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PHACE syndrome: A review

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ABSTRACT

PHACE syndrome is a neurocutaneous disorder consisting of *p*osterior fossa brain abnormalities, facial infantile *h*emangioma, *a*rterial anomalies, *c*ardiac anomalies (most commonly coarctation of the aorta), and *e*ye anomalies. While the cutaneous finding of infantile hemangioma represents the most clinically apparent feature, extracutaneous findings—specifically, developmental abnormalities of the aorta and medium-sized thoracic, cervical, and cerebral arteries—are common and pose significant potential morbidity and mortality. Cerebral arteriopathy can be progressive and lead to arterial ischemic stroke in childhood and increased stroke risk in adulthood; headache and neurodevelopmental symptoms are also common. Thus, it is important for pediatric neurologists to be familiar with this disorder and its potential structural and functional neurological sequelae. This review article summarizes the clinical features, diagnostic considerations, epidemiology, and management of this condition with an emphasis on features most pertinent to the practicing pediatric neurologist.

Introduction and Historical Context

A 1978 publication by Pascual-Castroviejo first described the association of external facial capillary hemangiomas with intracranial vascular malformations in a series of 7 patients, 3 of whom also had cyanotic congenital heart disease.[1] The acronym PHACE syndrome was initially proposed in 1996 by Frieden and colleagues in a publication that described 43 cases sharing features of large facial hemangiomas along with arterial, central nervous system, and ophthalmologic anomalies.[2] The occasional presence of ventral sternal defects such as sternal cleft or supraumbilical raphe has led some to use the acronym PHACES to describe the syndrome. In 2009, Metry and colleagues proposed initial diagnostic criteria for definite or possible PHACE syndrome, based on the presence of major and minor criteria involving cerebrovascular, structural brain, cardiovascular, ocular, and ventral/midline organ systems, in addition to the characteristic facial hemangioma.[3] A multidisciplinary expert panel subsequently published revised diagnostic criteria in 2016, along with recommendations to guide screening and diagnostic evaluations in at-risk patients and proposed guidelines for ongoing clinical care.[4]

Clinical Features

Cutaneous Manifestations

The hallmark of PHACE syndrome, seen in nearly all cases, is the presence of a large, segmental infantile hemangioma (IH) involving the face, scalp, or cervical region. The term "segmental" indicates a lesion covering an anatomic territory or region, rather than a single focal point. In a 2010 multicenter prospective study of 108 infants with large (greater than 22 cm^2) IH, nearly one-third (33 infants, or 31%) had more than 1 extracutaneous finding meeting criteria for PHACE.[5] Infants with larger hemangiomas or IH affecting the upper face (frontotemporal and frontonasal segments) were more likely to have PHACE syndrome. While the face is by far the most common location, large and segmental IH on the occipital, upper thoracic, trunk, and proximal upper limb regions have also been described in individuals meeting criteria for PHACE syndrome.[6] IH may appear as telangiectasia, solitary lesions, confluent plaques, or small papules in a specific distribution.[7] The hemangioma may be absent or faintly present as a precursor lesion at the time of birth, proliferating over the first several months of life before stabilizing and, over the course of years, often undergoing spontaneous involution.[8] Fig. 1 demonstrates 2 examples of infantile hemangioma involving the frontotemporal and maxillary facial segments.

Neurological Manifestations

The neurological manifestations of PHACE syndrome include structural abnormalities of the brain parenchyma and of the major blood vessels of the head and neck, as well as signs and symptoms largely attributable to these structural anomalies. Abnormalities of the brain parenchyma are typically unilateral, found ipsilateral to the facial

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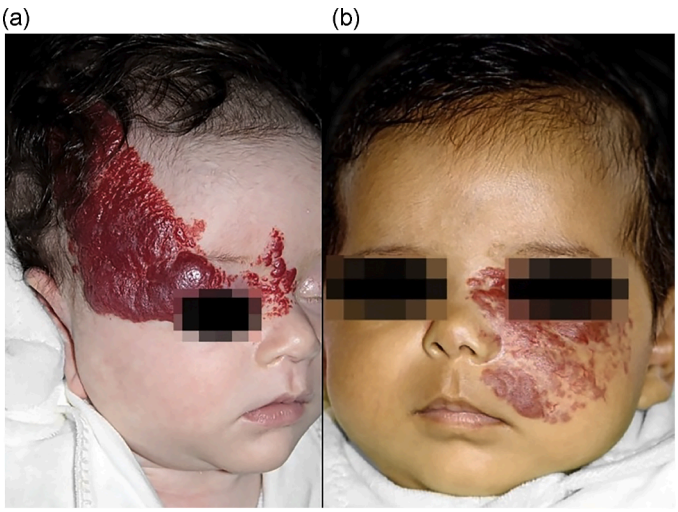

