

A report of two cases with dolichosegmental intracranial arteries as a new feature of PHACES syndrome

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Abstract

Background We describe two previously unreported cases with complete or incomplete expression of PHACES syndrome, a rare congenital syndromal pediatric disorder, which is characterized by posterior cranial fossa malformations, large facial hemangiomas, arterial anomalies, coarctation of the aorta and cardiac defects, abnormalities of the eye, sternal and supraabdominal raphe defects.

Case reports These two children exhibited a feature not reviewed extensively in the literature, namely, segmental elongation and dilatation of intracranial arteries associated with intracranial occlusive arterial disease, predominantly on the anterior division of the internal carotid artery (ICA) and on the P2 segment of the posterior cerebral artery. This dolichoectasia was found at the distal cervical internal carotid artery, the intradural segment of the ICA before the division, the trigeminal artery, and the posterior division of the ICA. We presume that the different forms of arterial involvement in PHACES syndrome (arterial stenoses, segmental agenesis of vessels, and the dolichoectasia

described in this study) constitute a spectrum of angiogenic dysfunctions related to an embryonic event involving several cephalic neural crest segments of the dorsal aorta.

Keywords PHACES syndrome · Hemangiomas · Arterial anomalies · Segmental arterial identity · Dolichoectasia · Cerebral arteries

Introduction

PHACES syndrome is a rare congenital syndromal pediatric disorder with less than 150 cases reported in the literature. Its name is an acronym derived from the spectrum of clinical findings that can be displayed in affected patients, i.e., *Posterior cranial fossa malformations, Hemangiomas, Arterial anomalies, Coarctation of the aorta and cardiac defects, abnormalities of the Eye, Sternal and supraabdominal raphe defects* [1–7]. Recently, arterial intracranial stenoses have been added as an additional feature of this syndrome that might lead to pediatric strokes and a Moya–Moya-like appearance of the distal ICA [7]. While the hallmark of PHACES syndrome is the large “plaque-like” facial hemangioma, the spectrum of associated clinical and imaging findings might be complete or incomplete and most patients display only one or two extracutaneous manifestations. In the following manuscript, we describe two previously unreported clinical cases of PHACES syndrome that exhibited a specific angiographic feature that has not been described in greater detail in the previously reported cases, i.e., segmental elongation and dilatation of the intracranial arteries in a dolichoectatic type. This segmental vascular involvement might shed light on the pathophysiology of arterial anomalies encountered in PHACES syndrome.

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Case reports

Case 1

This 4-year-old girl with an extensive left maxillofacial hemangioma spreading over the forehead, eyelids, cheeks, cervical region, and upper thorax was referred to our hospital for angiographic and clinical evaluation (Fig. 1). Pregnancy and delivery at full term were uneventful with a birth weight of 3,450 kg. Since birth, a flat facial hemangioma was present. Although steroids were immediately started, the lesion grew in size and ulcerated at 3 months of age. During the first 2 years of life, various treatment strategies including interferon and vincristine were tried without success. The hemangioma progressively covered the left eye and the patient developed amblyopia. By the age of two, it regressed partially in size. There was no history of bleeding from mouth or nose and no difficulty to breathe. Due to the mass effect produced by the hemangioma, she needed a gastrostomy.

At the age of 1, she suffered from a left posterior cerebral artery (PCA) stroke presenting with a sudden onset of right sided hemiparesis. She subsequently developed seizures that are sufficiently controlled with Phenobarbital.

Cranial computerized tomography (CT) on admission revealed enlargement of the left orbit associated with facial and cranial bone thickening adjacent to the hemangioma and the sequelae of the PCA infarct as confirmed by the hypodensity in the left occipital and parietal lobe and ipsilateral dilatation of the occipital horn and body of the lateral ventricle. Thorax CT showed diathesis of the lower sternum. Digital subtraction angiography (DSA) revealed several cerebrovascular and aortic arch anomalies, namely, right aberrant subclavian artery, common origin of the common carotid arteries persistence of a trigeminal artery, and incomplete persistence of the stapedia artery, the hemangioma blush, and the avascular area described in the cranial CT (Figs. 1 and 2). There was pronounced ectasia and elongation of the C2 segment, posterior division

