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Case Report

PHACE syndrome: a frequently overlooked entity

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ABSTRACT

Infantile hemangiomas are the commonest vascular tumors of infancy. About 10% are associated with PHACE syndrome, a rare condition presenting with multiple systemic anomalies along with large cervicofacial hemangiomas**.** We present two case reports of this rare entity. First, a six year old female, with cutaneous hemangiomas involving the face and oral cavity, and extracutaneous hemangiomas involving the parotid glands, choroid and peripapillary region of the eye. MRI brain revealed presence of vascular malformations in the circle of Willis along with impingement of optic nerve. MRI head and neck region confirmed the presence of hemangiomas in bilateral parotid gland, right upper eyelid near medial canthus and in the suprasternal region. Second, a three-month-old female presenting with stridor along with hemangiomas involving segment 3 of face, oral cavity and parotid glands. CECT neck and Chest showed hemangiomas involving bilateral parotid and submandibular glands. Mediastinal involvement with extraluminal compression of airway was noted. Microlaryngobronchoscopy did not reveal presence of any airway hemangiomas. Ophthalmological examination showed signs of optic nerve hypoplasia. In both the cases, all the clinico-radiological findings were put together to establish the diagnosis. Both of them also showed significant response to the oral propranolol therapy. Due to the rarity and overlapping features of this syndrome, there is a high chance to overlook this diagnosis. A high index of suspicion and awareness about the features is needed to identify this condition and provide specific treatment.

Keywords: Infantile hemangiomas, Mutltisystemic involvement, Neurocutaneous syndrome

INTRODUCTION

PHACE syndrome is a rare neurocutaneous syndrome, with less than 400 reported cases in the literature. The acronym PHACE was first used by Frieden et al in 1996, encompassing a constellation of anomalies: Posterior fossa malformations (P), hemangiomas (H), arterial anomalies (A), coarctation of aorta and cardiac defects (C), and eye abnormalities (E). When associated with ventral developmental defects like sternal clefting and/or supraumbilical raphe, it can be referred to as PHACES syndrome.[1] Facial segmental hemangiomas are the hallmark feature of the syndrome, with association seen in about 2%-3% of infantile hemangioma cases. Seventy percent patients present with only one other extracutaneous manifestation.[1,2] Here we present two case reports of PHACE syndrome highlighting the multisystemic manifestations.

CASE REPORT

A six-year-old female child, presented to the OPD with complains of swelling of the lips with a vascular appearing lesion, first noted at around three months of life, that started to gradually increase in size since last one year. This was associated with intense pain, difficulty in eating and swallowing, along with ulceration and crusting over the lips. She also had history of progressive loss of right sided vision and severe headaches since last

4-5 years. ENT examination revealed diffuse vascular swelling over the lips (lower>upper), with extension into inner labial mucosa. The swelling had a nodular surface with crusted erosions. Multiple ill-defined bright erythematous patches were also noted over the hard palate, ventral surface of tongue and floor of mouth (Figure 1A). Similar lesions were seen over the pre and post auricular area, medial canthi of eyes, dorsum of nose, lateral side of neck. A swelling, approximately (3x2 cm) was present over the right parotid region, which was soft, non-tender, non-fluctuant (Figure 1B-C).

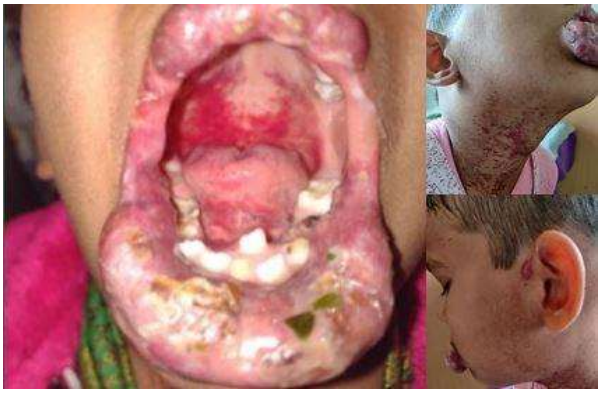

Figure 1: Cutaneous hemangiomas involving, A) oral cavity, B) neck, C) pre auricular area.