Fig. 1. Infantile facial hemangioma involving the frontotemporal segment (a) and maxillary segment (b). Used with permission from Rotter et al, 2018.

hemangioma. Most common are posterior fossa malformations, seen in up to 80%.[4] These include focal cerebellar dysplasia and various cystic malformations, including Dandy-Walker malformation.[9] A wide range of cerebral malformations has been described, including congenital cystic lesions, dysplasia, diffuse cerebral volume loss, neuronal migration abnormalities, and midline and pituitary defects.[9] Very rarely, extracutaneous hemangioma may occur intracranially, including in the auditory canal or cavernous sinus, ipsilateral to cutaneous IH and CNS anomalies.

Vascular malformations of the head and neck represent the most common extracutaneous anomaly in PHACE syndrome, occurring in at least 70% to 90% of cases.[10,11] These typically affect the large- and medium-sized arteries of the head and neck, nearly always ipsilateral to the cutaneous hemangioma. In a review of 115 patients with PHACE syndrome, 89 (77.4%) had congenital and/or progressive vascular anomalies.[11] Hess and colleagues characterized the arteriopathy in 70 individuals with PHACE syndrome: the most common abnormality was dysgenesis (including tortuosity and aneurysms), seen in 56%, followed by anomalous course and/or origin, narrowing, or nonvisualization.[10] In this series, arteriopathy most commonly affected the internal carotid artery (ICA) and its embryonic branches, followed by the middle cerebral artery (MCA), anterior cerebral artery (ACA), and posterior cerebral artery (PCA). Additional anomalies include persistent embryonic arterial segments including some embryonic carotid-basilar connections. Fig. 2 shows examples of typical vascular anomalies. Serial neuroimaging has identified a small but significant percentage of steno-occlusive arterial lesions to be progressive, and moyamoya-like vasculopathy has been observed.[11,12] While the vast majority of cases affect the arterial system only, cavernous malformations and arteriovenous malformations have been reported.[13,14]

Individuals with PHACE syndrome are at increased risk for arterial ischemic stroke (AIS). Risk factors include presence of flow-limiting arterial narrowing, often progressive, and risk of thromboembolism related to cardiac and supra-aortic lesions, described in further detail below. In a 2012 case series and review, Seigel and colleagues reviewed 22 published cases of AIS in individuals with PHACE syndrome.[15] Twenty-one of the 22 had a severe underlying arteriopathy: in the 20 cases in which magnetic resonance angiography (MRA) or conventional angiography was obtained or available for review, 19 (95%) had narrowing or nonvisualization of at least 1 great cerebral vessel; anterior and posterior arteriopathy was noted in 16 (80%) and moyamoya-like vasculopathy in 4 (20%). Cardiovascular anomalies were also seen in 15 of 22, most commonly coarctation of the aorta in 13. Age at stroke presentation ranged from 3 months to 5 years, with the most common presenting symptoms being seizure and/or hemiparesis. In a 2024 analysis published by Wisniewski et al., the strongest predictors of cerebrovascular accident (CVA) in PHACE syndrome were severe tortuosity, hypoplasia, or absence of at least 1 main cerebral artery, and presence of persistent embryonic arteries.[16]

Headache represents a significant neurological symptom in PHACE syndrome. Multiple longitudinal case series and surveys have reported headache prevalence of up to 89%.[17–19] In a cross-sectional survey of families in 2 PHACE syndrome registries, 62.7% of respondents reported headache, with the mean age of onset of 48.8 months; this represents a younger age of onset and higher frequency of headaches compared to children without PHACE syndrome.[17] Migraine features were common, including nausea, vomiting, photophobia, and phonophobia. While a significant percentage of individuals ultimately receive a primary headache diagnosis, most commonly migraine, secondary headache may occur due to stroke, moyamoya syndrome, or hydrocephalus. New headache should therefore prompt evaluation for secondary cause with updated MRI. Of note, arterial abnormalities are a relative contraindication to vasoconstrictive medications frequently prescribed for migraine treatment, including triptans and dihydroergotamine, necessitating alternative treatment options for many of these individuals.

