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Multicenter Study of Long-Term Outcomes and Quality of Life in PHACE Syndrome after Age 10

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Objective To characterize long-term outcomes of PHACE syndrome.

Study design Multicenter study with cross-sectional interviews and chart review of individuals with definite PHACE syndrome ≥10 years of age. Data from charts were collected across multiple PHACE-related topics. Data not available in charts were collected from patients directly. Likert scales were used to assess the impact of specific findings. Patient-Reported Outcomes Measurement Information System (PROMIS) scales were used to assess quality of life domains.

Results A total of 104/153 (68%) individuals contacted participated in the study at a median of 14 years of age (range 10-77 years). There were infantile hemangioma (IH) residua in 94.1%. Approximately one-half had received laser treatment for residual IH, and the majority (89.5%) of participants were satisfied or very satisfied with the appearance. Neurocognitive manifestations were common including headaches/migraines (72.1%), participant-reported learning differences (45.1%), and need for individualized education plans (39.4%). Cerebrovascular arteriopathy was present in 91.3%, with progression identified in 20/68 (29.4%) of those with available follow-up imaging reports. Among these, 6/68 (8.8%) developed moyamoya vasculopathy or progressive stenoocclusion, leading to isolated circulation at or above the level of the circle of Willis. Despite the prevalence of cerebrovascular arteriopathy, the proportion of those with ischemic stroke was low (2/104; 1.9%). PROMIS global health scores were lower than population norms by at least 1 SD.

Conclusions PHACE syndrome is associated with long-term, mild to severe morbidities including IH residua, headaches, learning differences, and progressive arteriopathy. Primary and specialty follow-up care is critical for PHACE patients into adulthood. *(J Pediatr 2024;267:113907)*.

The term PHACE syndrome was first coined in 1996 to describe the association between posterior fossa (PF) abnormalities, facial infantile hemangiomas (IHs), arterial anomalies, cardiac anomalies, and eye anomalies (Online Mendelian Inheritance in Man 606 519).[1] Sternal clefting, supraumbilical raphe, and other midline developmental anomalies, including hamartomatous growths, may also be present.[2,3] In 2001, Metry et al published a case series and review of the literature to determine the prevalence of each diagnostic feature.[4] Diagnostic criteria were created in 2009 and updated with consensus-derived care recommendations in 2016.[5,6] A recent comprehensive review discusses the history of PHACE in detail and provides updates since the

AIS	Acute ischemic stroke
IH	Infantile hemangioma
PF	Posterior fossa
PROMIS	Patient-Reported Outcomes Measurement Information System

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publication of the 2016 guidelines.[7] Long-term outcomes are largely unknown. Our study aimed to systematically measure health outcomes and health care utilization by people with PHACE syndrome in adolescence and adulthood.[8,9] The data provided will help to guide clinicians in counseling families at diagnosis and conducting health care maintenance over time.

Methods

This was a multicenter study with 16 participating sites identified through the Pediatric Dermatology Research Alliance and Hemangioma Investigator Group (**Supplemental File 1**; available at www.jpeds.com). Participating sites identified patients ≥10 years of age diagnosed with definite PHACE per Garzon et al.[6] Notification via the PHACE Syndrome Community and the PHACE Registry led to recruitment of 6 additional patients. Data collection and interviews for these participants were done by authors D.H.S., S.N.J., and J.K.B. After consent and assent were obtained, chart review was conducted by site-specific investigators using a standardized data abstraction form (**Supplemental File 2**; available at www.jpeds.com). A cross-sectional interview with each participant was conducted between July 2021 and September 2022 by investigators over video or in person, and data were collected with standardized intake templates (**Supplemental File 3**; available at www.jpeds.com). Data were entered into a shared REDCap database.[10]

All data collected through chart review were confirmed with patients/parents during the cross-sectional interview. Brain imaging reports at close to 1 year of life and most recent were reviewed and entered into REDCap.