Otoscopy revealed erythematous lesion over the external auditory canal and the tympanic membrane (Figure 2). Pure tone audiometry showed bilateral mild to moderate sensorineural hearing loss. Laryngeal examination was within normal limits. Owing to the visual complaints, an ophthalmological examination was done, which revealed right disc cupping, choroidal and peripapillary hemangiomas on fundoscopy.

Figure 2: Hemangioma involving the tympanic membrane.

This constellation of findings was further investigated, and a USG was done for the bilateral parotid swelling showing bilaterally enlarged bulky lobes, with increased vascularity on color flow, suggesting haemangioma. MRI scan confirmed presence of multiple hemangiomas, seen as hypointense on T1 and hyperintense on T2 in bilateral parotid gland, right upper eyelid near medial canthus and in the suprasternal region. MRI brain with orbital cuts was done in view of the eye findings, which revealed the incidental finding of vascular malformation in Circle of Willis (Figure 3).

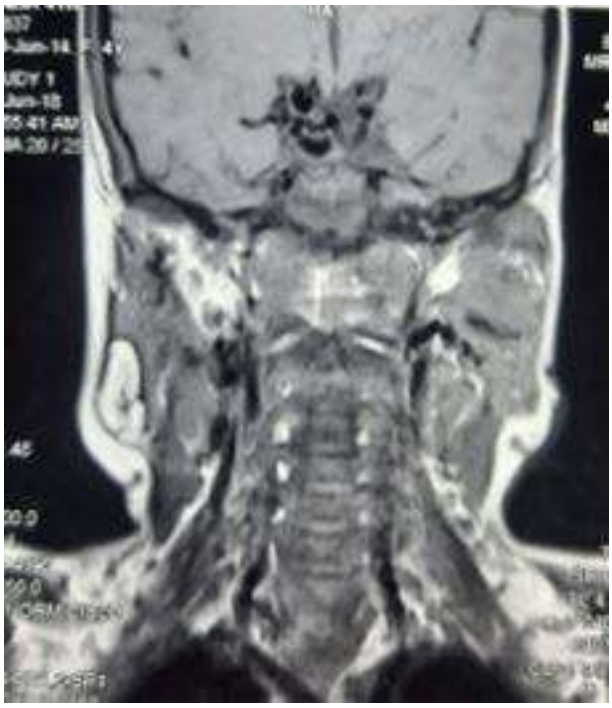

Figure 3: MRI brain showing vascular malformation in circle of Willis.

Impingement of right optic chiasma and nerve by tortuous vascular channels was also noted. Echocardiography done as part of the described syndrome workup was within normal limits. Putting together the history, clinical and radiological findings into the given diagnostic criteria (Table 1), diagnosis of PHACE syndrome was established.

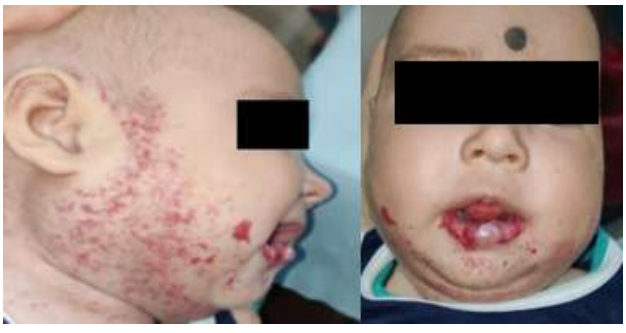

Figure 4: Hemangiomas involving segment 3 of face.

The patient was started on systemic steroids for the acute exacerbation and oral propranolol (1 mg/kg/dose), following which the lip swelling reduced and the patient had symptomatic relief. The parotid swelling reduced and

the cutaneous lesions also showed significant response to the propranolol therapy. Patient also remains in follow up with neurology and ophthalmology department. A three month female was referred to the ENT OPD for evaluation of stridor present since one month after birth. There were intermittent episodes of noisy breathing throughout the day, associated with fast breathing and suprasternal retractions. On examination of the patient, multiple cutaneous erythematous lesions were noted on the face of the child. With the presentation of these segmental facial hemangiomas along with stridor, a possible diagnosis of PHACE syndrome was considered, and a detailed history and examination was done.

Table 1: PHACES syndrome diagnostic criteria-revised.