Hearing impairment impacts a significant proportion of individuals with PHACE syndrome.[20] Sensorineural hearing loss may occur ipsilateral to the IH if the IH involves cranial nerve VIII. Less commonly, conductive hearing loss may result from eustachian tube compression or tympanic membrane involvement.

Developmental delay and long-term neurocognitive impairment have also been reported in a significant percentage of patients with PHACE syndrome. The most common developmental delays impact speech and language, gross motor, and less commonly fine motor skills.[21] Speech and language delays may occur secondary to hearing loss, prolonged hospitalizations, lip or oropharyngeal or airway hemangiomas, or brain structural abnormalities. In a multicenter, retrospective study characterizing long-term outcomes in individuals with

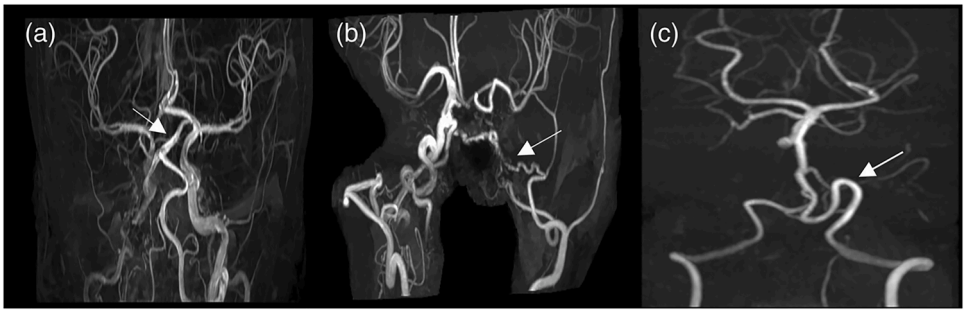

Fig. 2. Magnetic resonance imaging and maximum intensity projection time-of-flight magnetic resonance angiography showing arterial abnormalities seen in patients with PHACE syndrome. (a) Persistence of primitive vessels (arrow). (b) Diffuse narrowing (arrow). (c) Vessel tortuosity, with kinking of vertebral artery (arrow). Adapted with permission from Hausman-Kedem et al., 2023.

PHACE syndrome, 47 of 104 patients reported learning difficulties, and 41 were in special education classes or had an individualized education plan. Attention-deficit/hyperactivity disorder and dyslexia were the most frequent diagnoses, in 18.3% and 9.6%, respectively.[18]

Lastly, neurological manifestations may include neurological examination abnormalities and epilepsy. Neurological examination abnormalities, reported in up to 50% of patients, include speech abnormalities, gait abnormalities, hypotonia, hemiparesis, and cranial nerve palsies. Tangtiphaiboontana and colleagues found supratentorial structural abnormalities to be predictive of abnormal neurodevelopmental assessment.[21] Epilepsy occurs in a small percentage and may be secondary to stroke history or cerebral cortical malformation.[19,22]

Cardiovascular Manifestations

After cerebrovascular findings, cardiovascular anomalies constitute the most common extracutaneous manifestations of PHACE syndrome. Cardiac and/or aortic abnormalities are reported in up to two-thirds of individuals.[23,24] In a 2013 review of the International PHACE Syndrome Registry, the most common cardiovascular finding was aberrant origin of the subclavian artery, present in 21% of patients, followed by coarctation of the aorta, present in 19% of patients.[24] These two findings often co-occur, and coarctation may be missed clinically on 4-extremity blood pressure assessment due to the subclavian artery arising distal to the obstruction. Intracardiac involvement may include ventricular septal defect, atrial septal defect, pulmonary stenosis, aortic valve defect without arch anomaly, and rarely complex congenital heart disease such as tetralogy of Fallot or tricuspid atresia.[5,24] Notably, congenital heart disease is a predictor of cervical or cerebral arterial anomalies, with 92% of registry patients with cardiovascular anomalies also demonstrating cervical or cerebral arterial involvement.[24]

Other Manifestations

Named in the syndrome's acronym, eye abnormalities constitute an important manifestation of PHACE syndrome, most often co-occurring with an ipsilateral facial hemangioma. These include microphthalmia, optic nerve hypoplasia, persistent fetal vasculature, and morning glory disc anomalies.[3] Morning glory disc anomaly, so named after its resemblance to a morning glory flower, consists of a funnel-shaped excavation in the optic disc, with surrounding chorioretinal pigmentary abnormalities and an unusual distribution pattern of retinal blood vessels radiating outwards from the disc margin. Facial hemangioma may involve the ocular structures, and amblyopia, proptosis, and ptosis are commonly seen when the eye is involved; less common are cataracts, optic atrophy from optic neuropathy, and heterochromia.[25]

Dental anomalies have been more recently recognized in PHACE syndrome. Enamel hypoplasia was identified in nearly 30% in a 2012 study of 18 children with PHACE, all of whom had intraoral hemangiomas.[26] Early dental screening is critical for these individuals due to increased risk of dental caries.