Relevant Patient-Reported Outcomes Measurement Information System (PROMIS) scales available at https://www.healthmeasures.net/ were selected. Measured outcomes for children included: Global Health 7, Anxiety Short Form 8a, Depressive Symptoms Short Form 8a, and Peer Relationships Short Form 8a. Corresponding parent proxy forms (Parent Proxy Global Health 7, Parent Proxy Anxiety Short Form 8a, Parent Proxy Depressive Symptoms Short Form 6a, Parent Proxy Peer Relationships Short Form 7a) were also utilized. Forms for adult participants included: Global Health 10, Anxiety Short Form 8a, Depression Short Form 8a, and Ability to Participate in Social Roles and Activities Short Form 8a. T-scores were calculated using the HealthMeasures Scoring Service through the PROMIS website. For each scale, a t-score of 50 represents the average score of the healthy population with a SD of 10. T-scores of more or less than 50 denote more or less of each concept that a scale is measuring. Scoring ≥1 SD is considered clinically significant. PROMIS measures have been widely studied across the general population and multiple disease states and are considered valid and reliable. Further information on the validation process can be found at https://www.healthmeasures.net/explore-measurement-systems/promis/measure-development-research.

Imaging Review

All head/neck imaging reports were reviewed by a neuroradiologist with expertise in PHACE syndrome (either E.G. or C.P.H.). Stratification of cerebrovascular arteriopathy into low, intermediate, and high risk was established by the reviewers in accordance with criteria published by Garzon et al.[6] Risk was assigned as unknown if there was inadequate information on imaging reports or if there was not an available report from infancy. Progressive arteriopathy was defined as 1) increase in risk stratification score between the two scans, 2) evidence of progression of arteriopathy (new sites of arteriopathy or worsening involvement of known sites of arteriopathy as evidenced by new ectasia or tortuosity, new/progressive narrowing, or involvement of additional vessel segments) without change in risk score based on imaging report review, 3) mention of progression of arteriopathy in the report even if initial report was not available, or 4) report or description of moyamoya syndrome (a progressive arteriopathy), even if initial report was unavailable. In addition, two subgroups were further identified: those with moyamoya syndrome and those with new or progressive arteriopathy resulting in an "isolated" circulation at or above the level of circle of Willis (eg, moderate or severe narrowing or occlusion of intracranial vessels without collateral filling). A more detailed neuroradiologic analysis will be published separately.

Statistical Analysis

Logistic regression analyses were used to examine the following outcomes: participant-reported satisfaction with IH residua, IH late growth, progressive arteriopathy, participant-reported learning differences, special education/individualized education plans, and headaches/migraines. Variables included demographics such as age, sex assigned at birth, race, ethnicity; IH features including size, location (S1, S2, S3, S4), systemic treatments (propranolol alone, systemic steroids alone, propranolol + systemic steroids, none), subtype, morphology, history of ulceration in infancy; and manifestations of PHACE syndrome including presence of PF/structural brain abnormalities, cardiac anomalies, arterial anomalies, eye anomalies, and presence of >2 diagnostic features as a clinical severity proxy.

Given frequency of IH and potential impact on childhood development, multivariable analyses were run to evaluate patient self-confidence. Similar analyses were run on progressive arteriopathy in an effort to identify risk factors that would impact long term screening. Variables were identified a priori and included age, sex, race, IH size, location, subtype, morphology, residua size, surgical treatment in infancy, and ulceration in infancy to investigate self-confidence. IH size, location, arterial risk score, each diagnostic feature individually, and total number of diagnostic features met were used to investigate progressive arteriopathy. Given fewer number of cases of progressive arteriopathy, a series of multivariable models were run on sets of variables. Analyses were performed with SAS 9.4 (SAS Institute Inc, Cary, NC).