Organ system	Major criteria	Minor criteria
Arterial anomalies	Anomaly of major cerebral or cervical arteries.* Dysplasia# of large cerebral arteries. Arterial stenosis or occlusion with or without moyamoya collaterals Absence or moderate-severe hypoplasia of 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).	Aneurysm of any of the cerebral arteries.
Structural brain	Posterior fossa brain anomalies, Dandy-Walker complex, other hypoplasia/dysplasia of the mid and/or hindbrain.	Midline brain anomalies, malformation of cortical development.
Cardiovascular	Aortic arch anomalies, coarctation of the aorta, dysplasia, Aneurysm, aberrant origin of the subclavian artery with or without a vascular ring.	Ventricular septal defect, right aortic arch/double aortic arch, systemic venous anomalies.
Ocular	Posterior segment abnormalities, persistent hyperplastic primary vitreous, persistent fetal vasculature, retinal vascular anomalies, morning glory disc anomaly, optic nerve hypoplasia, peripapillary staphyloma	Anterior segment, abnormalities, microphthalmia, sclerocornea, coloboma, cataracts
Ventral/midline	Anomaly of the midline chest and abdomen, sternal defect, sternal pit, sternal cleft, supraumbilical raphe	Ectopic thyroid hypopituitarism Midline sternal papule/hamartoma
Definite PHACE		
Hemangioma >5cm of the head including scalp PLUS 1 major criteria or 2 minor criteria, hemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 2 major criteria		
Possible PHACE		
Hemangioma >5cm of the head including scalp PLUS 1 major criteria or 1 minor criteria, hemangioma of the neck, upper trunk or trunk and proximal upper extremity PLUS 1 major criteria 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 dolichooectasia.

The facial lesions were first noted at around day 10 of life, involving the oral cavity, which gradually progressed to involve the segment 3 of face. Multiple erythematous non blanchable lesions, were seen involving the oral cavity (lips, floor of mouth, ventral surface of tongue), perioral area, the neck extending upwards involving both preauricular areas and the sternal region (Figure 4). During the course of workup, patient developed bilateral parotid region swelling which was soft, non-tender with overlying skin covered with discrete vascular lesions. With high index of suspicion, the child was admitted for a full workup of PHACE Syndrome. A CECT Neck was done, which revealed the presence of multiple large lobulated avidly enhancing lesions involving bilateral parotid and submandibular glands. Mediastinal involvement, with large extraluminal hemangiomas causing airway compression was also noted (Figure 5). MRI brain did not reveal any intracranial abnormality. Echocardiography revealed, patent foramen ovale with a left to right flow and an ejection fraction of 65%. On ophthalmological examination, vision was normal, however, on fundus examination, the right disc was pale with attenuated vessels and parapapillary atrophy and therefore denoting optic nerve hypoplasia. Microlaryngobronchoscopy under general anaesthesia revealed no intraluminal hemangiomas.

Assembling all the findings, a diagnosis of PHACE syndrome was made and the child was put on oral propranolol therapy (1mg/kg/day). After one month following the therapy, the cutaneous lesions and episodes of stridor significantly decreased. The patient is on

monthly follow up since last six months, showing significant improvement.

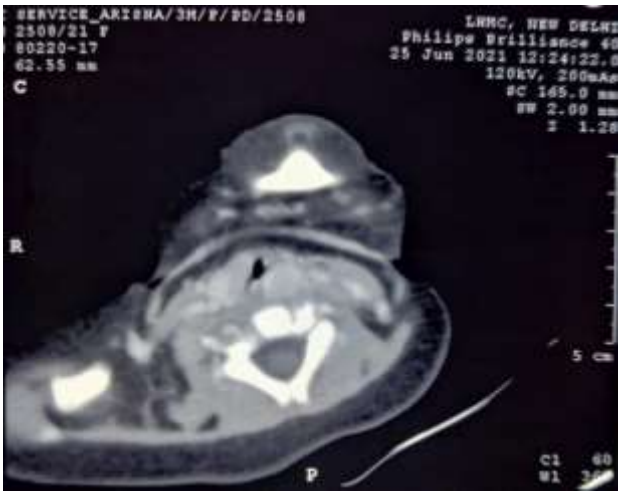

Figure 5: CECT showing hemangioma compressing the trachea on the left side.