Dysphagia and feeding disorders are also reported, typically related to location of facial hemangioma or poor oral motor coordination. Similar factors impact speech and language development. Risk is highest in those with posterior fossa malformations, hearing loss, history of cardiac surgery, and hemangiomas involving the lip, oropharynx, or airway.[27]

PHACE syndrome carries increased risk of endocrine disease, most frequently thyroid dysfunction and hypopituitarism with growth hormone deficiency.[28,29] Hypopituitarism may also manifest as hypogonadotropic hypogonadism and adrenal insufficiency, and may impact linear growth.[28] Ectopic thyroid tissue and dysgenesis or malformations of the thyroid have been reported, as well as pituitary dysgenesis manifesting as empty sella turcica on MRI.[29,30] Neonatal hypoglycemia in infants with suspected PHACE should prompt endocrinological evaluation. Early or delayed puberty is seen in some individuals, and long-term challenges with infertility have been reported in a small number.[18]

PHACE syndrome also poses challenges in psychological well-being and quality of life for both patients and families. Families of infants with IH report disbelief, guilt, sadness, panic, and fear related to their child's hemangioma.[31] Even after treatment, skin changes from scarring or residua of IH in some individuals may impact self-confidence. In their 2024 multicenter longitudinal outcomes study of patients with PHACE syndrome older than 10 years of age, Braun and colleagues elicited reports of clinically diagnosed depression in 20%, anxiety in 30%, and psychological distress not medically addressed in more than 32%.[18]

Etiology and Pathophysiology

The pathogenesis of PHACE syndrome is unknown. Based on the pattern of the segmental IH, which correlates with early segments in embryonic craniofacial development, and ipsilateral associated malformations, it is hypothesized that an error in or insult to embryogenesis between 3 and 12 weeks of gestation may account for the constellation of findings.[11,32,33] A genetic etiology has not been identified, and the syndrome does not appear to be hereditary.

Epidemiology

The exact incidence of PHACE syndrome is not well described, but well over 300 cases have been reported in the literature.[8,33] Risk of PHACE syndrome in an infant with IH is 2% to 3%, and if the IH is large (surface area of 22 cm^2 or greater) or segmental, the likelihood of associated findings consistent with PHACE syndrome is 20% to 31%.[5,8] It predominantly affects females, with a female to male ratio of 9:1.

Diagnostics

Diagnostic Criteria

In 2016, Garzon and colleagues published revised diagnostic criteria for PHACE syndrome, displayed in Table 1. The updated criteria accounts for variation in location of the typically occurring facial hemangioma. A definitive diagnosis may be made in a child with hemangioma of the face or scalp greater than 5 cm in diameter who also has either 1 major or 2 minor criteria, or in the presence of hemangioma of the neck, upper trunk, or trunk and proximal upper extremity along with 2 major criteria. Rarely, a child does not have a hemangioma but has multiple other associated anomalies typically seen with the syndrome. Possible PHACE syndrome may be attributed if there is hemangioma of the head greater than 5 cm in diameter along with 1 minor criterion; hemangioma of the neck, upper trunk, or trunk and proximal upper extremity with 1 major or 2 minor criteria; or no hemangioma with 2 major criteria.[4]

Screening and Surveillance

In their 2016 consensus publication, Garzon and colleagues also addressed clinical screening, surveillance, and care guidelines for PHACE syndrome.[4] All infants with a large segmental IH on the face or scalp should undergo screening evaluation for PHACE. Screening evaluation should also be undertaken in those without IH but who have 2 major criteria of PHACE syndrome, and considered in infants with 1 major criterion and large segmental hemangioma of the neck, upper trunk, or trunk and proximal upper extremity. Evaluation should include a complete physical examination; screening echocardiogram followed by cardiac MRI/MRA for further delineation of arch and brachiocephalic anatomy if abnormalities are identified; and brain MRI with and without gadolinium contrast and MRA of the head, neck, and aortic arch. Gadolinium contrast is helpful to demonstrate the full extent of cutaneous

Table 1
Revised diagnostic criteria, reproduced with permission from Garzon et al., 2016.