Table I. Patient demographics and PHACE syndrome criteria (n = 104)

Sex assigned at birth		**Diagnostic criteria**	
Female	89/104 (85.6%)	Hemangioma	104/104 (100%)
Male	15/104 (14.4%)	PF/Structural Brain	49/104 (47.1%)
Gender		Arterial anomalies	95/104 (91.3%)
Female	83/104 (79.8%)	Cardiac anomalies	54/104 (51.9%)
Male	14/104 (13.5%)	Eye anomalies	27/104 (26%)
Transgender male	1/104 (0.96%)	Midline anomalies	7/104 (6.7%)
Nonbinary	1/104 (0.96%)	**IH treatments**	
Race/ethnicity		Systemic	78/104 (75%)
Indigenous	3/104 (2.9%)	Propranolol	27/78 (34.6%)
Asian	7/104 (6.7%)	Nadolol	1/78 (1.3%)
Black	4/104 (3.8%)	Systemic steroids	64/78 (82%)
White	76/104 (73.1%)	Interferon alpha	5/78 (6.4%)
Other	4/104 (3.8%)	Laser	37/104 (35.6%)
Hispanic	21/104 (20.2%)	Surgical procedure	13/104 (12.5%)
Non-Hispanic	78/104 (75%)	Topical	9/104 (8.7%)

Results

A total of 104 of 153 patients who were contacted about participation enrolled in the study (68.0%). Demographics, clinical features, and morbidities are summarized in Table I. Average age was 16.5 years (SD = 8.5 years), median age of 14 years, and range of 10-77 years. Primary morbidities are described in detail below, with additional morbidities outlined in Table II.

IH

All but 1 patient (103/104) had a facial IH, and all but 1 (103/104) received treatment for their IH in infancy. The patient without a facial IH met criteria for definite PHACE by having a segmental IH of the neck, chest, and upper extremity.[6] Initial IH treatments are included in Table I. Thirteen of the 78 who received systemic treatments received oral beta-adrenergic blockers alone, 43/78 received systemic steroids alone, and 15/78 received both. Facial segment distribution is displayed in Figure 1, online; available at www.jpeds.com.

Most of the cohort (98/104; 94.2%) had some IH residua at the time of the interview (Figure 2, online; available at www.jpeds.com). Table III summarizes prevalence of each residua type, residua treatments, and participant-reported impact thereof. One-half (52/104) received treatments for IH residua, the most common being laser (46/104; 44.2%), predominantly pulsed-dye. Most reported being either "Very Satisfied" (45/104; 43.3%) or "Satisfied" (48/104; 46.2%) with the appearance of the IH and reported that the IH at the time of the interview either had "No Impact" on self-confidence (64/104; 61.5%) or "Only Somewhat of an Impact" (20/104; 19.2%). Those who had surgical resection or experienced ulceration in infancy were less likely to report a minimal impact on self-confidence (OR: 0.145 [0.045-0.465] $P = .001$; OR: 0.291 [0.104-0.812] $P = .018$). In multivariable analyses, surgical resection was still associated (OR 0.037 [0.002-0.813] $P = .036$) with a psychological impact but ulceration was not (OR 0.260 [0.035-1.928] $P = .19$). Other variables were not associated with satisfaction including type of systemic treatment in infancy or laser therapy for residua IH.

Head and Neck Arterial Anomalies

Arterial anomalies were present in 95/104 (91.3%). Imaging reports at around 1 year of life were available for 66/104 (63.5%), and follow-up imaging reports in childhood, adolescence, or adulthood were available for 68/104 (65.4%). On neuroradiologist review, 19/66 (28.8%) were considered low risk, 29/66 (43.9%) were intermediate risk, and 7/66 (10.6%) were high risk on imaging from approximately 1 year of life. Eleven of the 66 (16.7%) did not have enough detail to determine a risk category.

