Kanem J Med Sci 2023; 17(1): 40 - 48

ISSN 2006-4772
https://doi.org/10.36020/kjms.2023.1701.007

Case report

PHACE syndrome in a Nigerian newborn: case report and literature review

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Abstract

Background: PHACE syndrome is a rare neurocutaneous disorder characterised by large cervicofacial haemangiomas and associated anomalies of the brain, cerebro-vasculature, aorta, heart, and eyes. This case report describes the clinical presentation, management, and literature review of the disorder. **Case Report:** An hour-old term baby girl presented with a large midline facial haemangioma, microcephaly with absent anterior fontanelle, right microphthalmia, and absent left eye. She also had multiple seizures. There were telangiectatic areas all over the extensor surfaces of both the upper and lower limbs. There was a wide disparity between the heart rate and pulse rate with a radio-radial delay. The respiratory and digestive systems were essentially stable. Transtemporal and trans-posterior fontanelles USS showed hydrocephalus in the lateral ventricles. A brain CT scan showed intracranial defects in the posterior fossa. Based on the haemangioma, posterior fossa brain malformation, cardiovascular, ocular, and signs of cerebrovascular anomalies, the diagnosis of PHACE syndrome was made. A multi-disciplinary treatment approach was implemented. However, the patient died on the 29th day of life. **Conclusion:** PHACE syndrome is a rare condition that has only been described three hundred times in medical literature. The Multidisciplinary approach to management can be challenging in low-resource settings. However, knowledge of the features is crucial for the diagnosis and proper management of PHACE syndrome patients.

Keywords: *Haemangioma, Neurocutaneous disorder, Newborn, PHACE syndrome*

Introduction

PHACE syndrome, first described by Frieden *et al* in 1996, is a congenital neurocutaneous disorder characterised by large facial or cervical haemangiomas along with congenital anomalies of the cardiovascular system, brain, and eye.[1] The acronym PHACE stands for **P**osterior fossa malformations, **H**aemangiomas, **A**rterial abnormalities, **C**ardiac defects, and **E**ye anomalies.[1] When developmental defects such as sternal clefting or supraumbilical raphe are also present, the acronym PHACES is used instead.[2,3] This rare congenital disorder occurs in 2%-3% of infantile haemangiomas (IH) which are the most common neurocutaneous vascular tumours in infancy. The majority of infantile haemangiomas are benign and have a self-limited course.[4,5] However, in about one-third of infants, they are associated with extracutaneous anomalies consistent with the diagnosis of PHACE(S) syndrome.[6]

Cite this article as: Adenike O. Jimoh, John E. Ekedigwe, Maryam Shehu, Hassan Shehu, Sunday I. Gargadi, Ngozi Rex-Onuh.; PHACE syndrome in a Nigerian newborn: case report and literature review. Kanem J Med Sci 2023; 17(1): 40 - 48.

Received: 9th February 2023 **Accepted: 23rd May 2023** **Published: 20th June 2023**

Case report

An hour-old baby girl presented to the special care baby unit (SCBU) with a large midline facial haemangioma. She was delivered via spontaneous vaginal route at 39 weeks + 2 days gestation to a Para 4 +1 (3 alive) mother. She had an APGAR score of 5 at 1 minute and 6 at 5 minutes, a birth weight of 3kg, and a length of 45cm. The pregnancy was noticed by the mother to be larger than previous ones and an USS done confirmed polyhydramnios. Otherwise, the pregnancy was uneventful. Her parents were non-consanguineous and did not have a family history of haemangiomas.