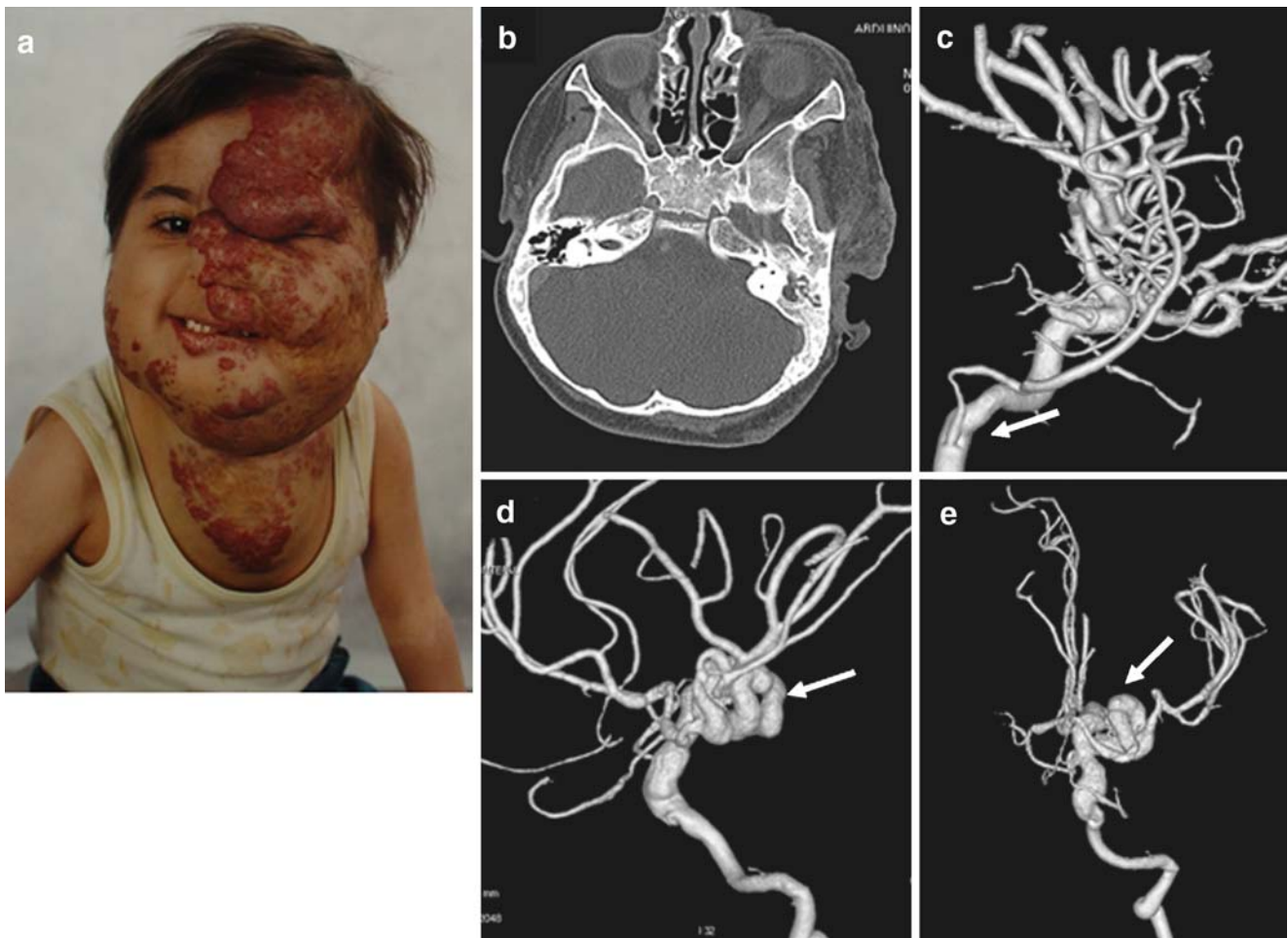


Fig. 1 Case 1. **a** Two-year-old child with a left facial/upper thorax hemangioma. **b** CT reveals osseous thickening of the cranial base on the left side. **c** Tridimensional DSA shows right side incomplete

persistence of the stapedia artery (*arrow*). **d** and **e** Tridimensional DSA shows ectasia and elongation of the posterior division of the ICA (*arrow*) and C2 extra cranial segment

of the ICA and trigeminal artery. Posterior fossa malformation was not present; however, the diagnosis of PHACES syndrome was based on the coexistence of plaque-like facial hemangioma, cerebrovascular and aortic arch anomalies, and diathesis of the lower sternum. No treatment was inaugurated because the hemangioma started to regress, on clinical follow-up 16 months later; the facial hemangioma has further regressed in size and the patient's epilepsy is sufficiently controlled with Phenobarbital. No new strokes were encountered. Follow-up imaging was therefore not esteemed necessary.

