A Patient With PHACE Syndrome With Marked Ipsilateral Cerebral Atrophy

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1. Introduction

PHACE syndrome, first proposed by Frieden et al1 in 1996 is a neurocutaneous disorder characterized by large cervicofacial infantile hemangiomas (100%) associated with posterior fossa malformation (74%), cerebrovascular abnormalities (41%), coarctation or cardiac defects (26%) and eye abnormalities (23%). The most commonly reported central nervous system abnormalities have been those involving the posterior fossa, especially the Dandy-Walker malformation, which is characterized by a hypoplastic or absent cerebellar vermis and a posterior fossa cyst continuous with the fourth ventricle.2−8 Cerebrovascular abnormalities, including absence, abnormal origin, tortuosity or stenosis of the major cerebral arteries, are the second most common manifestation.1,3,9 However, abnormalities of the cerebrum itself have rarely been mentioned until recently, when large intracranial hemangioma, progressive intracranial arterial stenosis or occlusion, moyamoya-like vasculopathy and ensuing ischemic strokes have been reported.10−12 We report an unusual PHACE patient with an absent internal carotid artery and severe ipsilateral cerebral atrophy. Possible explanations for this abnormal finding are discussed from the view point of altered hemodynamics. We suggest that cerebral abnormality represents one of the many aspects of PHACE syndrome.

2. Case Report

A 1-year-old girl was referred to our cardiac clinic by a plastic surgeon due to a cardiac murmur. She had been born to a healthy 30-year-old mother at a gestational age of 36 weeks after an uneventful pregnancy. Her birth weight was 3.13 kg, and the Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. A large cavernous hemangioma was noted over her left face and left neck immediately after birth. Brain computed tomography performed at an age...
of 1 month revealed marked left cerebral and cerebellar hypoplasia ipsilateral to the facial hemangioma. Delayed developmental milestones were noted when she was 5 months old.

On physical examination, the patient’s body weight was 7.7 kg (third percentile), height 72 cm (twenty-fifth percentile), and head girth 42 cm (under third percentile). The large cavernous hemangioma was noted on the left face covering the eyelid, maxilla, ear lobe, mandible and left neck. There was no cranial bruit. She had regular sinus rhythm with a heart rate of 120 beats/minute. Her right-arm blood pressure was 116/46 mmHg and left-arm blood pressure 82/42 mmHg. Left ventricular heave was felt and a grade 2/6 systolic murmur was heard over the left upper sternal border. Bilateral femoral pulses were weak.

Neurological examination revealed marked developmental retardation and muscular hypotonia over the patient’s neck, trunk and limbs. Right-sided spastic hemiplegia was also evident. Flash goggle visual evoked potential examination was performed and revealed bilateral prolongation of P100 latency, especially during left eye stimulation, suggesting visual pathway dysfunction.

Chest film showed mild cardiomegaly, and no pulmonary congestion. Two-dimensional echocardiography and Doppler examination showed hypertrophy of the left ventricle, dilated ascending aorta and long segmental narrowing of the aortic arch and a discrete stenosis in the juxtaductal area. There was no shunting of the ductus arteriosus. The pressure gradient across the coarctation was 36 mmHg measured by continuous wave Doppler.

Cardiac catheterization and angiography showed a long segmental narrowing of the aortic arch between the left common carotid and the left subclavian artery (type B coarctation) and a discrete narrowing at the juxtaductal area (Figure 1). The origin of the left subclavian artery was positioned lower in the juxtaductal area, and its orifice was also stenotic. The pressure gradient across the coarctation measured during catheterization was 50 mmHg. The ductus arteriosus was obliterated. Selective left common carotid angiography showed absence of the left internal carotid artery. The external carotid artery was dilated, tortuous and cobbled up two loops at the neck (Figure 2), and then drained mostly into the cavernous hemangioma. Selective left subclavian artery angiography revealed that the contrast medium also drained into the hemangioma.