Physical examination revealed a conscious, pink baby with oxygen saturation of 90% in room air. She had a large frontonasal haemangioma measuring 6.5 x 4.5cm in its widest diameter. (Figure 1a). She had a cleft lip and palate with an extension of the haemangioma through the defect. There was right microphthalmia and an absent left eye, rudimentary left ear pinna with no meatal opening but the right ear was present and well-formed with meatal opening. There were telangiectatic areas over the extensor surfaces of both the upper and lower limbs. (Figure 1b). She also had microcephaly (occipitofrontal circumference = 26cm), absent anterior fontanelle but a patent posterior fontanelle about 0.5 x 0.5cm. No defect along the vertebrae. The heart rate was 160 beats per minute, but the pulse rate was 120 beats per minute with radio-radial delay. The apex beat was at the 4th left intercostal space, midclavicular line, heart sounds were 1st and 2nd only, and there were no abnormal auscultatory findings. The respiratory rate was 60 cycles per minute, with equal chest expansion, and breath sounds were vesicular. The abdomen was full, moved with respiration and there were no enlarged organs. The anus was patent and normally placed with a normal sphincteric tone. She had normal female external genitalia.

On the 5th day, there was an episode of mild bleeding from the haemangioma which resolved spontaneously and by the second week of life the haemangioma spontaneously started regressing. The colour changed from a dark purplish red colour to a pale colour. (Figure 1c). She also developed neonatal jaundice on the 5th day of life, which was managed with phototherapy. In the 3rd week of life, she developed seizures, described as multifocal clonic seizures involving both upper and lower limbs and twitching of the face.

As part of the workup for the clinical diagnosis of PHACE syndrome, an echocardiogram was done which showed normal findings; a transtemporal and transfontanelle (posterior fontanelle) ultrasound scan which revealed a hydrocephalus in the lateral ventricles; a brain CT scan was done which showed a posterior cranial defect in the occipital bone and an empty orbit. There was asymmetrical lateral ventriculomegaly with the left lateral ventricle being larger than the right. The left orbit was empty. There was no anterior fontanelle and no left external auditory meatus.

The posterior cranial fossa was smaller than normal for the age. (Figure 1 d, e, & f).

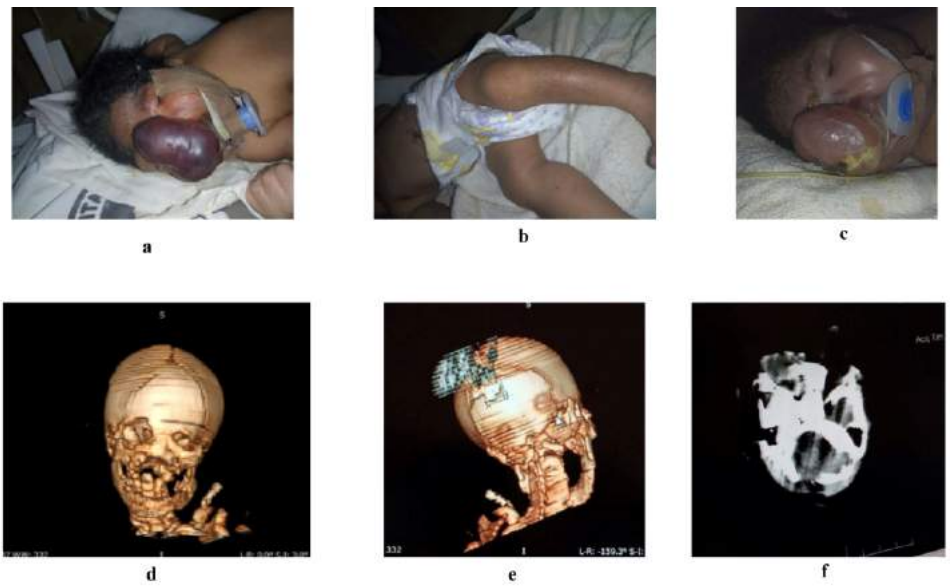

Figure 1: Midline frontonasal haemangioma (a); telangiectasia on lower limbs (b); Involuted haemangioma by second week (c); Brain CT scan: volume rendered image of skull showing defect of left orbit (d), posterior fossa defect (e), empty left orbit and absent left external auditory meatus (f)

A multi-disciplinary treatment approach was implemented. The airway was maintained using an oropharyngeal airway while feeding was through an orogastric tube. Counselling and supportive care were given to the parents. Parents were in denial of the patient's condition and also had serious financial constraints. The cost of care was mainly from the benevolence of the managing team. However, due to financial constraints, the parents signed and left the hospital against medical advice. The patient was reported to have died three days later, at 29 days of life.

