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Clinical Diagnosis of Charge Syndrome: A Case Report in A Low Resource Setting

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Abstract

Introduction

The Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and development, Genitourinary anomalies, and Ear abnormalities (CHARGE) syndrome is a rare, autosomal dominant but usually sporadic condition with an estimated prevalence of 1 in 100,000 births. An early diagnosis of CHARGE syndrome is challenging especially in our settings with the absence of advanced genetic testing thus leading to neglect and under-reporting of similar cases. We highlight application of the existing modified diagnostic criteria to diagnose CHARGE cases in resource-limited settings like ours, where genetic testing is difficult to access.

Case Presentation

We report a male African neonate born at term and referred from a nearby district hospital immediately post-delivery due to respiratory distress with cyanosis and multiple congenital anomalies. He was noted to have dysmorphic features, bilateral microphthalmia, and severe microtia with facial palsy. He also had ankyloglossia and hypertelorism of the nipples and was noted to have a unilateral right-sided choanal atresia after failure to pass a nasogastric tube and cotton wisp test. Cardiovascular and genitourinary screening detected conotruncal heart defect and unilateral cryptorchidism with left solitary kidney respectively. Based on his presentation and workup that could be completed in the ward, there was a high index of suspicion of CHARGE syndrome. Application of the updated Blake criteria revealed several major and minor features consistent with the diagnosis, to be confirmed on further multidisciplinary workup. The infant was discharged home in relatively stable condition during the second week of life, with planned follow-up at the cardiology, ophthalmology, and ENT clinics. Unfortunately, he passed away at home before definitive interventions could be initiated, likely due to complications related to his underlying condition.

Conclusion

In low-resource settings like ours, the absence of diagnostic facilities and limited management resources, often means neonates presenting with multiple congenital anomalies go without a confirmed diagnosis or timely multidisciplinary intervention. This can lead to unintentional neglect and delayed escalation of care. However, application of existing updated CHARGE syndrome criteria can serve as a valuable tool to support early recognition and guide initial management potentially preventing avoidable deaths in these patients.

Keywords: *CHARGE syndrome, Choanal atresia, Microphthalmia, Microtia.*

Introduction

Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and development, Genitourinary anomalies, and Ear abnormalities (CHARGE) syndrome. It is a rare, autosomal dominant, but usually sporadic condition with an estimated prevalence of 1 in 100,000 births (1). The highest reported incidence, observed through the Canadian Paediatric Surveillance Programme between 2001 and 2004 was approximately 1 in 8,500 live births (2). To date, no comparable monitoring efforts have been documented in African countries. CHARGE syndrome is most likely caused by denovo mutations in the CHD7 gene (chromodomain helicase DNA binding protein 7), leading to dysblastogenetic and dysneurulative process resulting in disrupted neural crest development affecting several developmental pathways and thus explaining the pleiotropic nature of its phenotypic spectrum. It may also result from in-utero exposure to teratogens or maternal diabetes (1). CHARGE syndrome was first described in 1981, and has been recognized as one of the major causes of congenital anomalies with multi-organ involvement as described above. Additional features include cleft lip and palate, hearing loss, tracheoesophageal fistula, and cranial nerve dysfunction. Over time, diagnostic criteria have evolved, with the Blake criteria undergoing refinement by an international consortium in 2009. The updated guidelines recommend a clinical diagnosis based on the presence of either four major features or three major plus three minor features (3). Confirmatory diagnosis usually requires CHD7 mutation analysis by direct sequencing and Fluorescence in situ hybridization analysis (FISH). Such testing is rarely available in low resource settings, In these contexts, diagnosis must rely solely on clinical assessment and the application of established diagnostic criteria.

Case Presentation

We report a male baby of African origin seen on the 1st day of life referred from a peripheral hospital due to dysmorphic features and difficulty breathing for further evaluation. Mother booked at 13 weeks GA made 8 visits and received the standard antenatal care package. She was non-reactive to syphilis and HIV testing and was euglycemic and normotensive throughout her pregnancy. However, she reported having pruritic vaginal discharge with dysuria and an increase in urinary frequency during the second trimester of pregnancy, which was managed conservatively at home; thus, she continued to have these symptoms on and off. She denied any history of fevers, lower backache, or haematuria. The mother was a social drinker and reported consumption of local alcohol brew early on in pregnancy and admitted to taking a quarter-liter twice a day 2-3 times per week which she continued on and off till 26

weeks of gestation, after which she was advised to stop. She had 4 antenatal ultrasounds, all reported as normal with normal amniotic fluid index.

During her last antenatal visit at 41 weeks, she was noted to be post-date with no signs of progressing labor and thus was induced with oxytocin and was delivered vaginally with an outcome of a male baby with a birthweight of 3.2 kgs and Apgar scores of 7 and 8 in the 1st and 5th minute respectively.

