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Neurodevelopmental Abnormalities in Children With PHACE Syndrome

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Abstract

Prior case reports have identified neurodevelopmental abnormalities in children with PHACE syndrome, a neurocutaneous disorder first characterized in 1996. In this multicenter, retrospective study of a previously identified cohort of 93 children diagnosed with PHACE syndrome from 1999 to 2010, 29 children had neurologic evaluations at ≥1 year of age (median age: 4 years, 2 months). In all, 44% had language delay, 36% gross motor delay, and 8% fine motor delay; 52% had an abnormal neurological exam, with speech abnormalities as the most common finding. Overall, 20 of 29 (69%) had neurodevelopmental abnormalities. Cerebral, but not posterior fossa, structural abnormalities were identified more often in children with abnormal versus normal neurodevelopmental outcomes (35% vs. 0%, P = .04). Neurodevelopmental abnormalities in young children with PHACE syndrome referred to neurologists include language and gross motor delay, while fine motor delay is less frequent. Prospective studies are needed to understand long-term neurodevelopmental outcomes.

Keywords

PHACE syndrome, neurodevelopmental abnormalities, cerebrovascular disease, brain structural abnormalities, retrospective analysis

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Infantile hemangiomas are common benign neoplasms of the vascular endothelium that are absent at birth, grow rapidly during infancy, and slowly regress over time.¹ Most infantile hemangiomas are small and well localized; “segmental” infantile hemangiomas, however, involve a territory of skin and may be associated with extracutaneous structural abnormalities.²,³ PHACE, an acronym proposed in 1996, is a neurocutaneous syndrome that describes the association of segmental infantile hemangiomas with one or more of the following structural abnormalities: posterior fossa malformations, arterial anomalies (cervical and intracranial), cardiovascular anomalies, and eye anomalies.²,⁴ In a prospective study of 108 infants with facial hemangiomas that measured ≥22 cm², 33 (31%) met criteria for PHACE.³

Cerebrovascular anomalies, present in 91% of children with definite PHACE, is the most common extracutaneous feature of the disorder, followed by cardiac (67%) and structural brain anomalies (52%).³ A study of children with cervical and intracranial arterial anomalies in PHACE found that the most common abnormalities were dysgenesis (56%), anomalous course or origin (39%), and narrowing (39%).⁵ Structural brain abnormalities have been reported in the posterior fossa (32%) and cerebrum (14%).⁵ These neuroanatomical and cerebrovascular anomalies may lead to the neurological sequelae that have been reported in PHACE syndrome, including seizures, stroke, and developmental delay.³
Our objective was to use a previously identified cohort of children with PHACE syndrome to describe their neurodevelopmental abnormalities. A secondary objective was to determine whether brain structural abnormalities could predict these neurodevelopmental outcomes.

**Methods**

This was a multicenter retrospective study of a previously identified cohort of children with PHACE syndrome from the University of California, San Francisco Benioff Children’s Hospital, Texas Children’s Hospital, and Children’s Hospital of Wisconsin. Approval from an ethical standards committee to conduct this study was received at each site; consent was waived.

**Participants**

Inclusion criteria were (a) diagnosis of PHACE syndrome by a pediatric dermatologist at any of the 3 participating study centers, meeting consensus criteria of definite PHACE, between 1999 and 2010, (b) age < 18 years, and (c) a documented clinical evaluation at ≥ 1 year of age by a child neurologist at any of the 3 participating study centers. Although the reason for a referral to a neurologist could not be well categorized in this retrospective study, chart review suggested that these children were typically referred for abnormalities seen on brain or cerebrovascular imaging, for concerns regarding development, or simply because of a diagnosis of PHACE syndrome, without specific neurologic or developmental concerns.

**Medical Record Review**

Clinical data were collected from medical records using standardized data abstraction forms with detailed data abstraction instructions to ensure consistency across the sites. A single reviewer at each site performed medical record abstraction; University of California, San Francisco investigators centrally reviewed and analyzed completed data collection forms. When questions arose regarding the abstracted data, University of California, San Francisco investigators reviewed redacted copies of source data, and made coding decisions regarding specific variables.