Discussion and Literature Review

PHACE syndrome is considered to be a non-hereditary condition though the aetiology is not fully understood. Numerous causes have been hypothesized, including somatic mutations in the cancer pathways,[7] defective embryogenesis between weeks three and 12 of gestation[8] before or during vasculogenesis, and altered haemodynamic,[9] but none has been definitively identified. Most cases of PHACE syndrome are sporadic with a female predominance of 9:1, raising further suggestions by some authors that the aetiology may be correlated with a mutation on the X gene.[9,10] Correlation between the haemangioma incidence and prenatal illness or drug use is, however, yet to be demonstrated.[11]

The index patient presented with the main feature of the neurocutaneous disorder- a large haemangioma greater than 5cm. The haemangioma may be absent, subtle at birth, or obvious after birth. However, nearly all are present at the end of the first month of life. It can present as telangiectasias, solitary lesions, confluent plaques, small papules that assume a specific distribution, or as tumours with deeper involvement,[12] as was seen in the index patient. The distribution pattern in some cases suggests dermatomal involvement with trigeminal division V1 being the most commonly affected dermatome.[3] It can occur unilaterally or bilaterally, but left-sided facial haemangiomas predominate.[3,13] Reports are linking the distribution of facial haemangioma and extracutaneous manifestations leading to the division of the face into four segments, not related to the dermatomes but to the prominences of facial development:[8,11] frontotemporal (segment 1), maxillary (segment 2), mandibular (segment 3), and frontonasal (segment 4). Haemangiomas on the frontotemporal and frontonasal segments have a higher risk of ocular, cerebrovascular, and brain involvement, whereas those on the mandibular segment correlate with a potential risk of midline and cardiovascular defects.[11,14] This link between the frontonasal haemangioma and the specified extracutaneous features was manifest in this patient. The haemangiomas, progress in three phases, irrespective of location. They undergo a proliferative phase, a stabilization phase, and finally, an involution phase which often leads to complete regression.[15,16] The natural course is a rapid proliferative phase in infancy characterized by rapid growth of abnormal blood vessels during the first six months of life and extending to the first 10–12 months of life. This is followed by a gradual involutional phase at about one year of age and can take years for complete involution.[17,18]

However, it was observed that involution of haemangioma in the index patient occurred within the first three weeks of life, though complete regression did not occur up till the demise of the patient. This rapid involution raises a possibility that the haemangioma could have been a rapidly involuting congenital haemangioma (RICH), which has been postulated to be a variant of infantile haemangioma exhibiting prenatal growth.[19] The extracutaneous findings consistent with PHACE syndrome make infantile haemangioma a more likely differential diagnosis in this case, though a genetic study to identify the glucose transporter protein isoform 1 (GLUT1) expressed by the latter[19] would have further clarified the assumption.

The cerebrovascular involvement in PHACE syndrome accounts for 91% of the extracutaneous presentation.[14,20] It is typically related to the ipsilateral internal carotid artery. There may be stenosis or occlusion of the internal carotid artery leading to Moyamoya disease, aneurysmal dilatation of the carotid artery, agenesis, or hypoplasia of the carotid artery.[14,21] Other vascular abnormalities include dilated cerebrovascular vessels and persistent (primitive) trigeminal arteries.[21] Seizures, strokes, and even death are the most striking presentations of cerebrovascular abnormalities.[13,22] The seizures the index patient had reflects a likelihood of cerebrovascular

