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Case report

PHACES Syndrome – Case Report and Literature Review

Jelena Roganović and Denise Adams

Division of Hematology and Oncology, and Comprehensive Hemangiomas and Vascular Malformations Clinic, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, USA

A B S T R A C T

The case of a 2-month-old female infant with PHACES syndrome is reported. PHACES represents a broad spectrum of congenital anomalies, including the following primary features: posterior fossa brain malformations, large facial hemangiomas, arterial anomalies, cardiac defects and aortic coarctation, eye abnormalities, and ventral developmental defects. The literature on this rare condition is reviewed.

***Key words**: PHACES syndrome, hemangiomas*

Introduction

Hemangiomas are the most common tumors of infancy, occurring in up to 10% of children less than 1 year of age and usually involving the head and neck with marked female predominance[1]. Unlike vascular malformations, hemangiomas are rarely associated with systemic abnormalities[2]. PHACE syndrome is a rare neurocutaneous syndrome with the following major features: *P*osterior fossa brain malformations, Hemangiomas, *A*rterial anomalies, *C*oarctation of the aorta and *C*ardiac defects, and *E*ye abnormalities. When *S*ternal clefting and/or *S*upraumbilical raphe is present, the association is referred to as PHACES syndrome[3,4].

Recognizing and understanding of PHACES is important in the evaluation and management of affected children. Most reports in the literature are isolated cases or small series, and there are a few larger studies[4,5]. We report on a case of a 2-month old girl with a complex PHACES syndrome whose primary manifestations include large facial hemangiomas, cerebral vascular malformations, right optic nerve hypoplasia, and ventral developmental defects.

Case Report

Our patient was born at term after an uncomplicated pregnancy of a 38-year-old gravida 2, para 2, by spontaneous vaginal delivery with APGAR scores 8 and 9. Tracing back her history, gestation was uneventful. No exposure to known teratogenic agents was found. Family history was without consanguinity, remarkable for a paternal aunt with a retroauricular birthmark and a maternal grandmother also with a small birthmark over her facial skin.

Birth weight was 3,145 grams (50^{th} centile for gestation), length 51,0 cm (75^{th} centile), and head circumference 33,5 cm (50^{th} centile). On initial examination, she was noted to have irregular vascular appearance of the cheek and mandible bilaterally, sternal cleft defect, and midline supraumbilical raphe extended from the abnormal sternum to the umbilicus. Shortly after birth multiple hemangiomas had appeared over her forehead, left eyelid (not obstructing her vision), nose, left brow, bottom of left cheek, bottom of right cheek, the back of the head, right side of the face, right ear, lower lip, the upper part of the chest, her mouth and tongue. The hemangiomas started to proliferate rapidly, and she developed ulceration of her cutaneous ear lesion. She was also noted to have some stridor and the diagnosis of an epiglottic hemangioma was made after laryngoscope examination. In the course of the disease she became tachypnoic with respiratory rate between 60 and 80. Chest radiography at that time showed left lung opacity representing pneumonia versus atelectasis. Chest computed tomography showed some anterior compression of tra-

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chea secondary to overlying right brachiocephalic artery. Bronchoscopy disclosed significant epiglottal stenosis and tracheal malacia. The narrowing secondary to brachicephalic artery was mild. She had extensive hemangiomas in the epiglottic and subglottic area, and along the trachea.

As a part of the work-up for PHACES, echocardiography was done that revealed patent foramen ovale with left to right flow. There were no other abnormalities of the heart or aortic conformation. Magnetic resonance imaging of the head showed some abnormalities of the size of the carotid artery but without aneurysms and there were no posterior fossa brain abnormalities. Magnetic resonance angiography revealed a mild diffuse narrowing of the left cavernous carotid artery relative to the right, which showed mild fusiform enlargement. The right M1 segment of the middle cerebral artery was irregular and showed fusiform enlargement. The M1 segment of the left middle cerebral artery and the right posterior cerebral artery were very tortuous and irregular in contour, with a somewhat beaded appearance. The vertebral, left posterior cerebral and anterior cerebral arteries were normal in caliber.

Ophthalmologic evaluation confirmed the presence of right optic nerve hypoplasia and pigmentation of retina. Abdominal ultrasound revealed no hemangiomas of the liver and spleen. Thyroid anomalies were excluded and a thyroid function was normal.

At the age of 3 weeks, systemic steroid treatment was undertaken with stabilization of her respiratory symptoms. Her cutaneous ulcer healed and hemangiomas lightened in color. At the age of 2 months, she had sternal cleft repair which she tolerated well.