Case 2

This 14-month-old girl was born with a ventricular septal defect that was operated at 3 months of age. She had a flat

hemangioma at the posterior aspect of the neck in the midline and right superior eyelid that appeared after birth, continued to grow until her 6 months of life and regressed after her first birthday. Brain magnetic resonance imaging (MRI) performed after an episode of fever and hypotonia revealed serpiginous vessels adjacent to the hypothalamus (Fig. 3). Three months later, a digital subtraction angiography revealed a dolicho posterior division of the ICA on the left and dolicho internal carotid arteries bilaterally (C4 and C7 segment of the right ICA and C2 and C7 of the left ICA) and bilateral stenosis of M1 segment of the middle cerebral arteries. In addition, there was a capillary hemangiomatous stain of the right superior orbit. Ophthalmological examination was normal. PHACES syndrome was diagnosed due to the presence of hemangioma, arterial anomalies, and cardiac malformation although posterior

Fig. 2 Case 1. **a** Left vertebral angiogram showing persistence of a dolichotrigeminal artery (*white arrow*) and occlusion of the terminal branches of the PCA (*gray arrow*). **b** CT showing extensive infarct of the left occipital and parietal lobes. **c** Aortic arch DSA with right aberrant subclavian artery (*arrow*) and common origin of the common carotid arteries. **d** Thorax CT showing sternal cleft (*arrow*)