abnormalities as the brain CT scan had also revealed multiple intracranial anomalies. Cardiovascular findings constitute 67% of the extracutaneous manifestation.[14,20] The cardiac defects can present as patent ductus arteriosus, ventricular septal defects, atrial septal defects, pulmonary stenosis, cor triatriatum, tricuspid atresia and stenosis, tricuspid aortic valve, atrial enlargement, ventricular hypertrophy, tetralogy of Fallot, ectopia cordis, or patent foramen ovale.[23,24] The most frequent cardiovascular abnormalities, however, are aberrant subclavian artery, with or without vascular rings, and coarctation of the aorta, which are present in 19-30% of cases.[13] While the echocardiogram showed a normal finding, a radio-radial delay, as elicited in our patient suggests a narrowing of the aorta proximal to the left subclavian artery stenosis, in the context of aortic coarctation.[25] Other aortic anomalies that have been reported in PHACE syndrome include subclavian or innominate artery aneurysms, ascending aorta or aortic arch aneurysms, anomalous left superior vena cava, congenital valvular aortic stenosis, ischaemic steal syndrome, cervical aortic arch, right aortic arch, hypoplastic descending aorta, double aortic arch, and double aortic coarctation.[1,21] The brain abnormalities seen in about 50% of cases mainly involve the posterior fossa, particularly the Dandy-Walker malformation and less commonly cerebral hypoplasia and cortical dysgenesis.[20,25] Other abnormalities that have been reported include transverse sinus thrombosis, hypoplasia of corpus callosum or septum pellucidum, ipsilateral-frontal lobe calcifications, microcephaly, and absence of foramen lacerum.[26] Our patient presented with microcephaly and a posterior fossa defect (occipital cranial bone defect, underdeveloped posterior cranial fossa). Children with PHACE syndrome may also present with Horner syndrome, auditory deficits, headaches, and developmental delays.[27-29] Tangtiphaiboontana *et al.*[30] reported 20 children with delays in speech and gross motor domains, out of 29 children with PHACE syndrome. Eye abnormalities have been reported in about one-third of cases.[31] Most of the abnormalities are on the same side of the haemangioma. A large number of ophthalmologic abnormalities have been reported including microphthalmia, optic nerve hypoplasia, optic atrophy, morning glory disc anomaly, persistent hyperplastic primary vitreous, iris vessel hypertrophy, iris hypoplasia, formation of a staphyloma, congenital cataracts, sclerocornea, exophthalmos, cryptophthalmos, corneal opacity, posterior embryotoxin, and coloboma.[32-34] Other abnormalities that have been reported include endocrine changes (hypopituitarism, hypothyroidism, adrenal insufficiency), feeding difficulties, dysphagia, and enamel hypoplasia.[35-37] The sternal defects seen in PHACES are evident clinically and may be partial, consisting of a subtle sternal pit without underlying soft tissue or bony loss, or complete.[38] They have been observed in about 30% of the cases with the S3 segment most commonly involved.[27,39]

The diagnosis of PHACE syndrome is made following the identification of characteristic features, detailed history, thorough clinical examination, and a series of specialized tests. A consensus-based diagnostic criteria was first established in 2009[40] and updated in 2016.[41] These diagnostic criteria are stratified into two categories: definite PHACE syndrome and possible PHACE syndrome. Definite PHACE requires the presence of a characteristic segmental haemangioma or haemangioma >5cm on the face or scalp plus one major criterion or two minor criteria. Possible PHACE requires the presence of a haemangioma >5cm on the face or scalp plus one minor criterion.[29] (Table 1). Our index patient had a large frontonasal haemangioma and in addition, two major criteria: the posterior fossa defect (structural brain anomaly), a feature of subclavian artery stenosis (cardiovascular abnormalities), and one minor criterion: right microphthalmia (ocular abnormalities).

