinatal arterial ischemic stroke (PAIS) are at risk for later neurocognitive and behavioral deficits, yet the clinical predictors of these outcomes are understudied. We examined the influence of clinical and infarct characteristics on attention and executive functioning in children following PAIS. **METHODS:** Forty children born at term (≥37 weeks' gestation) with PAIS (28 with neonatal arterial ischemic stroke and 12 with presumed PAIS) underwent a comprehensive neuropsychological battery at age three to 16 years (median age 7.2 years; 58% male) to assess attention and executive functioning. Parents also completed questionnaires regarding real-world functioning. Clinical variables including perinatal stroke subtype, infarct characteristics (location, laterality, and volume), and the presence of comorbid epilepsy were ascertained from the medical record. **RESULTS:** Presumed PAIS, larger infarct volume, and comorbid epilepsy negatively influenced the performance on attention and executive functioning measures. These clinical variables were also associated with greater functional problems on parent reports, including a higher frequency of attention-deficit/hyperactivity disorder symptoms and greater difficulties in some subdomains of executive functioning. Infarct location and laterality were not associated with performance measures or parental report of functioning. **CONCLUSION:** Although all children with PAIS are at risk for later deficits in attention and executive functioning, those with presumed PAIS, larger infarct size, and comorbid epilepsy appear to be the most vulnerable. As they approach and reach school age, these children should undergo neuropsychological assessment to ensure timely implementation of therapeutic interventions and behavioral strategies.

Keywords: perinatal stroke, neonatal ischemia, cognition, outcome, predictors

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Introduction

Perinatal arterial ischemic stroke (PAIS) frequently results in long-standing neurological sequelae, including cognitive and behavioral deficits. Moreover, PAIS has been shown to negatively affect cognitive development, with the deficits becoming increasingly evident with age.[1,2] Prior studies have attempted to identify specific clinical and neurophysiologic factors that account for the cognitive impairment after PAIS, including the stroke subtype,[1,3] the infarct characteristics,[1-9] and the presence of comorbid epilepsy.[4,9-12] However, these factors remain poorly understood, as reported outcomes have varied due to heterogeneous study populations, outcomes measures, and the

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age at assessment. Moreover, prior studies have emphasized global functioning, rather than specific neurocognitive or neurobehavioral domains, such as attention and executive functioning.

We recently reported that children with PAIS demonstrate mild to moderate attention and executive function impairments and have a higher frequency of clinically elevated attention deficits compared with the population norms.[13] The gender and age at the time of assessment were not associated with the outcome, with the exception of a negative correlation between older age and working memory. In the current study, we sought to more thoroughly evaluate the clinical factors predictive of attention and executive functioning deficits in a well-defined PAIS cohort utilizing a rigorous neuropsychological battery specifically targeting these subdomains of neurocognitive function. Furthermore, we aimed to examine which factors put children at greater risk for worse outcomes in these neuropsychological domains to better predict how children with perinatal stroke develop skills and function when compared with their peers throughout development. Based on prior studies, we hypothesized that children with presumed PAIS, larger volume infarctions, and comorbid epilepsy would have worse neurocognitive outcomes.

Methods

This was a cross-sectional, observational study of a convenience sample recruited from the Children's Hospital of Philadelphia Pediatric Stroke Registry. The institutional research review board approved the study, and informed consent and assent (when appropriate) were obtained for all subjects.

Inclusion criteria

The study population comprised children who presented to the Children's Hospital of Philadelphia with PAIS and were enrolled in the institution's Pediatric Stroke Registry between January 1, 2004, and March 31, 2015. The subjects were aged three to 16 years at the time of neuropsychological testing, and only children with English as the first language in the home were included. The recruitment methodology has been previously described.[13] As per the National Institutes of Health Common Data Element stroke subtype definitions,[14] the diagnosis of PAIS included both neonatal arterial ischemic stroke (NAIS) and presumed PAIS. NAIS was diagnosed in term neonates ($\geq$37 weeks' gestation at birth) with acute neonatal encephalopathy (seizures, altered mental status, or focal neurological deficits) developing in neonates aged $\leq$28 days with an acute infarction in an arterial territory on brain magnetic resonance imaging (MRI). Presumed PAIS was diagnosed in children with normal perinatal neurological histories who developed neurological deficits or seizures after 28 days of age and had a remote focal infarction in an arterial territory on MRI.[3]