Almost immediately after birth, the baby was found to have a bluish discoloration which improved post-oxygenation with nasal prongs. He was reported to have a poor cry and suck reflex for which a nasogastric tube was inserted and was noted to have right nostril blockage with a patent left nostril admitting the tube normally.

On examination; the baby appeared to have dysmorphic features with facial asymmetry, microphthalmia, down-slanting eyes, sloping forehead, and flattened nasal tip (Figure 1A, 1B, and 1C). He appeared to have a dusky hue (Figure 1C), was anicteric, and had ankyloglossia and hypertelorism of the nipples (Figure 1A and 1B). He was found to have small completely malformed ears bilaterally with absent pinnae, auditory canal, or tags (grade 3 microtia) (Figure 1D and 1E). On cardiovascular examination, the infant had normal and synchronous pulse rate, rhythm, and volume with normal heart sound, no added sounds were detected on auscultation. On neurological examination, he had left infra-nuclear lesion facial palsy with normal primitive reflexes and motor exam. His musculoskeletal system examination was unremarkable. Other systems were essentially normal also. He had a normal penile length of 2.6cm with only a left palpable testicle. On Anthropometric measurements, weight was between the 3rd and 10th percentile signifying Intra uterine growth restriction, while the length was borderline at the 10th percentile, and his Occipital-Frontal Circumference (OFC) was normal at the 50th percentile for age and sex.

On admission, the baby was put on oxygen 1-2litres/min, saturated well above 90% with no signs of respiratory distress, and fed through a nasogastric tube with expressed breast milk gradually weaned to cup feeding and eventually to breastfeeding every 3 hours with no signs of intolerance or spitting up by one week of life. He was eventually weaned off oxygen by the second week of life and had bouts of severe cyanosis only when excessively crying which improved with intermittent oxygen therapy. Once the infant was calm the cyanosis was no longer apparent.

Workup of the baby included basic full blood counts, C-reactive protein (CRP), and renal/electrolytes including serum calcium and normal liver function tests. Echocardiography revealed a double outlet right ventricle with pulmonary atresia and a 6mm mal-aligned ventricular septal defect with a right to left shunt. He also had a large 3mm vertical Patent

Ductus Arteriosus. The ejection fraction was normal at 87%. Abdominal ultrasound screening detected right renal agenesis. The cranial ultrasound done at the bedside was normal. Computerized Tomography (CT) of the head to visualize the choanae and temporal bones was ordered but could not be done due to financial constraints. Genetic studies were unattainable in our setting. Based on the clinical features and in keeping with the diagnostic criteria (Table 1), a diagnosis of CHARGE syndrome was highly entertained.

Fig. 1A

Fig. 1B

Fig. 1C

Fig. 1D

Fig. 1E

Table 1: Clinical characteristics of the patient in relation to the CHARGE diagnostic criteria

Features of CHARGE syndrome		**Patient features**
Major		
Ocular coloboma	Coloboma of iris, choroid, disc, microphthalmia	Microphthalmia
Choanal atresia	Unilateral/bilateral or cleft palate	Unilateral Choanal atresia
Cranial Nerve anomalies	Olofactory tract anomalies, facial palsy, velopharyngeal incoordination	Left facial palsy
Characteristic ear anomalies	Lop or cup shaped, ossicular malformations, chronic serous otitis, mixed deafness, semi-circular canal+/-choclear defects	Grade 3 Microtia
Minor		
Cardiovascular malformations	All types especially conotruncal defects, Tetralogy of Fallot, AV canal defects, aortic arch anomalies	Double outlet RV with pulmonary stenosis, with VSD and PDA.

Genital hypoplasia	Micropenis, cryptorchidism, delayed pubertal development	Right sided cryptochidism
CHARGE facies	sloping forehead, flattened nasal tip	Sloping forehead, flat nasal tip
Occasional		
Renal anomalies	Duplex system, vesicoureteric reflux	Right renal agenesis

Management and follow-up

The mother was counselled about the condition of her baby including the possibility of it being a genetic disease and long-term care treatment and follow up plans required. She urged to be discharged home so she could inform the father (who was not present) of the condition so they could make a uniform decision and care-plan for their baby. She was reluctant to make surgery plans herself without the involvement of her family members. We tried to obtain genetic tests following genetic counselling but did not manage to access them.

The baby was discharged home on D16 of life in a fairly stable condition feeding and oxygenating well at 95-97% in room air, with scheduled follow-up visits at the cardiac center, ENT and ophthalmology unit. At discharge the mother was advised to continue breastfeeding 3-hrly, eye care with an eye patch and artificial tears were prescribed. They performed a cotton wisp test during the ENT review and scheduled an elective naso-pharyngoscopy and auditory brain response test to assess hearing. In the third week, he attended the cardiac center for a detailed ECHO, where they confirmed the cardiac findings and was listed for instilling a Glenn shunt the following week. Two days later, on the 28th day of life, the baby developed a sudden onset of worsening bluish discoloration, difficulty breathing, and inability to breastfeed. He was brought to the emergency department but died before arrival. The exact cause of death could not be confirmed; however, it was elucidated that it could be because of the closure of the PDA resulting in respiratory failure and cardiac arrest.