We collected data regarding gender, race, maternal age at delivery, PHACE syndrome characteristics, and pharmacological treatment for the hemangioma (steroids, propranolol, or vincristine). Congenital heart defects were defined as the presence of aortic arch anomalies or other cardiac anomalies associated with PHACE syndrome. Patent ductus arteriosus and patent foramen ovale were not categorized as defects.

Outcome variables for developmental delay included documented presence of motor or language delay, use of or referral to physical, occupational, or speech therapy, and pathological early handedness. Developmental delay was defined as any documented physician diagnosis of fine motor, gross motor, or language delay, or documentation of delayed milestones: walking at ≥ 15 months (gross motor delay); scribbling at ≥ 18 months (fine motor delay); first word at ≥ 14 months, less than a 5-word vocabulary at 18 months, or combining 2 words at ≥ 2 years (language delay).

Outcome variables for neurological examination included head circumference percentile, hypotonia (appendicular or axial), ataxia, and gait and speech abnormalities. Ataxia included limb ataxia (dysmetria) and midline ataxia (truncal or gait ataxia). Gait abnormality was defined as an unsteady, ataxic, or otherwise impaired gait. Speech abnormality was defined as dysarthria, aphasia, or other documentation of impaired expressive or receptive language. Other aspects of the neurological assessment that were abstracted included other cognitive and behavioral concerns, cranial nerve palsy, Horner’s syndrome, sensorineural hearing loss, hemiparesis, and hemiatrophy. Records were also reviewed for diagnoses of stroke, epilepsy, and chronic headaches.

**Neuroradiologic Review**

Two neuroradiologists (CPH and AJB), blinded to the clinical data, reviewed all available brain MRI and magnetic resonance angiography studies. Arterial anomalies were categorized into dysplastic or anomalous vessels, and stenotic or hypoplastic vessels. Brain structural abnormalities were categorized as either infratentorial, involving the brainstem or cerebellum, or supratentorial, involving the cerebrum.

**Segmental Hemangioma Review**

Data regarding the segmental hemangiomas were collected by the study pediatric dermatologist at each site (LIF, DWM, BAD) on review of photographs taken with patient consent. Segments were categorized into S1-S4 on a previously published facial map. S1 is defined as frontotemporal, with involvement of lateral frontal and anterior temporal scalp. S2 is defined as maxillary, involving the medial and lateral cheek sparing the preauricular region, nasolabial sulcus, and philtrum. S3 is defined as mandibular, including the skin overlying the mandible, the vermilion lip, and the preauricular region. S4 is defined as the frontonasal region. Segmental hemangioma data were further characterized as partially (< 50%) or fully (> 50%) occupying the specified segment.

**Statistical Analysis**

All statistical analyses were performed using Stata 11 (College Station, Tex) and alpha was set at .05. Because our sample was limited by referral bias, as only a subset of children with PHACE syndrome was referred to neurology, our primary analyses were descriptive. In an exploratory analysis, we tried to identify predictors of neurodevelopmental abnormalities within this select group of children referred to neurology. To determine whether data from the 3 sites could be combined, cohort characteristics and outcome variables were compared between sites using chi-squared test (or Fisher’s exact, where appropriate) for dichotomous variables and Kruskal–Wallis rank sum tests for continuous variables. After determining that there were no significant differences between sites, the data were combined for the remaining analyses.

In our analysis of predictors of neurodevelopmental abnormalities, our primary outcome variable was a dichotomous composite variable of abnormal neurodevelopmental outcome, defined as documentation of any developmental delays and/or any neurological exam abnormalities, or ongoing need for services (physical, occupational, or speech therapy) after one year of age. Secondary outcomes included motor delay, language delay, and hypotonia. Predictor variables assessed were gender, race, location of segmental hemangiomas (S1-S4), brain structural abnormalities (infratentorial or supratentorial), arterial anomalies, congenital heart defect, and pharmacological treatment of the hemangioma. Because hemangioma locations were not mutually exclusive, each segment (S1-S4) was treated as a dichotomous variable. Proportions of children with and without abnormal
neurodevelopmental outcome were analyzed using the chi-squared test (or Fisher’s exact when appropriate). Univariate logistic regression analysis was used to test for associations and determine odd ratios and 95% confidence intervals. Similar analyses were done for secondary outcomes.