Twenty of the 68 (29.4%) with available follow-up imaging had evidence of progressive arteriopathy on imaging reports with a median age of identification of 10.5 years (range = 0.8-19 years) (Table IV). Five of these 20 (25%) were rated as "low risk" on initial imaging. The development of persistent headaches prompted reimaging in 9/20 (45%), while progressive arteriopathy was identified in 7/20 (35%) on routine screening without inciting symptoms. The presence of symptoms was unknown in the remaining 4/20. Progressive arteriopathy was associated with S4 IH location (OR: 4.7 [1.303-16.6] $P = .018$) and PF/structural brain anomalies (OR 10.2 [2.5-41.4] $P = .0012$). With multivariable analyses, the relationship observed between progressive arteriopathies and S4 IH location was attenuated when controlling for IH size (OR 3.4 [0.831-14.1], $P = .089$), additional facial segment involvement (OR 4.2 [0.865-20.3], $P = .075$), and diagnostic features individually (OR 3.2 [0.703], $P = .13$), but was not attenuated by initial arterial risk scores (low, intermediate, or high) (OR 9.0 [2.0-40.3], $P = .0041$) or multiple diagnostic features met by an individual (OR 3.9 [1.011-14.8], $P = .048$). The presence of PF/structural brain anomalies was still significantly associated with progressive arteriopathy when controlling for IH size (OR 15.9 [3.1-81.3], $P = .0009$), IH location (OR 8.7 [1.794-42.5], $P = .0073$), arterial risk score (OR 16.3 [2.8-94.2], $P = .0018$), other diagnostic features (OR 14.6 [2.6-82.4], $P = .0024$), and multiple diagnostic features met by an individual (OR 7.4 [1.551-35.1], $P = .0012$). The presence of progressive arteriopathy was not impacted by propranolol use in infancy (OR 2.1 [0.653-6.7], $P = .21$).

A subgroup analysis identified 6/68 (8.8%) with moderate to severe progressive changes. Five had evidence of moyamoya vasculopathy, while 1 had progressive stenoocclusion leading to an isolated circulation without collateral filling. All of these patients were either intermediate or high risk on initial arterial risk stratification. Severe progression was identified in children as young as 3 years old (in two patients) and up to the age of 18 years old (in 1 patient, likely due to lack of previous imaging). Two were on aspirin therapy prior to development of severe progression and three more started aspirin after moyamoya was identified. One patient was treated with propranolol in infancy, three were treated with systemic steroids, 1 with laser, and the other with

Table II. Additional findings identified among the cohort

IH late growth	13/104 (12.5%)	**Vision difficulty**	56/104 (53.8%)
Increased color	11/13 (84.6%)	Unilateral legal blindness	5/104 (4.8%)
Deep growth	2/13 (15.4%)	Eye surgeries	26/104 (25%)
Increased volume	6/13 (46.2%)	**Hearing loss**	18/104 (17.3%)
Additional neurologic		Conductive	3/18 (16.7%)
Seizures*	15/104 (14.4%)	Sensorineural	3/18 (16.7%)
Speech difficulty	36/104 (34.6%)	Mixed	6/18 (33.3%)
Participated in speech therapy	30/104 (28.8%)	Unknown	3/18 (16.7%)
Balance problems	28/104 (26.9%)	Use of hearing aids	12/104 (11.5%)
Difficulty swallowing	11/104 (10.6%)	**Dental**	
Tic disorders†	6/104 (5.8%)	Dental root problem	16/104 (15.4%)
Learning diagnosis		Defects in enamel	31/104 (29.8%)
ADHD	19/104 (18.3%)		
Dyslexia	10/104 (9.6%)		

ADHD, attention-deficit/hyperactivity syndrome.
*Report of ever having had a seizure.
†Including Tourette's, intention tremors, psychogenic movement disorder.

intralesional steroid injections. None of these patients progressed to acute ischemic stroke (AIS).

Two patients (1.9%) sustained an AIS, 1 at the age of 64 years and the other at the age of 16 years. The 64-year-old's stroke occurred spontaneously, while the 16-year-old's was perioperative in the setting of a corpus callosotomy for epilepsy. Initial arterial risk score was unavailable for both participants.