Organ systems	Major criteria	Minor criteria
Arterial anomalies	Anomaly of major cerebral or cervical arteries*	Aneurysm of any of the cerebral arteries
	Dysplasia† of the large cerebral arteries	
	Arterial stenosis or occlusion with or without moyamoya collaterals	
	Absence or moderate-severe hypoplasia of the large cerebral and cervical arteries	
	Aberrant origin or course of the large cerebral or cervical arteries except common arch variants such as bovine arch	
	Persistent carotid-vertebrobasilar anastomosis (proatlantal segmental, hypoglossal, otic, and/or trigeminal arteries)	
Structural brain	Posterior fossa brain anomalies	Midline brain anomalies
	Dandy-Walker complex	Malformation of cortical development
	Other hypoplasia/dysplasia of the mid- and/or hind brain	
Cardiovascular	Aortic arch anomalies	Ventricular septal defect
	Coarctation of the aorta	Right aortic arch/double aortic arch
	Dysplasia*	Systemic venous anomalies
	Aneurysm	
	Aberrant origin of the subclavian artery with or without a vascular ring	
Ocular	Posterior segment abnormalities	Anterior segment abnormalities
	Persistent hyperplastic primary vitreous	Microphthalmia
	Persistent fetal vasculature	Sclerocornea
	Retinal vascular anomalies	Coloboma
	Morning glory disc anomaly	Cataracts
	Optic nerve hypoplasia	
	Peripapillary staphyloma	
Ventral/midline	Anomaly of the midline chest and abdomen	Ectopic thyroid hypopituitarism
	- Sternal defect	Midline sternal papule/hamartoma
	- Sternal pit	
	- Sternal cleft	
	- Supraumbilical raphe	

Definite PHACE		
Hemangioma >5 cm in diameter of the head including scalp PLUS 1 major criterion or 2 minor criteria	Hemangioma of the neck, upper trunk, or trunk and proximal upper extremity PLUS 2 major criteria	
Possible PHACE		
Hemangioma > 5 cm in diameter of the head including scalp PLUS 1 minor criteria	Hemangioma of the neck, upper trunk, or trunk and proximal upper extremity PLUS 1 major or 2 minor criteria	No hemangioma PLUS 2 major criteria

*Internal carotid artery, middle cerebral artery, anterior cerebral artery, posterior cerebral artery, or vertebrobasilar system.
† Includes kinking, looping, tortuosity, and/or dolichoectasia.

hemangioma and delineate subglottic, periorbital, and intracranial hemangioma(s). Genetic testing is not part of the recommended diagnostic evaluation. Electroencephalogram may be performed as clinically indicated but is not recommend as part of routine screening.

Ongoing neurological and/or neurosurgical surveillance is often warranted based on initial imaging findings. In general, the presence of a structural brain lesion warrants referral to a pediatric neurologist and/or neurosurgeon to evaluate for associated symptoms, including developmental delays, headaches, seizures, or signs of increased intracranial pressure. While most structural brain lesions in PHACE syndrome are static, posterior fossa cystic abnormalities such as Dandy-Walker malformation and arachnoid cyst may develop cystic enlargement and hydrocephalus and should be monitored by a pediatric neurosurgeon.

Related to risk of AIS, Garzon and colleagues propose three risk categories—low, intermediate, and high—to guide ongoing surveillance based on the results of initial MRA, although further evidence is needed to formally validate this stratification.[4] The low-risk category includes vascular anomalies seen in the general population thought to have no or minimal hemodynamic impact, such as persistent embryonic arteries, anomalous arterial origin or course, or circle of Willis variants. The intermediate-risk category includes nonstenotic arterial dysgenesis, or narrowing or occlusion of arteries proximal to the circle of Willis, assuming patency of the circle of Willis. Those in the high-risk category include individuals with significant (greater than 25%) narrowing or occlusion of 1 of the arteries at or above the circle of Willis, or multiple arterial stenoses, without adequate collateral circulation; cerebrovascular stenosis concomitant with coarctation of the aorta; and brain parenchyma findings indicating chronic or silent ischemia. Individuals at more than low risk of stroke ideally should be evaluated by a specialist with expertise in pediatric stroke. Optimal timing of ongoing surveillance imaging has not been clearly defined, but it has been proposed that individuals in the intermediate-risk category should have at least one instance of repeat MRI and MRA imaging, ideally at an age when sedation is no longer needed; and those at high risk should have repeat imaging at 6 months and 1 year, and thereafter on a case-by-case basis. If progressive vascular changes are identified, evaluation with catheter angiography may be warranted. The desire to monitor progression of vascular pathology must be balanced with the need to undergo repeated rounds of anesthesia to obtain good-quality imaging in small children.