Results

Cohort Characteristics

A total of 93 children received a diagnosis of PHACE syndrome from a pediatric dermatologist at 1 of the study centers and were entered into a registry. Of these, 29 (31%) had a clinical assessment by a child neurologist at ≥ 1 year of age and were therefore included in this analysis. The proportion with a neurological evaluation after the first birthday varied by site: 10/21 (48%) at University of California, San Francisco Benioff Children’s Hospital, 10/35 (29%) at Texas Children’s Hospital, and 9/37 (24%) at Children’s Hospital of Wisconsin. Cohort characteristics are summarized in Table 1; characteristics were similar among the 3 sites (data not shown). As is typical of PHACE, the majority of patients in the cohort were female (90%) and white/Caucasian (69%). A total of 13 patients (45%) were diagnosed with congenital heart defects at the median age of 3 months (range 0-39 months); the most common defect was coarctation of the aorta. In all, 10 patients received corrective cardiac surgery, and 1 patient was placed on bypass (duration, 72 minutes). Most of the 29 children had clinical imaging studies available for review: brain MRI (n = 26) and magnetic resonance angiography (n = 25). Brain structural abnormalities were seen in 50% of patients with imaging, and nearly all (92%) had cervical or cerebral arterial anomalies. Of 29 patients, 24 (83%) received corticosteroid treatment with either prednisone or prednisolone for their hemangioma. These patients were treated prior to the common use of propranolol in hemangioma treatment.

Neurodevelopmental abnormalities

Dates of neurological assessments ranged from June 2002 to July 2010, with the majority of assessments (90%) taking place in an outpatient setting. A total of 17 patients (59%) had multiple assessments (> 1 visit). The median age at time of the last assessment was 4 years, 2 months (range: 1 year 1 month to 12 years). Developmental assessments were documented in 27 (93%) of the 29 children with neurological assessments.

Overall, 19 (70%) of 27 had evidence of developmental delay, and 15 of 29 (52%) had an abnormal neurologic exam (Table 2). Motor delay was the most common developmental delay observed (44%); gross motor delays predominated over fine motor delays (36% vs 8%). However, the gross motor delay tended to be mild: the median age at walking among those 9 children who met our study definition of gross motor delay was 17 months, with a range of 14-30 months. The child who walked at 14 months met our study definition because of a documented physician diagnosis of gross motor delay; the child’s gross motor skills were noted to be clumsy. Of the 25 children with documented motor development, only 4 (16%) walked after 18 months of age. Language delay was documented in 40% of patients, and all those with language delay were receiving or were referred to speech therapy. Also, 7 patients (24%) were noted to have other cognitive and behavioral concerns including impulsivity (n = 2), attention-deficit/hyperactivity disorder (n = 2), “tactile sensitivity” (n = 1), oppositional defiant behaviors (n = 1), moderate mental retardation (n = 1), and dyslexia (n = 2).

Of the 17 patients who had their head circumference measured, 3 patients were macrocephalic (> 95th percentile), and 1 was microcephalic (< 5th percentile). Half of the children had
Table 2. Neurological Assessment of 29 Children With PHACE Syndrome Evaluated by a Neurologist at ≥ 1 Year of Age.

<table>
<thead>
<tr>
<th>Developmental assessment</th>
<th>No.</th>
<th>Totala %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at assessment, median (range)</td>
<td>4 years 2 months (1-12 years)</td>
<td></td>
</tr>
<tr>
<td>Head circumference percentile (n = 17), median (range)</td>
<td>55 (3-100)</td>
<td></td>
</tr>
<tr>
<td>Any abnormalities on neurologic exam</td>
<td>15</td>
<td>29 52</td>
</tr>
<tr>
<td>Abnormal speech (dysarthria, aphasia)</td>
<td>9</td>
<td>27 33</td>
</tr>
<tr>
<td>Abnormal gait</td>
<td>6</td>
<td>29 21</td>
</tr>
<tr>
<td>Hypotonia</td>
<td>5</td>
<td>29 17</td>
</tr>
<tr>
<td>Ataxia</td>
<td>4</td>
<td>29 14</td>
</tr>
<tr>
<td>Hemiparesis</td>
<td>3</td>
<td>29 10</td>
</tr>
<tr>
<td>Cranial nerve palsy</td>
<td>2</td>
<td>29 7</td>
</tr>
</tbody>
</table>

a The total reflects the number of children who had documented presence or absence of that feature or finding in their neurological evaluation.