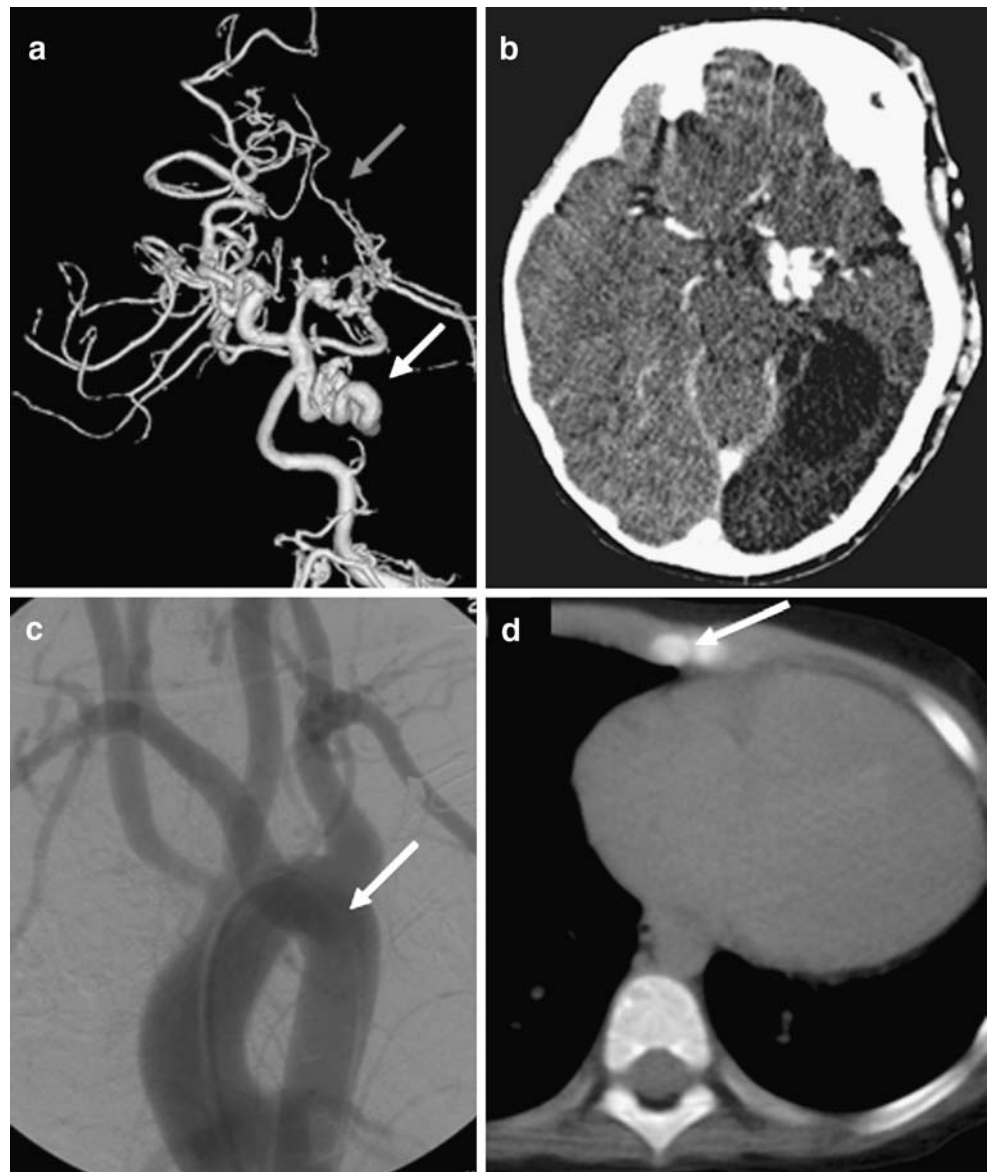
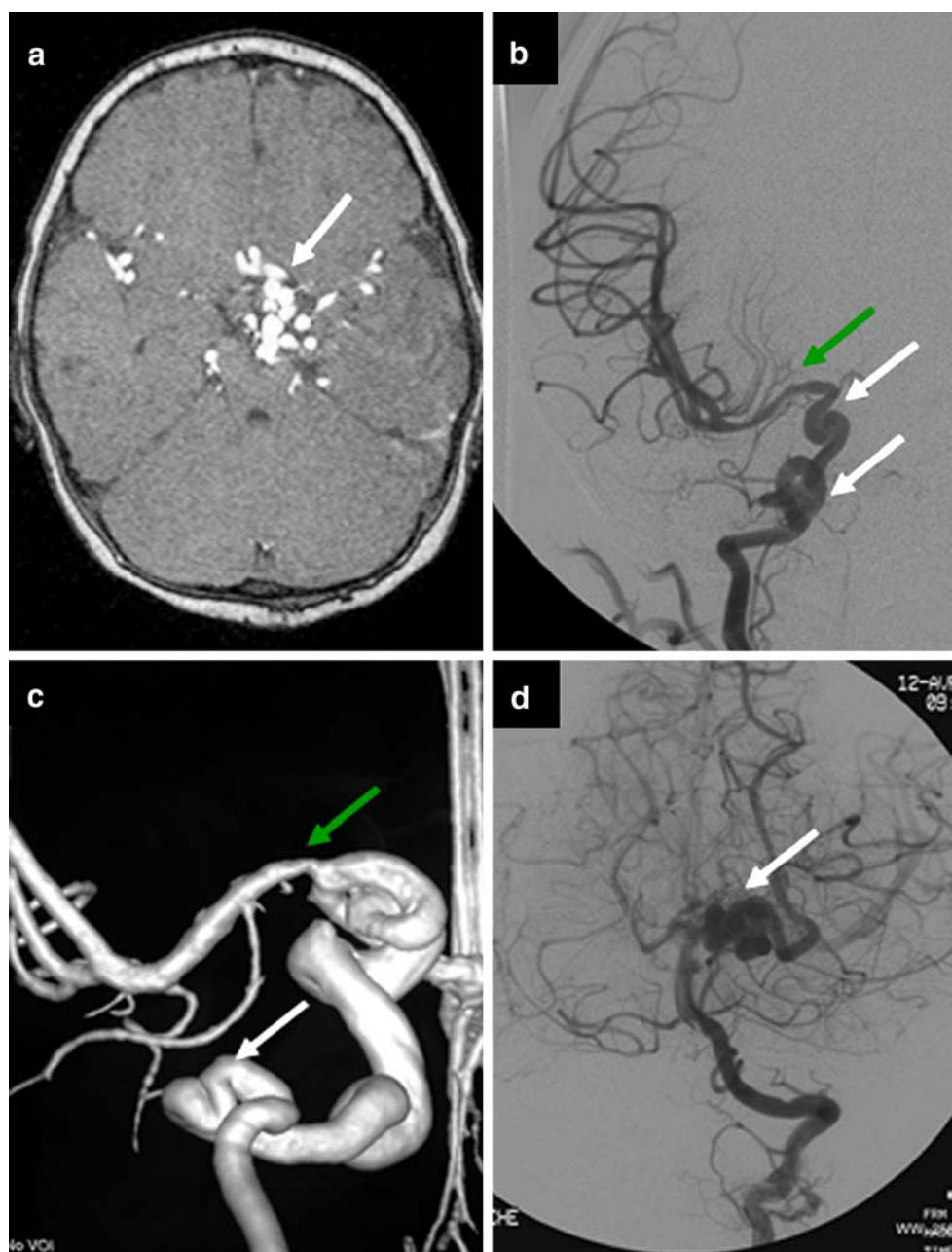


Fig. 3 Case 2. **a** Brain MRI showing serpiginous vessels adjacent to the hypothalamus (arrow). **b** and **c** DSA of the right (anterior view) and left ICAs (posterior view 3-D reconstruction) showing elongated and tortuous arteries (white arrows) (segments C4 and C7 of the right ICA and C2 and C7 of the left ICA). Note bilateral stenosis of the proximal MCAs (green arrows). **d** Dolichoectasia of the left posterior division of the ICA (arrow)



fossa malformations were not present. Because the dolicho vessels were considered as a segmental dysplasia without an increased risk of hemorrhage or stroke, no treatment was performed. The patient is awaiting follow-up for her hemangioma.