We performed selective right internal carotid angiography to determine if there was collateral blood supply from the right hemisphere to the left side. It showed almost no contrast medium draining into the left hemisphere.

Magnetic resonance imaging (MRI) of the cranium showed severe hypoplasia of the left cerebrum, dilated left lateral ventricle and mild hypoplasia of the left cerebellum (Figure 3). Brain 99mTc-hexamethylenepropylene amine oxime single photon emission computed tomography showed a large area of excessive tracer accumulation on the left side of the neck and face, which was compatible with a large cavernous hemangioma. There were several focal areas of tracer nonperfusion in the regions of the left cerebellum, the middle and inferior portion of...
the left parietal lobe, the anterior portion of the left temporal lobe and anterior portion of the left occipital lobe. The left hemisphere was markedly atrophic.

Chromosome analysis revealed a 46XX karyotype, and a fluorescence in situ hybridization study with probes for 22q11.2 LSI DiGeorge/VCFS and 22q13 LSI ARSA showed normal findings.

Excision of the coarctation and an end-to-end anastomosis was performed soon after the cardiac catheterization. The patient recovered from the procedure well and was discharged uneventfully 10 days after operation.

After discharge, her hemangioma was treated with several local injections of Kenacort-A and sclerosing agents, along with dye laser therapy and our scar revision at our plastic surgery department. The hemangioma was almost invisible by the age of 5 years. She also received regular and intense physical therapy, and was able to walk alone with the aid of a splint.

Cardiac catheterization, selective carotid angiography and brain MRI were repeated at the age of 5 years. An aortogram revealed mild narrowing of the aortic anastomosis with a pressure gradient of 20mmHg. Selective left carotid angiography showed that the external carotid artery was still dilated and tortuous, and formed two loops in the neck. The internal carotid artery was still invisible. Brain MRI showed marked atrophy of the left cerebral hemisphere, dilated left lateral ventricle and mild atrophy of the left cerebellum.

3. Discussion

Pascual-Castroviejo\textsuperscript{3} first reported on seven female patients with facial or scalp capillary hemangiomas in 1978. All of these patients had extracranial and intracranial vascular malformation on the same side as the hemangioma, including arterial angioma, and abnormal origin and intracranial distribution of some of the major cerebral arteries. Two of the patients had congenital absence of the carotid artery, and three had intracranial abnormalities including Dandy-Walker disease, partial agenesis of the cerebellar vermis and arachnoid cyst of the posterior fossa. Several cases of neurocutaneous lesions involving the head and neck have subsequently been reported by other authors.\textsuperscript{4,7,10} Schneeweiss et al\textsuperscript{13} reported four cases of face and neck hemangioma associated with coarctation of the aorta and aneurysm of the subclavian or innominate artery in 1982. The authors proposed that this combination could represent a new syndrome, with a suggestion that the coarctation was secondary to increased flow to the hemangioma and decreased flow to the distal arch.

In 1993, Goh and Lo\textsuperscript{6} reported two female patients with facial cavernous hemangiomas, interruption or coarctation of the aortic arch at the level between the left common carotid and left subclavian artery, and cerebellar hypoplasia.\textsuperscript{6} They referred to the triad as a ‘new 3C syndrome’. Both patients also had an aberrant right subclavian artery arising distal to the coarctation.

In 1996, Frieden et al\textsuperscript{1} reported two cases and reviewed 41 previously reported similar cases and proposed the acronym of ‘PHACE’ syndrome. The authors emphasized the characteristic findings of this neurocutaneous syndrome as (1) posterior fossa malformations, (2) hemangiomas, (3) arterial anomalies, (4) coarctation of the aorta and cardiac defects, and (5) eye abnormalities.