DISCUSSION

Our patients presented with multiple manifestations of the Syndrome, which were identified and put together to reach the diagnosis. Therefore, it is important for the clinicians to be aware of this rare entity, to properly approach and manage such cases. PHACE syndrome is a rare disorder and therefore limited literature is available worldwide. The etiopathogenesis of the syndrome is unclear till now, the most accepted proposed hypothesis being developmental error expressed between 6-8 weeks of gestational age.[1] The syndrome shows a striking female preponderance with a male: female ratio of 1:9. This could be attributed to an X-linked dominant condition with lethality in males.[1-4] Both of our patients were females too. The syndrome presents with multiple anomalies, involving multiple organ systems. Facial hemangioma is the hallmark feature and it has been observed that segmental or large facial infantile hemangiomas, have about 20-31% chance of being associated with PHACE syndrome.[2]According to the cases reported, exclusively left sided facial hemangiomas predominate (43%) over right sided (29%) and bilateral lesions (27%).[2] Extracutaneous hemangiomas have been reported in 22% cases, and airway hemangiomas have been seen in 52% cases, with subglottis being the commonest site.[1,5,6]

Cerebrovascular anomalies are the most commonly seen extracutaneous manifestation, mostly involving posterior fossa, most common being Dandy-Walker malformation. Reported arterial anomalies include aneurysmal dilatations and major cerebral or cervical artery anomalies. Case 1 presented with vascular malformation in the circle of Willis. Cardiac anomalies are seen, in more than one third cases, with coarctation of aorta being the commonest defect. Ophthalmological features are usually seen ipsilateral to facial hemangiomas and include colobomas, choroidal hemangiomas, microphthalmos, optic atrophy, optic nerve hypoplasia, congenital cataracts. Case 1 had right disc cupping, choroidal and peripapillary hemangiomas and case 2 showed signs of optic nerve hypoplasia. Association with ventral developmental defects like sternal clefting, supraumbilical raphe, which are visible on cutaneous examination have also been reported.[1-4,5,7,] A consensus was reached for establishing a diagnostic criterion for PHACE syndrome in 2009 by stratifying the patients into 2 categories: definite PHACE syndrome, possible PHACE syndrome, based on the presence of major and minor features. This was then modified in 2016 (Table 1).[8] The syndrome shows a wide spectrum of features, but most of the patients present with only one of the extracutaneous features and hence, there are high chances to overlook this syndrome while making the final diagnosis.

In a patient presenting with infantile hemangiomas possibility of PHACE syndrome should be considered and full workup should be done, so that specific interventions are timely taken to avoid complications. The workup should include complete general physical examination, a complete cardiac, neurological and ophthalmological evaluation. Apart from the findings described in the criteria, there were some rarely reported findings we came across while examining our patients. Airway hemangiomas have been reported as the leading cause for stridor and breathing difficulties in patients of this syndrome.[5,6] However, in case 2,we found a very rare finding of multiple hemangiomas of the mediastinum causing extraluminal airway compression leading to stridor.

Hearing loss has been reported in only about 13 patients of PHACE syndrome till now, most common being sensorineural hearing loss.[9] Case 1 showed a similar pattern of hearing loss. We observed tympanic membrane hemangioma in case 1, that is a rare examination finding and only one previously such reported finding in association of PHACE syndrome was found in the literature.[9] Reports of extracutaneous hemangiomas involving the parotid gland are also very few, and this observed in both our reported cases.[5,11] Management involves a multidisciplinary approach, with specific treatment of the manifestations by multiple specialty teams. Over the years, propranolol has emerged as a preferred drug for infantile hemangiomas, although controversaries remain over the risk of developing CVA in patients with arterial disease. Steroids (oral or intralesional) have showed symptomatic improvement in patients but followed by recurrence.

CONCLUSION

Though, Otorhinolaryngologic manifestations have not been included in the classically defined PHACE syndrome, we observed hemangiomas involving oral

cavity, parotid and submandibular glands, ear, mediastinum along with hearing loss. Therefore, ENT and Head and neck examination should be a part of the workup of the patient. Clinicians need to be aware of this frequently missed entity. More experiences with such reported cases can help establish the course, nature and proper management protocol of the syndrome.

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