Table 1 summarizes the findings of the two cases reported in this article.

Discussion

PHACES syndrome is a rare congenital anomaly with a broad spectrum of clinical manifestations [2–7] and as an

acronym recalls its characteristics: *P*osterior fossa malformations, *H*emangiomas, *A*rterial anomalies, *C*oarctation of the aorta and cardiac defects, *E*ye abnormalities, *S*ternum/abdominal raphe defects. Although its pattern of inheritance has not been established yet, there is a striking female predominance with a female–male ratio of 9:1 [1]. PHACES syndrome was described by Frieden et al. in 1996 as a complete syndrome yet in most instances; apart from the facial hemangioma, there are typically only one or two extracutaneous manifestations [2, 3, 8–10].

In the following, we will briefly discuss the different manifestations of PHACES syndrome with a special emphasis on the arterial anomalies.

Table 1 Clinical and imaging features of the reported patients

Age/sex	Clinical features	Posterior cranial fossa	Hemangiomas	Anatomic variations	AO/C	Eyes	Stenoses/occlusion	Sternum/abdominal midline defect	Intracranial dolicho segments
4 years, F	Left facial mass; neurological deficit; seizures	Normal	Left face, lip, orbit, upper thorax	Trigeminal, stapodial, (partial) lusoria	No	No	Unilateral PCA occlusion and MCA (M1) stenosis	Yes	Left C2 and C7 segment of ICA and posterior division
14 months, F	Right eyelid/cervical hemangioma	Normal	Midline neck, right eyelid	Right MMA origin from OPhA	VSD	No	Bilateral MCA stenoses	No	Left ICA C2, C7 and posterior division (PComA + P1) right ICA (C4/C7)

AO Aortic coarctation, C cardiac defect, VSD ventricular septal defect, ICA internal carotid arteries, MMA middle meningeal artery, OPhA ophthalmic artery, VA vertebral artery, MCA middle cerebral artery, PComA posterior communicating artery, PCA posterior cerebral artery.

Posterior fossa malformations

Posterior cranial fossa malformations are present in 32–74% of patients with PHACES syndrome and are represented by Dandy–Walker malformation and cerebellar hemisphere hypoplasia (which is typically homolateral to the facial hemangioma) [5, 6, 11, 12]. A possible case of intracranial hemangioma in the posterior fossa [1, 7, 13] and association of PHACES syndrome with cortical dysplasia has also been reported [14].

Hemangiomas

Hemangiomas are the most common benign tumors of infancy, occurring in up to 10% of children below one year of age [3, 15]. Infantile hemangiomas are common vascular lesions that are usually solitary. Less than half of the hemangiomas are present at birth, alternatively they appear in the first 3 months of life with rapid growth until 6–8 months. A stable “plateau phase” is achieved between 8–12 months, followed by a slow involution that continues until 5 to 10 years of age [16]. Apart from this typical pattern, two variants can be encountered: One subgroup of hemangiomas appears as fully grown tumors shortly after birth and resolve rapidly, often leaving pronounced atrophic skin changes. This variant is known as “rapid involuting congenital hemangioma” (RICH) [17]. The second, albeit rare variant is called “noninvoluting congenital hemangiomas” (NICH) which exhibits specific clinicopathologic/radiologic features and does not regress with time [18].

Facial hemangiomas can be classified as focal (tumor like lesions) or diffuse (plaque-like lesions with segmental

pattern). Diffuse lesions affect the mandibular segment in 38%, maxillary in 35%, and the frontonasal in 27% of cases; however, in 24%, more than one facial segment is involved [19]. Patients with segmental distribution of lesions have a higher female–male ratio, almost twice that of patients with focal lesions. The segmental plaque-like hemangiomas have been associated with PHACES syndrome [4, 14, 19–24], their clinical behavior resembles those of classical infantile hemangiomas.

Multiple hemangiomas of the skin (five or more) have traditionally been recognized as a clue to potential visceral hemangiomas, although this association can also be observed in segmental hemangiomas with less frequency [13]. Internal organs hemangiomas associated with multiple cutaneous hemangiomas are known entity distinct from PHACES syndrome [25–27].

Hemangiomas in PHACES are typically plaque-like, ulcerated facial lesions that are not strictly segmented in distribution. One third of patients demonstrate cutaneous hemangiomas in regions apart from the head and neck. As stated above, their clinical behavior (growth until 6–8 months of age, plateau phase until the 12th month and regression until 10 years of age) resembles those of the typical pattern of infantile hemangiomas, although in our first case described in this study, the growth period appeared to be somewhat longer.