Predictors of Neurodevelopmental Abnormalities

Overall, 20 of the 29 children met our composite study definition of abnormal neurodevelopmental outcome (Table 3). Brain structural abnormalities were present in 59% of children with abnormal outcomes, compared to 33% of those with normal outcomes (P = .22). Although supratentorial (ie, cerebral) structural abnormalities were less common than infratentorial ones, they appeared predictive, present in one third of children with abnormal outcome versus none of children with normal outcomes (P = .04). Infratentorial lesions were not predictive, although this study lacked sufficient power to detect a modest effect.

We performed additional analyses to explore the implications of infratentorial structural abnormalities on MRI. Of 12 children with infratentorial abnormalities, 6 (50%) had motor delay, 4 (33%) had language delay, and 3 (25%) had hypotonia. In univariate analyses, the presence of infratentorial abnormalities did not predict any of these secondary outcomes: odds ratio 3.0 (95% confidence interval 0.53-17) for motor delay, 1.1 (0.21-6.4) for language delay, and 2.0 (0.27-15) for hypotonia.

Pharmacological treatment for segmental hemangiomas (eg, steroids, vincristine, or propranolol) similarly did not predict either the primary or secondary outcomes (data not shown). Of the 24 patients who were treated with steroids and had a neurological assessment at ≥ 1 year of age, 5 patients (21%) had evidence of hypotonia, while 19 patients (79%) had normal tone.

Discussion

Knowledge of the neurological complications and neurodevelopmental outcomes in PHACE syndrome has been limited to case reports and small case series. We present the largest cohort to date of children with neurological assessments, and retrospectively describe their early neurodevelopmental abnormalities. The predominant findings included gross motor delay, language delay, gait and speech abnormalities, and hypotonia. Supratentorial brain structural abnormalities, though present in only a quarter of our cohort, appeared to be associated with abnormal neurodevelopmental outcome.

There are limited data on the neurological morbidity and outcomes seen in patients with PHACE syndrome. Reports describing smaller series of children with PHACE syndrome have described seizures, “borderline mental level,” and developmental delay. Although we cannot describe rates of abnormal outcomes in PHACE syndrome because of the obvious referral bias in our cohort, we found that 69% of those 29 children referred for a neurological assessment after their first birthday had a documented neurodevelopmental abnormality. If the 64 children who lacked a neurological evaluation are all neurologically normal, then the rate of neurodevelopmental abnormalities would be 22% (20/93), suggesting at least a lower limit of the rate of abnormal early outcomes. Gross motor and language delay were the most predominant findings. However, the motor delay tended to be mild; most children who met our study definition of gross motor delay still walked before 18 months of age. Our study measured only early outcomes; long-term consequences of the brain structural abnormalities in PHACE syndrome may not be apparent in infancy or early childhood, and children with PHACE syndrome may also acquire brain injury because of cerebral vascular anomalies. Hence, the full impact of PHACE syndrome on neurodevelopmental outcomes is underestimated by this study.

Other notable neurologic findings observed in this cohort included seizures, migraine-like headaches, and sensorineural hearing loss. Of the 3 patients with sensorineural hearing loss, 2 have been reported in a prior study. In that study, Duffy et al reported hearing loss in 6 patients and suggested that this may be an underrecognized risk. Steroid treatment in children can affect linear growth and diminish weight gain; however, these...
effects may be transient. Of children in our cohort who were treated with steroids, 21% had hypotonia; however, the incidence of hypotonia was not significantly increased in these children compared with those that did not receive steroids.