Brain Structural Abnormalities

Forty-nine of 104 (47.1%) had PF/structural brain anomalies, 13/49 (26.5%) had a Dandy Walker malformation, 30/49 (61.2%) had hypoplasia or dysplasia of the mid/hind brain, 9/49 (18.4%) had a midline brain anomaly, and 8/49 (16.3%) had malformation of cortical development (eg, polymicrogyria, gray matter heterotopia). Thirty-five had PF anomalies alone, and 14 had midline anomalies or a malformation of cortical development with and without concomitant PF anomalies.

Headaches

When asked if patients had ever had persistent, troublesome headaches either currently or in the past, 75/104 (72.1%) responded affirmatively; 47/104 (45.2%) had a migraine diagnosis. Nearly one-half (47/104; 45.2%) had severe enough headaches to require referral to neurology. **Table V**, online; (available at www.jpeds.com) provides additional detail on headaches. IH size of 10-15 cm in diameter was associated with headaches when compared with 5-10 cm (OR: 5.5 [1.235-24.1], $P = .025$).

Learning and Neurodevelopment

Forty-seven of 104 (45.1%) reported learning differences, and 41/104 (39.4%) were in or had needed special needs classes or individualized education plans. Four patients (3.8%) had severe developmental delay impacting daily life, two of whom were nonverbal. All four had PF/structural brain anomalies. Two had diagnoses of autism. PF anomalies alone (OR 2.7 [1.143-6.6], $P = .024$); OR 3.4 [1.347-8.5], $P = .0095$), structural brain anomalies with and without PF anomalies (OR 9.0 [2.4-33.7], $P = .0012$; OR 26.7 [3.2-220.5], $P = .0023$), and eye anomalies (OR 4.4 [1.433-13.5], $P = .0096$; OR 3.4 [1.222-9.6], $P = .019$) were associated with a higher frequency of learning differences and need for educational support, respectively. Of those without PF/structural brain anomalies (55/104), 12 (21.8%) reported

Table III. Types of IH residua, treatments, and patient reported impact

Residua type		**Residua treatments**	52/104 (50%)
Persistent IH	15/104 (14.4%)	Topical timolol	4/52 (7.7%)
Mix of IH and normal skin	20/104 (19.2%)	Oral propranolol	3/52 (5.8%)
Color change	74/104 (71.2%)	Steroid injections	1/52 (1.9%)
Textural change	41/104 (39.4%)	Systemic steroids	1/52 (1.9%)
Swelling/bulk	23/104 (22.1%)	Laser	46/52 (88.5%)
Difference in an anatomical landmark	33/104 (31.7%)	Surgical intervention	10/52 (19.2%)
Hair loss/thinning	11/104 (10.6%)		
Impact breast development	2/104 (1.9%)		
No residual changes	6/104 (5.8%)		
Patient reported satisfaction		**Patient reported impact on self-confidence**	
Very satisfied	45/104 (43.3%)	No impact	64/104 (61.5%)
Satisfied	48/104 (46.2%)	Somewhat of an impact	20/104 (19.2%)
Neither satisfied nor dissatisfied	8/104 (7.7%)	Moderate impact	8/104 (7.7%)
Dissatisfied	3/104 (2.8%)	Very impactful	5/104 (4.8%)
Very dissatisfied	0 (0%)	Extremely impactful	6/104 (5.8%)

Table IV. Details on progressive arteriopathies seen in the cohort (n = 20/68)

Average age	10.03 years
Median age	10.5 years
Age range	0.8-19 years
Arterial risk classification on initial imaging	
Low arterial risk	5/20 (25%)
Intermediate arterial risk	9/20 (45%)
High arterial risk	4/20 (20%)
Unavailable report or insufficient information	2/20 (10%)
Symptoms prompting reimaging	
Headaches	9/20 (45%)
None	7/20 (35%)
Unknown	4/20 (20%)
Progressive stenosis without moyamoya syndrome	8/20 (55%)
Progressive ectasia/tortuosity	7/20 (25%)
Progressive aneurysmal dilatation	5/20 (25%)
Moyamoya/critical stenosis (isolated circulation)	6/68 (35%)
Intermediate risk	3/6 (50%)
High risk	3/6 (50%)
Surgical intervention	3/6 (50%)
Aspirin therapy started	3/6 (50%)
Aspirin continued (already on medication)	2/6 (33.3%)