Cardiac abnormalities and aortic coarctation

These anomalies are seen in approximately one third of cases with the coarctation being the most common abnormality. Typically encountered cardiac anomalies in-

clude right sided aorta, persistent ductus arteriosus, ventriculo–septal defects, and pulmonary stenosis. It has been suggested that the side of the hemangioma and the side of aortic arch abnormality with or without coarctation are associated (95% of concordance on ipsilaterality) [12, 28, 29], as was the case in our first patient (left facial hemangioma and left sided origin of the right subclavian artery, and lusoria).

Eye abnormalities

Ophthalmologic findings are not as common as posterior fossa and arterial anomalies; however, colobomas, arcus corneae, optic nerve hypoplasia, increased retinal vascularity, and glaucoma have been described [30]. The large facial hemangioma on the right eyelid and cheek and the lack of light stimuli might explain our patient's low visual acuity.

Sternal and raphe disorders

In addition to the previously described various structural cardiac abnormalities and aortic coarctation, ventral developmental defects such as sternal pits, sternal clefting, and supraabdominal raphe should be sought for in suspected PHACES syndrome [3, 4]. Case 1 illustrates the sternal cleft finding and the anomalous subclavian artery which can be considered to belong to the generic group of "aortic coarction" described as "C" in PHACES acronym. Such disposition could also be pertaining to the group of "A": arterial anomalies. Several authors have speculated that the association of sternal clefting and facial hemangiomas probably develops between 8 and 10 weeks of gestational age [31, 32]. This association occurs in 7% of patients with PHACES syndrome [3].

Arterial anomalies

There seem to be at least four different types of arterial anomalies associated with PHACES syndrome: agenesis of major cervical arteries, embryological persistence of vessels, and arterial stenoses, which had already been described previously. The fourth type of vascular anomalies seems to be the dolicoectatic type of arterial segments presented in these two cases.

Persistence of embryonic arteries, such as the trigeminal artery (often ipsilateral to the cutaneous hemangioma) occurs most commonly, followed by partial or complete agenesis of major cervical arteries, which are also usually ipsilateral to the cutaneous lesion, as seen in our patient [3, 12]. Other anomalies of the intracranial vasculature and the brain have been described: hypoglossal, proatlantal, or stapediaal persistence, segmental agenesis of the internal carotid artery

with persistent basilar anastomosis, concomitant bilateral internal carotid artery agenesis and vertebrobasilar system agenesis and cerebellopontine angle mass consistent with an intracranial hemangioma [16, 13].

Segmental agenesis of the internal carotid artery is a common arterial abnormality found in PHACES syndrome [13]. Flow is usually reconstituted in the adjacent distal internal carotid segment through embryonic vessels anastomoses [33, 34] often involving the tympanic cavity.

Stenoses have recently been described as a further feature of PHACES syndrome. In the series of Burrows et al., the onset of occlusive disease was between birth and 18 months of age, which correlates with the proliferative phase of the hemangiomas [2], although in a previous study, the patients with occlusive arterial disease were older (4 to 14 years of age; [1]), which is in keeping with case 1. Occlusive arterial disease is most likely caused by mural angiogenesis, which normally leads to increase in caliber, when the correct remodeling signals induce the apoptosis of the unnecessary vessel–wall components. Lack of remodeling produces centripetal proliferation, and thereby luminal reduction [1].

In our cases, we have found striking dolichoectatic intracranial arterial segments. Dolichoectasia usually means an elongated, tortuous, and dilated artery; however, because dilatation is often the most striking feature, this condition is now often referred to as dilatative arteriopathy. Dilatative arteriopathy is frequently asymptomatic in children; however, in adults it may be associated with stroke, subarachnoid hemorrhage, cranial nerve palsy, compression of the midbrain, or obstructive hydrocephalus [35–37]. Intracranial arterial dolichoectasia in adults has been found in 12% of stroke patients [38]. The reduced blood flow in the dolichoectatic vessel promotes stagnation of the blood column and thrombus formation within the dilated arterial segment [37, 39, 40]. However, the symptoms and pathophysiology of nonsegmental dilatative arteriopathy as described in adults is unlikely to be the same in children due to different etiologies and vessel wall physiology.

Dilatation and elongation may affect the arteries in a nonsegmental pattern (being spread over the arterial tree) or a segmental pattern (expressing a geotropism which might be related to focal mural weakness or dysfunction).