Although our cohort was biased because it included only those children referred to neurology, we performed an exploratory analysis to identify potential predictors of neurodevelopmental abnormalities. Supratentorial structural abnormalities were uncommon but were the only predictor of abnormal outcome observed in our cohort. These abnormalities included agenesis of the corpus callosum, gray matter heterotopia, and polymicrogyria, all of which have been associated with motor delay, language delay, behavioral disorders, and epilepsy outside of the setting of PHACE syndrome.

Infratentorial structural abnormalities were identified in 53% of patients who had an abnormal neurodevelopmental outcome, versus 33% of those with a normal outcome (odds ratio 2.3, 95% confidence interval 0.42-12). Although this difference was not significant, our study may have been underpowered to detect a difference, and prior literature indicates that the posterior fossa may play an important role in neurodevelopment. Cognitive and psychomotor developmental delays are not uncommon in patients with posterior fossa abnormalities (such as Dandy–Walker complex or enlarged cisterna magna). Speech and language disorders and severe behavioral disorders can also be seen, in addition to psychomotor developmental delay, in patients with unilateral cerebellar hypoplasia. Further studies are needed to assess the significance of infratentorial abnormalities in patients with PHACE syndrome. However, our study suggests that some children with such abnormalities may have normal outcomes.

The presence of congenital heart defects may also put children with PHACE syndrome at risk for abnormal neurodevelopmental outcome. Prior studies have identified motor delays in infants who received cardiac surgery, and suggested that those requiring surgery as neonates are at particularly high risk of adverse neurodevelopmental outcomes. Of 20 children in our study with abnormal neurodevelopmental outcomes, 6 (29%) had undergone cardiac surgery, compared to 4 (44%) of those with normal outcomes, but we were likely underpowered to detect a difference (P = .84).

Stroke, perhaps the most feared complication in PHACE syndrome, has been reported in several cases and in some cases been associated with a moyamoya pattern of vasculopathy.

### Table 3. Predictors of Neurodevelopmental Abnormalities Among 29 Children With PHACE Syndrome Evaluated by a Neurologist at ≥ 1 Year of Age (median: 4 years 2 months, range: 1 to 12 years).

<table>
<thead>
<tr>
<th>Neurodevelopmental Outcome</th>
<th>Abnormal n = 20</th>
<th>Normal n = 9</th>
<th>Odds Ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>18 / 20 (90)</td>
<td>8 / 9 (89)</td>
<td>0.89 (0.07-11)</td>
<td>.93</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td>.09*</td>
</tr>
<tr>
<td>White/Caucasian</td>
<td>12 / 20 (60)</td>
<td>8 / 9 (89)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Latino/Hispanic</td>
<td>6 / 20 (30)</td>
<td>0 / 9 (0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Black/African American</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Native American/Indigenous people</td>
<td>0 / 20 (0)</td>
<td>1 / 9 (11)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 / 20 (10)</td>
<td>0 / 9 (0)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Segmented hemangioma</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1</td>
<td>13 / 19 (68)</td>
<td>7 / 8 (88)</td>
<td>0.31 (0.03-3.1)</td>
<td>.32</td>
</tr>
<tr>
<td>S2</td>
<td>10 / 19 (53)</td>
<td>4 / 8 (50)</td>
<td>1.1 (0.21-5.8)</td>
<td>.9</td>
</tr>
<tr>
<td>S3</td>
<td>13 / 19 (68)</td>
<td>6 / 8 (75)</td>
<td>0.69 (0.11-4.7)</td>
<td>.73</td>
</tr>
<tr>
<td>S4</td>
<td>7 / 19 (37)</td>
<td>2 / 8 (25)</td>
<td>1.8 (0.27-11)</td>
<td>.59</td>
</tr>
<tr>
<td>Congenital heart defect</td>
<td>8 / 20 (40)</td>
<td>5 / 9 (56)</td>
<td>0.53 (0.11-2.6)</td>
<td>.44</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroid treatment</td>
<td>17 / 20 (85)</td>
<td>7 / 9 (78)</td>
<td>1.6 (0.22-12)</td>
<td>.64</td>
</tr>
<tr>
<td>Vincristine treatment</td>
<td>3 / 20 (15)</td>
<td>0 / 9 (0)</td>
<td>—</td>
<td>.22</td>
</tr>
<tr>
<td>Propanolol treatment</td>
<td>3 / 20 (15)</td>
<td>1 / 9 (11)</td>
<td>1.4 (0.13-16)</td>
<td>.78</td>
</tr>
<tr>
<td>Radiologic findings</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial anomalies, anya</td>
<td>14 / 16 (88)</td>
<td>9 / 9 (100)</td>
<td>—</td>
<td>.27</td>
</tr>
<tr>
<td>Dysplasia/anomalous</td>
<td>9 / 16 (56)</td>
<td>7 / 9 (78)</td>
<td>0.37 (0.06-2.4)</td>
<td>.29</td>
</tr>
<tr>
<td>Stenosis/hypoplasia</td>
<td>7 / 16 (44)</td>
<td>5 / 9 (56)</td>
<td>0.52 (0.12-3.2)</td>
<td>.57</td>
</tr>
<tr>
<td>Brain structural abnormalities, anyb</td>
<td>10 / 17 (59)</td>
<td>3 / 9 (33)</td>
<td>2.8 (0.52-15)</td>
<td>.22</td>
</tr>
<tr>
<td>Infratentorial abnormalities</td>
<td>9 / 17 (53)</td>
<td>3 / 9 (33)</td>
<td>2.3 (0.42-12)</td>
<td>.35</td>
</tr>
<tr>
<td>Supratentorial abnormalities</td>
<td>6 / 17 (35)</td>
<td>0 / 9 (0)</td>
<td>—</td>
<td>.04</td>
</tr>
<tr>
<td>Intracranial hemangiomasb</td>
<td>3 / 17 (18)</td>
<td>0 / 9 (0)</td>
<td>—</td>
<td>.18</td>
</tr>
</tbody>
</table>