Additional screening recommendations include hearing screening in neonates or at the time of PHACE syndrome diagnosis, if not previously completed. Those at higher risk for hearing impairment should have at least one follow-up hearing test. Children at high risk for speech and language impairment, including those with posterior fossa malformations, lip/oropharynx or airway hemangiomas, hearing loss, or history of cardiac surgery should be evaluated by a speech-language pathologist by the age of 24 months. If structural pituitary abnormalities are identified, referral to a pediatric endocrinologist is recommended. Finally, given potential for psychological comorbidities with PHACE syndrome, there should be a low threshold to refer patients for behavioral health assessment and support as needed.

Management

Management of PHACE syndrome primarily consists of treatment of the IH, management of cardiac disease, and monitoring for complications of cerebrovascular involvement. After an initial period of proliferation, facial hemangiomas tend to undergo a natural involution. However, pharmacological treatment of the hemangioma should be considered for those at highest risk of complications, including ulceration, impairment of vital function (vision or airway compromise), or risk of permanent disfiguration.[34] Due to the large size of the IH

characteristic of PHACE syndrome, this is a pertinent consideration for many individuals. Systemic propranolol is the treatment of choice and can be quite effective in inducing regression. The potential for adverse effects, such as hypotension, bronchoconstriction, hypoglycemia, bradycardia, and hyperkalemia, must be carefully weighed against the benefits; therapy initiation may take place in an inpatient setting to allow for close monitoring. Use of propranolol is somewhat controversial in those with significant arterial disease, as hypotension may increase the risk of CVA, and should be undertaken with caution.

Anomalies of the heart, aortic arch, or brachiocephalic arteries require close serial monitoring for progression and, in some cases, surgical intervention. Roughly one-third of patients with cardiac or arch anomalies undergo corrective surgical intervention, and a small percentage require a repeat procedure due to recurrent stenosis.[4,35] The presence of concomitant cerebrovascular lesions necessitates close neurological monitoring, particularly around the time of cardiopulmonary bypass, due to increased risk for ischemic brain injury.

Additional management considerations apply to individuals at intermediate or high risk of stroke. Unilateral narrowing or occlusion of a single artery may herald greater risk for CVA later in life, including due to atherosclerotic disease or traumatic vascular injury to the uninvolved side; these patients should avoid contact sports and activities involving extreme neck positions. In individuals suspected to be at high risk of AIS, prophylactic aspirin therapy at a dose of 4-5 mg/kg/d (up to 81mg daily) should be considered. Revascularization may be indicated for progressive steno-occlusive disease, and multiple groups have reported good response to pial synangiosis in individuals with PHACE syndrome and associated moyamoya vasculopathy.[36,37]

Differential Diagnosis

PHACE syndrome must be distinguished from other neurocutaneous vascular syndromes also presenting with facial vascular lesions in early infancy, most notably Sturge-Weber Syndrome (SWS). In the neonatal period, the early stage facial hemangioma characteristic of PHACE syndrome may resemble the “port wine stain” capillary malformation of SWS. While the facial hemangioma of PHACE syndrome typically evolves with time, proliferating over the first few months of life and later undergoing involution, the capillary malformation of SWS is fully present at birth and does not regress, with color frequently darkening over time. Another distinction lies in the intracranial vascular anomalies and neurological manifestations: the intracranial manifestations of PHACE syndrome typically include medium-sized vessel arteriopathy, while SWS is characterized by venous capillary malformations, or leptomeningeal angiomatosis. Clinically, SWS carries higher risk for venous strokes and stroke-like episodes, hemiparesis, and epilepsy.

Conclusion

PHACE syndrome is a cutaneous neurovascular syndrome presenting in infancy with multiple organ system involvement. Neurological complications include stroke, headache, and developmental and neuropsychological impairment. Attentive, multidisciplinary evaluation and management is critical to expanding our understanding of this complex disorder and caring for affected individuals.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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