Nonsegmental dilatative arteriopathy represents fragility of the entire arterial system when exposed to a specific trigger, such as hemodynamic stress [41]. Nonsegmental dilatative arteriopathy is most often found in adults due to atherosclerosis; however, it might also occur in children and adolescents. The pathophysiology in this age group is multifactorial, including genetic, infectious, inflammatory, immunological, and degenerative factors, such as alfa-glucosidase deficiency, Marfan's syndrome, Ehlers–Danlos

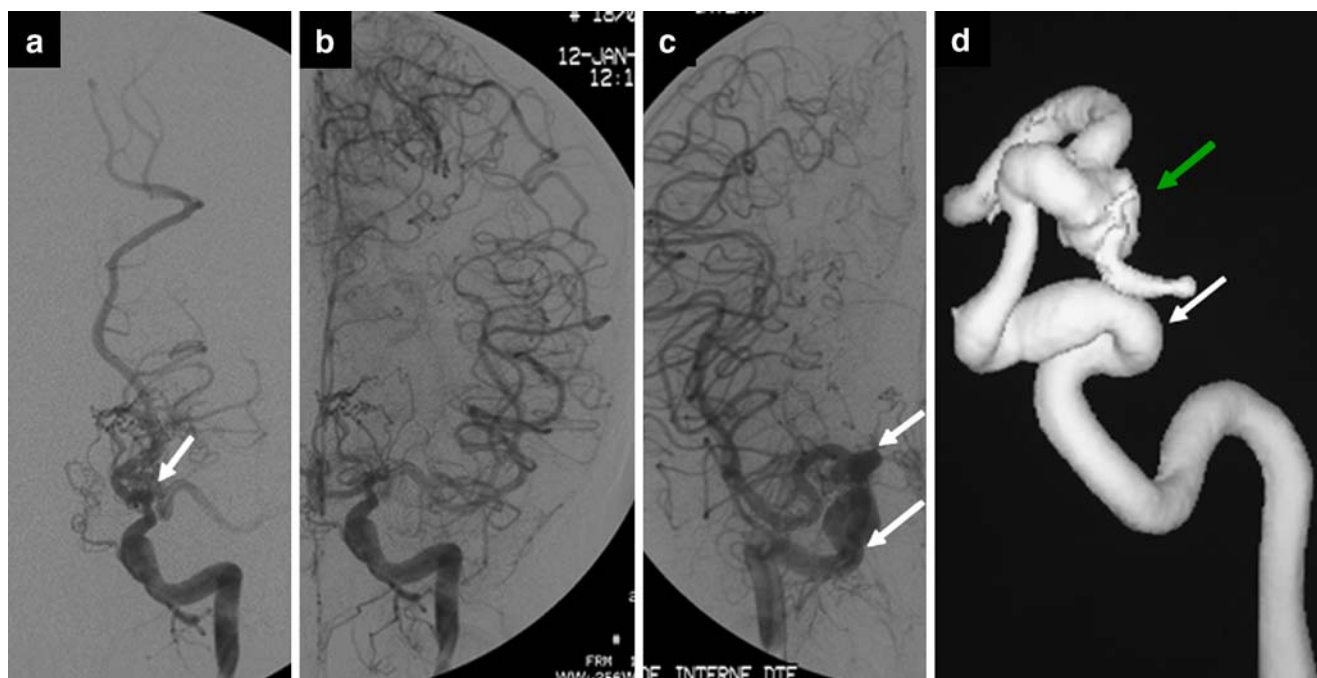


Fig. 4 Case 2. **a** and **b** Angiography shows stenosis of the left supraclinoid ICA and occlusion of the proximal MCA (arrow) and left A1 with extensive collateral circulation. **c** and **d** Dolichoartery

is present in the cavernous and supraclinoid segments on the right (white arrows) associated with dolicho-M1 segment of the MCA and ICA ectasia (green arrow)

syndrome, AIDS, Fabry’s disease and sickle cell disease [42–45].

Segmental dilatative arteriopathy, on the other hand, is related to the segmental identity of the vessel with an associated segmental vulnerability, a condition inherent to a specific portion of the artery that is structurally more susceptible to suffer transformation when exposed to (or identified by) a trigger.

During angiogenesis, various responses in a given (vulnerable) segment may be observed: increase in length (dolichoartery), centrifugal increase in diameter with lumen enlargement (aneurysm), or centripetal increase with lumen reduction (occlusion). The three types of response can coexist in contiguous segments, showing the difficulty in appreciating where the specificity of the trigger, of the target edges, or of the time intervenes to produce the detectable architectural change [33].