* P value represents chi-square test for whole group comparison.

* Of 20 children with abnormal outcomes, 16, and all of the 9 children with normal outcomes, had cerebrovascular imaging available for review.

* Of 20 children with abnormal outcomes, 17, and all of the 9 children with normal outcomes, had brain parenchymal MRI available for review.
our study, only 2 children had received a diagnosis of stroke, as previously reported. However, the retrospective study design severely limits the ability to understand the true incidence of stroke in this population. Although cerebrovascular anomalies were common, few had hemiparesis, which is the most common finding after childhood stroke.

As indicated above, our study’s greatest limitation was that we assessed a select cohort of children referred to neurology clinic; hence, we could not describe the true prevalence of neurodevelopmental abnormalities among children with PHACE syndrome. Furthermore, only 59% of the children included in our cohort had > 1 neurological assessment, and the median age at last assessment was only 4 years, 2 months. Therefore, we have not captured all neurological sequelae that may be manifested, or acquired, later in life. Long-term follow-up of children with PHACE syndrome is needed to better understand the full impact of this disorder. Our study is also limited by a small sample size and is underpowered to detect anything but strong associations. Other limitations are the retrospective study design, which can result in missing data and misclassification. Uncommon variables such as Horner’s syndrome were assumed to be absent if not mentioned in the medical records. This presumption may result in the underdetection of some measured variables within our study.

Children with PHACE syndrome should be monitored for neurodevelopmental abnormalities so that they can receive timely and appropriate therapeutic interventions. Dedicated study of the association of neurological sequelae with neuroanatomical abnormalities in this syndrome would provide important prognostic information to families. Longitudinal studies must be performed to better understand the risk of neurological disability associated with PHACE syndrome. Currently, there is an ongoing prospective study looking at neurologic, cognitive, and radiologic outcomes in children ages 4-6 years with a diagnosis of PHACE syndrome.

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Author Contributions
HJF was involved with conceptualization and study design. JT and HJF were involved in data analysis and interpretation. JT, CPH, MB, BAD, DWM, AIB, and IJF were involved with data collection for the study. JT, LMN, and HJF wrote the first draft of the manuscript, and all authors were involved in critically revising the manuscript for content. All authors approved the final version for publication.

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Ethical Approval
Approval from an ethical standards committee to conduct this study was received at each site; consent was waived.

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