Exclusion criteria

Subjects with the following comorbidities were excluded from participation: prematurity (less than 37 weeks' gestation at birth), *in utero* stroke (detected prenatally or the finding of encephalomalacia on MRI by ten days of age interpreted as evidence of chronic, rather than acute or subacute, infarction), intracerebral hemorrhage not attributable to hemorrhagic transformation of arterial ischemic stroke, cerebral sinovenous thrombosis, periventricular venous infarction, moderate to severe hypoxic-ischemic encephalopathy, congenital hydrocephalus, and infarctions related to cranial surgery, PHACES syndrome, Sturge-Weber syndrome, or neonatal moyamoya vasculopathy. We intended to exclude subjects from participation if they had severe intellectual disability or any severe sensorimotor impairment that would prevent valid administration or interpretation of the neuropsychological measures. Ultimately, no potential subject was excluded for these reasons.

Medical data collection and definitions

Medical record data were reviewed and entered into a Research Electronic Data Capture (REDCap) database.[15] These included (1) the demographic and clinical characteristics, including comorbid epilepsy diagnosis, (2) the infarct characteristics (location, laterality, number, and volume), and (3) the infarct vascular territory affecting the anterior cerebral artery (ACA), the middle cerebral artery (MCA), or the posterior cerebral artery (PCA).

Epilepsy was defined as (1) one unprovoked seizure after 30 days of age and one of the following (a) electroencephalography with epileptiform discharges; (b) treatment with an anticonvulsant; or (2) two or more unprovoked seizures occurring $\geq$ 24 hours apart after 30 days of age.

Two board-certified pediatric neuroradiologists (A.V., A.B.) reviewed the diagnostic neuroimaging and the associated reports for infarct characteristics and estimation of infarct volume. *Cortical-only* infarcts were defined as those that involved the cortex and the subjacent white matter. *Subcortical-only* infarcts were those that involved only the thalamus and/or the basal ganglia (caudate and lentiform nuclei). *Combined* infarcts were defined as those involving the cortex and the underlying white matter, along with the thalamus and/or the basal ganglia. Infarct volume was estimated using the Modified Pediatric Alberta Stroke Program Early Computed Tomography Score (modASPECTS), which correlates with infarct volume.[16,17] This scoring system requires acute brain MRI and was therefore only applied to the NAIS group. It is based on a 30-point scale; each hemisphere is subdivided into 15 regions, yielding a maximum of 15 points per hemisphere. One point is assigned for each region involved in the infarct: seven cortical MCA regions, two cortical ACA regions, two cortical PCA regions, and four subcortical regions (caudate, lentiform nuclei, internal capsule, and thalamus). Additionally, in subjects with infarcts involving the MCA territory, the infarct volume was further estimated by categorizing the infarct as anterior division, posterior division, or both divisions of the MCA, using either acute or chronic brain MRI. In this way, categorization could be done in all NAIS and presumed PAIS subjects.

Neuropsychological battery

Children aged three to 16 years completed an age-appropriate, single-session comprehensive neuropsychological battery targeting attention and executive functioning. Children aged three to five years (n = 16) were assessed with a preschool version of the test battery, whereas children aged six to 16 years (n = 24) were assessed with a school-age version. Testing lasted approximately 45 to 115 minutes (depending on the age) and included the Wechsler Preschool and Primary Scale of Intelligence—Fourth Edition (WPPSI-IV), the Wechsler Abbreviated Scale of Intelligence—Second Edition (WASI-II-2 subtest form), a Developmental Neuropsychological Assessment—Second Edition (NEPSY-II), the Working Memory Test Battery for Children (WMTB-C), the Test of Everyday Attention for Children (TEA-Ch), Tower of London DX—2nd Edition (TOL-Dx), and the Trail Making Test (TMT) Parts A & B. Additionally, parents completed questionnaires addressing real-world functioning, including the attention-deficit/hyperactivity disorder (ADHD) Rating Scale-IV and Behavior Rating Inventory of Executive Function (BRIEF-school age or preschool form). The full methodology has been previously published.[13]

Statistical analyses

Neuropsychological subtests and/or test subscores were categorized into seven domains of functioning (attention, working memory, verbal retrieval, inhibitory control, flexibility and/or shifting, planning and/or organization, and processing speed) based on an *a priori* test design and confirmatory expert survey.[13] Subsequently, *z* scores for each subtest (of