learning difficulties. S1 (OR 3.5 [1.333-9.0], $P = .011$) and S4 (OR 4.7 [1.983-11.2], $P = .0005$) IH locations were associated with a need for educational support. Arterial anomalies were not associated with learning difficulties (OR 7.6 [0.901-64.2] $P = .062$) or need for educational support (OR 4.6 [1.478-93.8] $P = .16$). Four of the 12 individuals who had head/neck arterial anomalies without other diagnostic criteria reported learning differences.

Cardiac, Aortic, and Brachiocephalic Vascular Anomalies

One-half (54/104; 51.9%) of the cohort had anomalies of the heart, aortic arch, or brachiocephalic arteries. Of these, 32/54 had aortic arch anomalies, 22 had coarctation of the aorta, and 8 had a right-sided aortic arch. Twenty-four of the cohort (23.1%) required surgery for aortic arch anomalies, and 6/24 (25%) needed repeat surgical repairs at ages 3 months to 22 years. Fifteen of 54 (27.8%) had an aberrant origin of the subclavian artery, and 2/54 (3.7%) had an aneurysm of a cardiac artery. Ten of the 54 (18.5%) had a ventricular septum defect.

Endocrine/Fertility

Nineteen of 104 patients (18.3%) had an endocrine disease including hypothyroidism (7/19), growth hormone deficiency (7/19), early/delayed puberty (4/19), hypopituitarism (2/19), and gonadotropin releasing hormone insufficiency (1/19). Three patients had been pregnant resulting in 7 healthy, full-term deliveries. Two of these patients experienced challenges with infertility but were ultimately able to become pregnant.

Psychosocial and Patient-Reported Outcomes

Twenty-one out of 104 (20.2%) had been diagnosed with depression, and 31/104 (29.8%) had a diagnosis of anxiety. Thirty-four of 104 (32.7%) reported experiencing psychological distress that had not been medically addressed. Of the 104 participants, 42 completed the pediatric PROMIS scales (42/81; 51.8%), 31 completed the parent proxy scales (31/81; 38.3%), and 18 adult participants completed the adult scales (18/23; 78.3%). Average T-scores and ranges are included in **Table VI**, online; (available at www.jpeds.com). Average global health scores were lower than population norms. Adults similarly scored lower than the population norm for "Ability to Participate in Social Roles and Activities."

Discussion

In this study, we aimed to characterize PHACE syndrome's long-term health outcomes in adolescence and adulthood. We identified a wide range in severity among long-term morbidities. Many participants reported no difficulties, and others had significant findings requiring long-term subspecialty follow-up. The knowledge from our current study will help inform anticipatory guidance and follow-up care, as well as serve as a basis for future studies. As has been previously reported, the major health impacts were in the following: IH residua, neurologic manifestations including headaches and to a lesser extent learning differences, and progressive cerebrovascular arteriopathy.

The IH of PHACE is typically large and prior studies have emphasized their increased risk for permanent sequelae.[11-13] Within our cohort, skin changes in the form of scarring or residual IH were high (94.2%), with 50% having received treatments for these residua. The prevalence is similar to those previously reported in other studies of severe IH in younger children.[14,15] Despite these skin changes, the majority of our participants reported satisfaction with the appearance of these residua at the time of the interview, though some commented on dissatisfaction in the past especially in middle school or elementary school years. Hermans et al documented a similar finding with 103 children reporting satisfaction on visual analog scales, which was weakly correlated with physician-rated residua severity.[15] Of note, 18.3% of our cohort reported that their IH had a moderate to extreme impact on their self-confidence, and history of ulceration and surgical treatments in infancy were associated with a greater impact. It is uncertain if this correlation relates to worse IH severity at baseline or subsequent scarring. The PHACE Syndrome Community (www.phacesyndromecommunity.org) may be particularly helpful for patients and families as a source of community support.