Discussion

A diagnosis of CHARGE syndrome should be considered in a neonate presenting with Coloboma and or microphthalmos/anophthalmus, choanal atresia, asymmetrical facial palsy or classical CHARGE ears in combination with other specific congenital anomalies (4). In utero exposure to alcohol has been implicated in a non-genetic cause of CHARGE syndrome, as had this patient (1).

Based on the clinical presentation, our patient had the 4 major criteria: choanal atresia, cranial nerve anomaly, characteristic CHARGE ears, and also had bilateral microphthalmia which has frequently been associated with coloboma (5). Our patient had no visible iris coloboma, but

missed the opportunity for an eye evaluation to detect a retinal coloboma which has been reported in up to 90% of cases with CHARGE syndrome (6). The patient also had a unilateral choanal atresia which was picked incidentally during insertion of the nasogastric tube, this represents an essential feature which highly speculates for CHARGE syndrome (7), especially in the presence of the other features. CT would have been ideal to differentiate whether it was membranous or osseous, as their management approaches would differ. Since it was unilateral, it was not an emergency considering the other morbid associating features.

Characteristically patients with CHARGE syndrome have unusual and cup-shaped ears with diminished cartilage and the outer ear with absent seventh cranial nerve innervation (1), however, our patient presented with severe microtia bilaterally, which can feature in CHARGE patients according to Verloes (1). The updated criteria for CHARGE diagnosis requires finding absent or dysplastic semi-circular canals, but this could not be confirmed in the absence of a temporal bone scan. The severity of microtia observed in this patient gives us a high index of suspicion to also suspect the latter (8). The patient had a left-sided facial palsy visible clinically, fulfilling the major criteria of cranial nerve palsy, and is seen to be a reliable predictor of sensorineural hearing loss (7). Temporal Bone CT or MRI could reveal hypoplastic incus, Mondini defect, and absent semi-circular canals. We could not prove sensorineural hearing loss. The absence of swallowing defects, GERD, and aspirations ruled out other cranial nerve involvement.

Cardiac anomalies occur in 50-85% of cases of CHARGE syndrome, as part of the minor criteria. Our patient presented with a conotruncal heart defect, namely double outlet RV with pulmonary atresia, with VSD and PDA. The severity of the lesion and co-existence of underlying genetic syndromes is a predictor of its outcome (9)(10).

Genito-urinary defects can be seen in 50-70% of patients with CHARGE syndrome with slight male preponderance (1). Our patient had a normal sized penis, but had a unilateral cryptorchidism, and, on screening for other renal anomalies, we found a solitary kidney which is reported in cases of CHARGE and fits the additional criteria (7). These may be detected incidentally, as in our case, or later in life due to delays in puberty or pubertal arrest secondary to hypo gonadotrophic hypogonadism (7).

Conclusion

We present this case to highlight the diagnostic, therapeutic and ethical challenges in settings like ours, and discuss the underlying mechanisms behind underreporting. Despite the fact cases are not documented, we still see these conditions on regular basis, which are regrettably neglected, due to the complexity of the numerous malformations coexisting, and fragmented

multi-disciplinary care for neonates, resulting in unduly early and un-intervened deaths of these neonates. Limitations in Molecular and genetic diagnostic facilities to diagnose these babies, is one of the core reasons why physicians lack interest to strive for these babies, thus resulting in them not surviving beyond the neonatal period even if they may not have an entirely poor prognosis. However, improving our awareness of utilizing the available diagnostic criteria which have proved their robustness in fitting CHD7 mutation phenotypes (1), will improve the recognition and reporting of these genetic conditions and allow us to prognosticate and prioritize which cases would be worth investing our limited resources in. This baby amongst many others, did not have critical underlying malformations to result in his early neonatal death, and attempts within our capacity could have been made to prolong life, while we tended to other disciplinary treatment care measures, as it has been recently seen that life expectancy improves if they survive their first year (2). The exact cause of death could not be confirmed through an autopsy but is highly likely to be of cardiac cause, due to the closure of the ductus arteriosus, which would naturally close unpredictably. The death could have been prevented if a confirmed genetic diagnosis had been made and timely cardiac intervention performed. However, due to the child's comorbidities, lack of social support, and financial constraints, timely decisions and appropriate testing and interventions were limited.

Declarations

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Availability of Data and Materials

Not applicable.

Competing Interest

The authors declare that they have no competing interests.

Consent for publication

Written informed consent was obtained from the patient's legal guardian (mother) for publication of this case report and any accompanying images. A copy of the written consent was submitted to the journal editor for review.

Author's contribution

FM and NN admitted the child and worked him up and followed him up. FM and OU collected all the information and prepared the manuscript for submission. TT is medical student who first clerked the case. All authors read and approved the full manuscript

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