Discussion

Hemangiomas of infancy are common vascular lesions, usually small and localized, involving the head and neck in more than half of cases[1]. Segmental lesions are larger and much more likely to be associated with complications and developmental defects[6]. The possible association of cervicofacial hemangiomas with vascular and non-vascular intracranial malformations was first recognized by Pascual-Castroviejo as long as 1978[7]. Schneeweiss et al. (1982) reported the association of hemangioma of the face and neck with coarctation of the aorta and/or aneurysms of the subclavian or innominate artery[8]. In 1993, Goh and Lo[9] identified a triad of cavernous facial hemangioma, ipsilateral cerebellar hypoplasia and aortic arch anomaly, and proposed a new »3C syndrome«. Finally, Frieden and coworkers (1996) observed that a more complex range of abnormalities may also occur. They introduced the acronym »PHACE« to emphasize characteristic findings of the syndrome: *P*osterior fossa brain malformations, *H*emangiomas, *A*rterial anomalies, *C*oarctation of the aorta and *C*ardiac defects, and *E*ye abnormalities. When developmental defects involving *S*ternal clefting and/or *S*upraumbilical raphe are present, the acronym should be expanded to »PHACES«[3]. It is now believed that PHACES represents a spectrum of anomalies that vary considerably from one case to another. The pathogenesis remains unknown. An overwhelming female predominance led to the speculation that it might represent an X-linked dominant condition with lethality in males[10]. Several lines of evidence point to the developmental error expressed between 3 and 12 weeks of gestational age[6], suggesting so-called developmental-field defect occurring from errors within morphoregulatory genes[11].

The hallmark of PHACES is large facial hemangioma. Hemangiomas are characteristically segmental and plaque-like (Figure 1). Distribution patterns suggest dermatomal involvement in some but not in all cases[4], with trigeminal division V1 being most commonly affected dermatome. Exclusively left-sided facial hemangiomas predominate, whereas the incidence of right-sided lesions and bilateral involvement is approximately the same. The extent and/or distribution of cutaneous involvement correlate in some instances with the type and severity of complications[12]. Hundred percent of children with either bilateral facial involvement or complete involvement of all three trigeminal dermatomes have underlying cerebrovascular anomalies, structural brain anomalies, or both[4,6]. Hemangiomas overlying the mandibular skin, which includes the preauricular skin, chin, anterior neck, and/or lower lip (in a so-called »beard« distribution) have known risk of upper airway or subglottic hemangiomas[13].

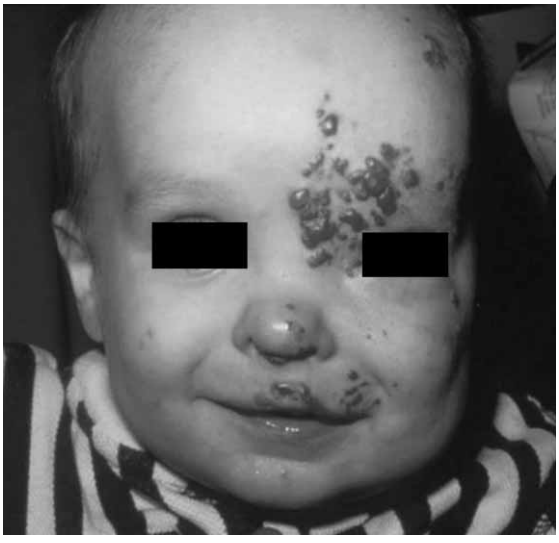

Fig. 1. Plaque-like facial hemangiomas in a child with PHACES syndrome.

The most common central nervous system abnormalities, seen in almost 50% of cases, involve the posterior fossa, most notably Dandy-Walker malformation. Less severe cerebellar impairments include cerebellar atrophy and arachnoid cyst with cerebellar hypoplasia, consistently homolateral to facial hemangioma[14]. There are also reports of supratentorial involvement such as massive en-

larged ventricles, transverse sinus thrombosis, hypoplasia of corpus callosum or septum pellucidum, ipsilateral-frontal lobe calcifications, microcephally, the absence of foramen lacerum, and cerebral cortical dysplasia[15].

PHACES is associated with a high incidence of wide spectrum of cervico-cerebrovascular anomalies. The most common is aberrant course or origin of arteries[16]. Many other structural vascular abnormalities include arterial stenosis and/or occlusion, agenesis or hypoplasia of carotid or vertebral arteries, aneurysmal dilatation of the carotid artery, dilated cerebrovascular vessels, and persistent (primitive) trigeminal artery[3,16]. Intracranial hemangiomas have been reported as a peculiar phenotype of PHACES[17]. The combined incidence of structural cerebral and cerebrovascular anomalies reported in PHACES is greater than 50%, and most of affected patients have developmental and neurologic sequelae[4]. The most striking reports are acute arterial ischemic strokes even with death[18,19]. It remains unclear whether occlusion results from hemangioma-associated overexpression of vascular growth factors or from pharmacological treatment of hemangiomas.