Neurologic manifestations were common, the most frequent being recurrent and functionally impairing headaches, reported in 72% of study subjects. More than one-third of our participants reported missing 1-2+ days of school or work per month due to headaches and 45.2% had seen neurology for headaches. Similarly, Yu et al reported headaches in 62.7% of 83 children with PHACE, while Stefanko et al reported 83% in 18 adult PHACE patients.[8,16] In our study, 38.7% reported headaches lasting >4 hours compared

with 39.6% in Yu et al's study and 63% in Stefanko et al's study. We found that larger IH size positively correlated with the presence of headaches and that headaches also occurred in people without severe arteriopathy. Possibly, headaches in PHACE may relate to less overt underlying vascular differences,[17] some of which may be too small to detect on conventional imaging modalities. Care providers need to be aware of the potential impact of headaches and–if persistent or severe–refer to neurologists with headache expertise.[7] Further research is necessary to identify best management practices to lessen headaches' impact on patients' lives.

Learning differences and developmental delay are important aspects of PHACE. A higher percentage of individuals reported learning differences (45.1%) and required individualized education plans (39.4%) than would be expected compared with national averages.[18] Similarly, in Stefanko et al's study of adult PHACE patients, 44% reported a learning disability.[8] There was a large range in reported deficits in our study, though our data were limited to participant report without formal testing. Prior studies have shown that, on average, individuals <18 years of age with PHACE do not score significantly lower compared with norms across multiple developmental domains; however, when analyzed individually more participants than expected scored at least 1 SD below the general population in ≥1 domain.[19,20] Based on these findings, we recommend regularly screening individuals with PHACE for learning challenges with formal evaluation and early intervention when indicated.[7] Management strategies need to be individualized to each patient. It is reassuring that arterial anomalies, the most common diagnostic criteria, were not associated with learning differences, though it is still possible for those with arterial anomalies alone to experience learning difficulties. Of those without PF/structural brain anomalies (55/104), a smaller number, 12 (21.8%), required educational support, which is closer to the United States national average of about 15%. Only 4 participants reported severe intellectual disability, emphasizing that this is likely uncommon.

When propranolol treatment for IH became widespread after initial reports of efficacy in 2008, a theoretical concern for effects on cognitive development was raised due to its ability to cross the blood brain barrier.[21] There has been report of early neurocognitive delay,[22] while other investigations in childhood and adolescence have not observed an increased risk.[23,24] Propranolol therapy was used for treatment of IH in infancy in 27/104 participants in our study and was not associated with patient-reported learning differences or educational support. Neurocognitive deficits relating to PF and structural brain anomalies is expected, though the etiology of deficits in participants without brain anomalies is less clear. The cause(s) of PHACE are not known, though there is evidence that it results from a genetic, environmental, or other event impacting fetal development between 6 and 9 weeks of gestation.[25] Resulting neurocognitive manifestations may arise from direct impact to developing neuroectoderm or from the sequelae of abnormal cerebrovascular development, possibly too small to identify on our imaging modalities. Further studies should continue to characterize learning differences and the possible risk factors identified herein (eg, PF anomalies with and without structural brain anomalies, eye anomalies, S1/S4 IH location) to identify best practices for evaluating development and establishing educational support.