Table 1: PHACE syndrome Diagnostic Criteria (2016)[40]

Organ system	Major criteria	Minor criteria
Arterial anomalies	Anomaly of major cerebral or cervical 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 for 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 anomalies	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	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 >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

The management was multidisciplinary. The index patient had a paediatric neurologist, paediatric haematologist, surgeon, radiologist, plastic surgeon, nurses, and counsellors in the managing team. There is no standardized treatment protocol for children with PHACE syndrome. The specialists and the treatment protocol depend on the extracutaneous manifestations of each patient. While previous reports have shown regression of haemangioma following the use of prednisolone, propranolol, or vincristine, surgery, or laser therapy, most do not

require treatment as they can spontaneously regress.[17,27,41,42] The main indications for treatment with propranolol and other treatment options are life-threatening infantile haemangioma (causing heart failure or respiratory distress), tumours posing functional risks (e.g. visual obstruction, amblyopia, or feeding difficulties), ulceration, and severe anatomic distortion, especially on the face.[41,43] The therapeutic choice depends on the recommendations of the multidisciplinary team, but oral propranolol is now recommended as first-line treatment and should be administered as early as possible to avoid potential complications from a large haemangioma.[41,43] The use should be considered carefully because of the risk of lowered flow and cerebrovascular accidents, especially when there are CNS arterial anomalies.[44] The index patient had a large haemangioma present at birth as a tumour located in the frontonasal region. The location of the haemangioma and the associated findings of ocular, cerebrovascular, and brain anomalies give credence to the reports[8,14] of specific abnormalities based on the location of the haemangioma. Considering the indications for treatment (large frontonasal haemangioma causing visual obstruction, respiratory and feeding difficulties), the index patient could have had propranolol, but the potential risk of a stroke, our limitation in carrying out a magnetic resonance angiography (MRA) to visualize the cerebral vessels for CVA risk stratification, and the rapid spontaneous regression made the use of propranolol less necessary.

Surgery may be necessary to treat some of the complications of PHACE syndrome including haemangiomas, certain heart defects, and blood vessel abnormalities. Hearing aids or restorative hearing surgery may be necessary to treat hearing loss. Affected individuals and families will also need psychosocial support and genetic counseling. The prognosis is variable and depends on the associated manifestations; though neurological and cognitive associations constitute the most significant source of morbidity.[45] Although our patient did not survive beyond the first month of life, patients will require regular follow-ups to watch for complications and to monitor development. PHACE syndrome should be considered as a differential diagnosis in patients who present with facial haemangioma. Periodic screening is mandatory to treat and prevent complications that may arise from the haemangioma, the extracutaneous features or even the treatment patient is undergoing. Where specialized investigations are not feasible, thorough clinical examination will help in clinching the diagnosis and differentiating from related disorders like Sturge-Weber syndrome, LUMBAR syndrome, Wyburn-Mason syndrome, or even segmental infantile haemangioma with laryngeal compromise.[20] This does not undermine the need for complementary studies to exclude associated malformations or systemic haemangiomas. A complete neurologic evaluation with neuroimaging studies (cranial ultrasound in infants with open fontanelles, brain CT scan, 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 serves as a minimum guideline in evaluating the patient. Our patient would have received a full complement of investigations but for the financial constraints, coupled with the initial denial that the parents had. All investigations done were paid for by staff. This highlights the challenge of managing rare diseases in low-resource settings. Nonetheless, efforts must be made to identify and manage these children

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Conclusion

PHACES syndrome, although uncommon, is probably still under-recognized. To the best of our knowledge, this is the first published article on PHACE syndrome in Nigeria. Facial haemangioma is a common dermatological disorder in children, and it is important to be aware of its potential association with cerebrovascular, cardiovascular, and neurological disorders.

Contribution Details: AOJ contributed to the preparation of the case report, literature review search, and writing of the manuscript, JEE contributed to writing the literature review and reviewing of the manuscript, MS, HS, SIG, and NRO all participated in reviewing the manuscript. All authors approved the final draft.

Conflict of Interest: None
Funding: None

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