PHACES syndrome seems to promote vascular changes that elongate, dilate arteries, or cause lumen constriction as illustrated by the dolichoectatic aspect of the posterior division of the internal carotid artery in both cases, the C2, C4, and C7 segments, the persistent trigeminal artery and stenosis/occlusion of middle and or posterior cerebral arteries (Figs. 1, 3, 4, and 5). When reviewing the thus far reported cases, Metry et al. [4] described two patients in a series of 14 cases with cerebrovascular dilatations that were referred to as “aneurysmal dilatations”, dysplasia and/or

elongation of arteries. In one of his cases, MRI revealed tortuosity and elongation of the C2 segment of the internal carotid artery and middle cerebral artery suiting the findings of our patients. Weon et al. [46] reported a case of incomplete PHACES syndrome with a dolicho-subclavian

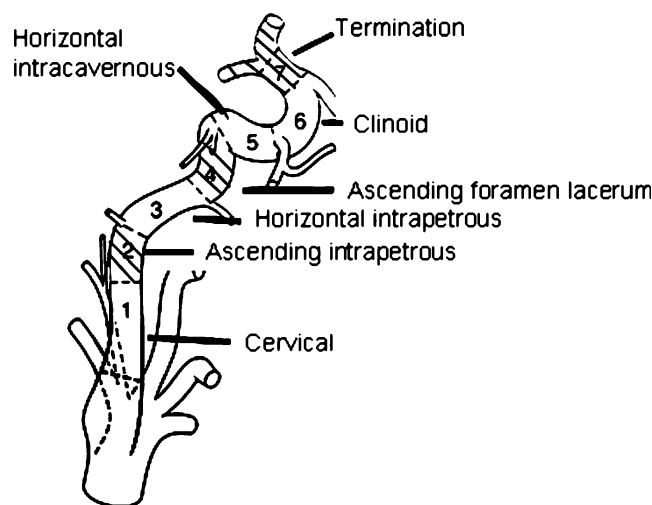


Fig. 5 Projection of the embryological segments of the ICA on its final disposition and segments affected in our cases of PHACES syndrome marked with lines (C2, C4, C7, and posterior division of the ICA= posterior communicating and proximal PCAs). Internal carotid artery branches originate between these segments. Modified and reprinted with permission [33]

artery. Dolichosegmental intracranial arteries of the C2 segment of the internal carotid artery, hypoglossal, and trigeminal persistence, have been noted in two other unpublished cases [personal communication, Berenstein, (United States) and Gupta (India)].

We presume that because PHACES syndrome affects the normal development of the dorsal aorta in some patients [29], the disease may be responsible to the segmental involvement of the internal carotid arteries observed in our cases. This hypothesis is based on the fact that different regions of the dorsal aorta are responsible for the origin of several segment of the internal carotid artery (Table 2). This hypothesis is supported by the segmental agenesis frequently observed in PHACES syndrome; the distal flow is reconstituted through embryonic vessels persistence.

We therefore postulate, that the different forms of arterial involvement in PHACES syndrome constitutes various phenotypes related to plurisegmental abnormal development of the neural crest involved in the dorsal aorta and cerebrofacial structures. The timing of the revealing trigger might lead to different phenotypes including agenesis, (with concomitant embryological persistence of vessels), stenoses, or elongation related to the same underlying vessel wall defect as well as segmentally arranged proliferative activities mostly ipsilaterally distributed.

Treatment of PHACES syndrome should be symptomatic and concerning the hemangiomas not differ from treatment strategies employed in nonsyndromal forms. Concerning the arterial anomalies, we would like to stress that the described segmental dysplasias do not constitute entities that should be treated and that they should not be

Table 2 Embryologic development of the internal carotid artery segments from the primitive aortic arches [33, modified]

Internal carotid segments	Embryologic origin
Segment 1	Third aortic arch
Segment 2	Dorsal aorta between the origins of the second and third aortic arches
Segment 3	Dorsal aorta between the origins of the first and second aortic arches
Segment 4	Dorsal aorta between the origins of the first aortic arch and the primitive maxillary artery- trigeminal artery
Segment 5	Dorsal aorta between the origins of the primitive maxillary artery and the dorsal ophthalmic artery
Segment 6	Dorsal aorta between the origins of the dorsal ophthalmic artery and opening of the ophthalmic artery
Segment 7	Terminal segment of the internal carotid artery between the origins of the ophthalmic artery and the origin of the posterior division (Post. Com.Art. + P1) of the ICA

misdiagnosed for arteriovenous malformations or aneurysms. On the other hand, we think that in the presence of dolichosegmental arteries in a child with a hemangioma, one should think of the diagnosis of PHACES and specifically look for other associated malformations.

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