Cerebrovascular arteriopathy is the most common extracutaneous finding in PHACE. The possibility of progressive arteriopathy and AIS is concerning to many families, and long-term outcomes have not been well characterized. Multiple small case series have described cases of worsening tortuosity, aneurysmal dilatation, and narrowing. A small number of cases progress to moyamoya syndrome, which may be treated with surgical revascularization to decrease the risk of stroke.[26-32] In our study, we found that 20/68 (29.4%) participants with serial imaging had progressive arteriopathy that ranged in severity. This proportion may be overestimated because of selection bias. Our study was also limited by lack of available imaging reports and lack of access to radiology images. In a prior study, 20.9% of 96 individuals with detailed radiologic imaging had some form of progressive arterial narrowing.[33] We found that PF/structural brain anomalies were associated with progressive cerebrovascular arteriopathy, suggesting that individuals with PF/structural brain anomalies may benefit from imaging surveillance for progressive changes. Future studies should be designed with systematic review of vascular imaging to further study this association. Importantly, not all progressive arterial changes will be clinically significant. Our subgroup analysis identified that <10% had significant progressive changes manifesting as moyamoya vasculopathy or isolated circulation. Due to the limited number of cases, further statistical analysis was not done on this subgroup. The frequency and number of repeat imaging to capture clinically significant progression is still not clear. Study methodology and sample size are not sufficient to determine whether propranolol has a protective effect on progressive arteriopathy, but the majority (5/6) of those with significant progression to moyamoya/isolated circulation did not receive propranolol therapy in infancy. Though propranolol's mechanism of action is not fully elucidated, it does influence vascular endothelial growth factor pathways that could alter progressive cerebrovascular changes.[34] Further prospective studies on propranolol's impact on progressive changes are needed. AIS, importantly, was rare in our cohort occurring in only 1.9% of subjects, but has been reported elsewhere.[27,28] It remains to be seen if arterial risk scores, originally created through expert consensus to estimate risk for AIS, are associated with this outcome.[6]

Other findings in PHACE may require long-term specialty follow-up with ophthalmology, endocrinology, audiology/ENT, and dentistry (**Table II**) as well as with other specialists such as mental health clinicians. Notably, almost one-third reported psychological distress that they felt had not been treated or addressed. This highlights the importance of clinicians inquiring into patients' mental health and providing necessary services when appropriate. Additionally, pediatric, parent proxy, and adult global health scores on average were lower than the general population. To put our participants' scores into context, both pediatric and parent proxy scores were lower on

average than children with uncontrolled asthma[35] and similar to pediatric patients with systemic lupus.[36] Our adults had lower scores than population norms for Ability to Participate in Social Roles and Activities but were higher than published averages among rheumatic conditions (eg, systemic lupus, rheumatoid arthritis).[37] Notably, regardless of these scores, there were multiple participants who reported very minimal impact from PHACE, and other forms for depression and anxiety did not differ from population norms. Further evaluation should aim to identify those at risk for impairment.

This is the largest cohort of adolescents and adults with PHACE. Given the overall prevalence of PHACE, obtaining significant numbers to ensure proper power for all outcomes was not possible. Additional limitations include selection bias and recall bias possibly resulting in over-representing individuals with severe disease. The higher prevalence of PF/structural brain anomalies in our cohort compared with prior studies may serve as evidence of this skew in severity.[38,39] The younger average age of the cohort limits generalizability to older adults. Reliance on self-reporting when data were missing may have impacted the prevalence of certain data. Rapid advancements in radiologic imaging quality make longitudinal comparisons difficult and may overestimate progressive arteriopathy. There are limitations to the neuroradiologist review of imaging reports which could have resulted in misclassification of risk score and progressive arteriopathy. Conducting interviews during the COVID-19 pandemic may have affected patient reported outcome scores.

Overall, PHACE is a condition that is typically diagnosed in infancy, and close medical attention is paid during the early years of life. However, follow-up may not continue which can result in a lack of patient and family support and less surveillance for longer-term sequelae. Our investigation gives new insights into long-term outcomes of PHACE and highlights symptoms and experiences during adolescence and adulthood. Though many participants reported minimal impact without concerns, given the range of outcomes identified and the possibility of findings with significant impact, we recommend that patients with PHACE have periodic and long-term follow-up for its potential associated morbidities. Recommendations for age-based evaluation have been proposed.[7] Studies should continue to investigate PHACE syndrome and its potential long-term outcomes to further update consensus guidelines in the future.■

CRediT Authorship Contribution Statement

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Declaration of Competing Interest

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