Whether this complex anomaly is a consequence of abnormal embryogenesis due to a chromosome/gene.
disorder, or a result of altered hemodynamics, is still not clear. Animal experiments have shown that, as the fetal neural tube evolves, a set of specialized cells develops along its dorsal crest and then detaches from the neural crest and begins to migrate extensively to populate three main regions: the cranium, heart and trunk. These neural crest cells contribute significantly to the formation of the brain, heart, visceral arch system and associated organs, including the dermis of the face and neck, and the walls of the large arteries (aorta, pulmonary arteries, branchiocephalic trunks and common carotid arteries). Because neural crest cells have a common origin, if those related to cranial formation are abnormal, then those related to cardiac and trunk formation may also be abnormal. This may explain why posterior fossa malformations, segmental hemangiomas, arterial anomalies, cardiac defects, eye abnormalities, and sternal or ventral defects occur simultaneously. Abnormalities of neural crest cells are probably at least partly responsible for the development of the metameric vascular neurocutaneous syndromes, including PHACE, Sturge-Weber, and craniofacial and spinal arteriovenous syndromes, as well as retinal and optic nerve/chiasm arteriovenous malformations.15

Among these neurocutaneous disorders, the symptoms and signs of Sturge-Weber syndrome most closely resemble those of PHACE syndrome. However, PHACE usually involves the posterior fossa, such as in Dandy-Walker malformation. In contrast, Sturge-Weber syndrome involves mainly the leptomeninges of the parietal and occipital areas. Regarding facial hemangiomas, PHACE is characterized by extensive facial cavernous hemangiomas, while Sturge-Weber syndrome manifests as port-wine stains on the face, typically in the ophthalmic and maxillary distributions of the trigeminal nerve.16 PHACE syndrome is also often associated with congenital cardiac diseases, coarctation of the aorta, and brachiocephalic arterial abnormalities, while Sturge-Weber syndrome rarely affects other body organs.

In addition to chromosome aberrations and genetic developmental errors, some investigators have postulated that reduced antegrade aortic blood flow in fetal life may cause aortic tubular hypoplasia and coarctation.17-19 Various congenital heart diseases that jeopardize forward aortic blood flow, such as congenital bicuspid aortic valve,20 malalignment ventricular septal defect,21 and congenital mitral valve stenosis and/or insufficiency,22,23 have commonly been found in association with tubular hypoplasia of the aortic arch.

The hemangioma in the current patient, and its extensive perfusion through the left external carotid artery may have reduced blood flow in the distal arch, resulting in arch hypoplasia and coarctation. This steal phenomenon of the left external carotid artery may also have resulted in an absence of the left internal carotid artery since fetal life. Poor collateral circulation results in severe atrophy of the left cerebral hemisphere. Low positioning of the left subclavian artery at the juxaductal area and stenosis of its origin also cause reduced blood supply to the vertebral artery and subsequent hypoplasia of the cerebellum.

To the best of our knowledge, no previously published articles on PHACE syndrome have mentioned the presence of marked cerebral hypoplasia or atrophy, as in our case. Lin et al reported a case of PHACE syndrome in 2003 that manifested progressive cerebral infarction, encephalomalacia and hydrocephalus due to internal carotid artery stenosis or occlusion at 6 months of age. Hayer et al also reported a patient with PHACE syndrome who developed a moyamoya-like vasculopathy and consequent ischemic strokes in 2006. Drolet et al later described five additional infants with facial hemangiomas and arterial anomalies of the head and neck, all of whom suffered arterial ischemic strokes during infancy due to progressive diseased arterial stenosis or occlusion. Our patient manifested marked cerebral atrophy and hemiplegia at the early age of 1 month. It was unclear if this cerebral atrophy was caused by cerebral infarction during fetal life. The current case and those mentioned above suggest a further expansion of the spectrum of PHACE syndrome to include other forms of cerebral disorder.

Facial hemangioma is a common dermatological disorder in children, and it is important to be aware of its potential association with cardiovascular and neurological disorders when it is extensive, plaque-like, and involves more than one dermatome.

References