A variety of structural cardiac abnormalities and aortic coarctation have been reported in approximately one third of PHACES patients. Cardiac defects manifest as patent ductus arterious, ventricular septal defects, atrial septal defects, pulmonary stenosis, cor triatriatum, tricuspid atresia and stenosis, tricuspid aortic valve, atrial enlargement, ventricular hypertrophy, tetralogy of Fallot, and patent foramen ovale[4]. The most common single defect is coarctation of aorta. Other aortic anomalies include aberrant origin of the subclavian artery, subclavian or innominate artery aneurysms, ascending aorta or aortic arch aneurysms and/or dilatation, anomalous left superior vena cava, congenital valvular aortic stenosis, »steal syndrome«, cervical aortic arch, right aortic arch, hypoplastic descending aorta, and double aortic arch and double aortic coarctation[20,21].

Ophthalmologic abnormalities have been reported in up to one third of patients[22]. A large number of manifestations, mostly ipsilateral to the side of facial hemangioma, have been described, including microphthalmos, optic atrophy, iris vessel hypertrophy, iris hypoplasia, optic nerve hypoplasia, congenital cataracts, sclerocornea, lens coloboma, exophthalmos, cryptophthalmos, corneal opacity, posterior embryotoxon, conjunctival and chorioidal hemangioma, retinal hyperemia, retinal dysgenesis, heterochromia, loss of eyelashes, and persistent fetal vasculature[23]. The unique finding is so-called »morning-glory deformity« of the retina, characterized by a funnel-shaped, excavated optic disc with elevated glial tissue in the center and a surrounding raised, pigmented area[24,25].

The associated ventral developmental defects in PHACES, including sternal clefting and supraumbilical raphe, are evident clinically. Sternal defects may be partial, consisting of a subtle sternal pit without underlying soft tissue or bony loss, or complete[27,28]. The supraumbilical midline raphe presents as a linear, scar-like plaque that extends above the umbilicus, and is generally seen in combination with a sternal defect[29].

Our case is the first reported PHACES syndrome in Croatian literature. At birth the baby girl was found to have sternal nonunion, supraumbilical raphe and facial red macules, that subsequently proliferated into more typical multiple hemangiomas. At the age of two weeks, she developed stridor and was found to have an epiglottic hemangioma. Within a few days she became tachypnoic, and extensive epiglottic, subglottic and paratracheal hemangiomas were diagnosed, necessitating active treatment. During the course of evaluation, magnetic resonance imaging/angiography revealed multiple intracranial arterial malformations, without structural brain anomalies. An echocardiography demonstrated atrial septal defect. Ophthalmologic evaluation showed optic nerve hypoplasia and retinal pigmentation. Systemic corticosteroid treatment induced partial regression of hemangiomas and improvement of respiratory symptoms. The close follow-up of this patient is mandatory.

Our case, along with those previously reported, suggests that PHACES represents a very broad spectrum of malformations caused by a common morphogenetic event or events in utero. The absence of one or more components does not exclude the diagnosis (as the absence of posterior fossa malformations and aortic coarctation in our patient), and several studies have stressed the heterogeneity of this association. Besides, although hemangiomas are the hallmark of PHACES, they may be nonexistent at birth and may not develop until later in early infancy.

PHACES association, although uncommon, is probably still being ignored and under-recognized[30–32]. Clinicians who treat children with large facial hemangiomas should consider PHACES in the differential diagnosis. Awareness of this entity and early recognition is of the crucial importance. We believe that in all these patients complementary studies should be conducted to exclude associated malformations or systemic hemangiomas. Suggested minimal guidelines include a complete neurologic evaluation with neuroimaging studies (cranial ultrasound in infants with open fontanelles, magnetic resonance imaging, magnetic resonance angiography) to rule out structural cerebral defects and intracranial vascular alterations; a careful cardiac examination including echocardiography and measurement of four limb blood pressures to exclude possible cardiac defects and aortic coarctation; and ophthalmologic evaluation. Children with intracranial arterial malformations are at risk of cerebrovascular disease due to progressive occlusion of the anomalous arteries, and close follow-up of neurologic status is required. The infants, especially those with hemangiomas in the mandibular area, are at high risk at developing life-threatening airway hemangiomas, and any appearance of stridor, cough, cyanosis, and hoarseness, should be promptly and carefully evaluated. To conclude, children with PHACES require careful, close and multimodality monitoring and treatment in specialized comprehensive clinics.

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J. Roganović

Pediatrics Clinic, University Hospital »Rijeka«, Istarska 43, 51000 Rijeka, Croatia
e-mail: jelena.roganovic@ri.t-com.hr

PHACES SINDROM – PRIKAZ SLUČAJA I PREGLED LITERATURE

SAŽETAK

U ovom prikazu iznosi se slučaj dvogodišnjeg ženskog nedonoščeta s PHACES sindromom. PHACES predstavlja široki spektar kongenitalnih anomalija, uključujući i slijedeće primarne osobine: malformacije mozga u stražnjoj lubanjskoj jami posterior, velike hemangiome na licu, arterijske anomalije, srčane mane i koarktaciju aorte, abnormalnosti oka te ventralne razvojne defekte. Prikazan je i pregled literature o ovom rijetkom oboljenju.