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Case Report

Neonatology Section

Vocal Cord Paralysis in Association with CHARGE Syndrome: A Case Report

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ABSTRACT

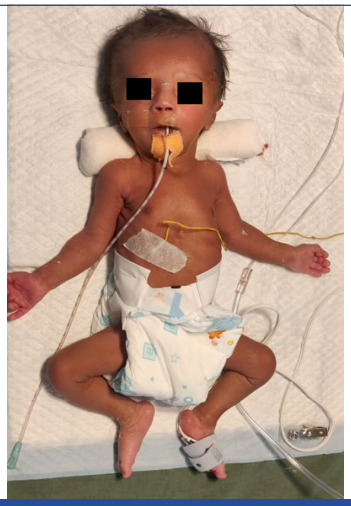
CHARGE (Coloboma, Heart defects, Atresia choanae (also known as choanal atresia), growth Retardation, Genital abnormalities and Ear abnormalities) Syndrome (CS) is a rare genetic disorder characterised by distinct physical and developmental abnormalities. This report presents a case of a seven-day-old male infant who exhibited respiratory distress, noisy breathing and feeding difficulties, was subsequently diagnosed with CS due to a pathogenic variant in the CHD7 gene. The infant exhibited vocal cord paralysis, bilateral profound hearing loss and other characteristic features of CS. Multidisciplinary management included Continuous Positive Airway Pressure (CPAP), antibiotics, laparoscopic gastrostomy, fundoplication and treatment for heart failure. Comprehensive evaluation and genetic testing confirmed the diagnosis of CS, underscoring the need for a multidisciplinary approach to managing associated conditions. This case highlights the importance of early recognition and management of CS. Furthermore, this case report contributes to the existing literature by emphasising the unique clinical manifestations and challenges associated with CS. Early diagnosis and management of this condition can significantly impact the quality of life and outcomes for affected individuals. This report underscores the importance of prompt recognition and referral to specialised care teams for optimal management of CS.

Keywords: CHD7 gene, Dysmorphic features, Genetic testing, Respiratory distress, Retromicrognathia

CASE REPORT

A seven-day-old male infant, born at 37 weeks' gestation via normal vaginal delivery with a birth weight of 3.1 kg, presented to the emergency department with respiratory distress and noisy breathing that worsened in the supine position and during feeding. Born to non consanguineous parents with no family history of inherited diseases, the infant had an uneventful perinatal course and was discharged on day 2 of life. However, on day 7, the mother noticed noisy breathing and feeding difficulties, prompting a paediatric consultation. The child was on breastfeeding and the feeding difficulties included weak sucking, swallowing problems, as well as gastroesophageal reflux.

Upon admission, the infant exhibited respiratory distress, stridor, and chest muscle indrawing that improved in the prone position. Physical examination revealed dysmorphic features, including low-set ears, retromicrognathia, abnormal ear shapes and a preauricular skin tag [Table/Fig-1].

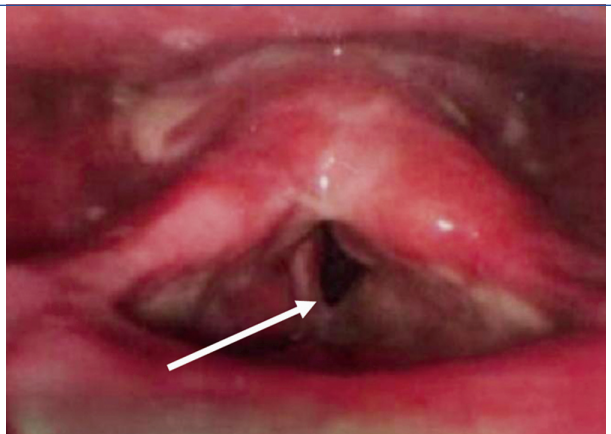


[Table/Fig-1]: Clinical picture.

Ophthalmologic examination was normal, but heart sounds revealed a soft systolic murmur (grade 2) on the left upper sternal border. The infant had generalised increased tone and brisk deep tendon reflexes.

Laboratory results indicated respiratory acidosis (pH 7.16, pCO_2 64 mmHg, HCO_3 20 milliequivalents per liter [mEq/L]), marginal leukocytosis (TLC: 12,700/cmm), SpO_2 86-87%, Random Blood Sugar (RBS) 92 mg/dL, and normal blood ammonia and lactate levels. Urine reducing substance and ketone tests were normal for three consecutive days. The infant was placed on CPAP and first-line antibiotics (ampicillin and gentamicin) after blood was withdrawn for culture.

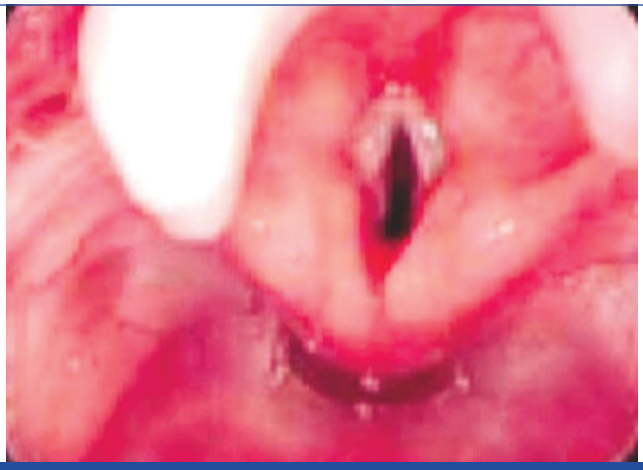
Multidisciplinary evaluation included flexible laryngoscopy, which showed an immobile right vocal cord and oedema of the nasal turbinate, bilateral arytenoids and vocal cords [Table/Fig-2]. Further testing revealed gastroesophageal reflux, and a 2D Echo showed a Patent Ductus Arteriosus (PDA) measuring 1.3 mm, causing heart failure. A hearing test (BERA) reported bilateral profound conductive and neurosensory hearing loss. Genetic testing confirmed CS due to a pathogenic variant in the CHD7 gene.



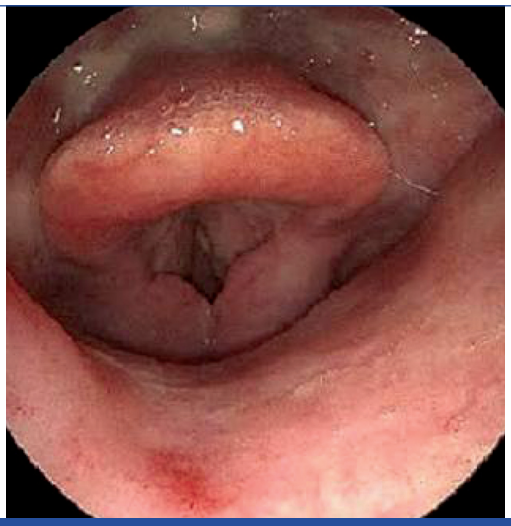
[Table/Fig-2]: Flexible laryngoscopy findings in a seven-day-old infant with CHARGE Syndrome (CS). The image shows an immobile right vocal cord (arrow) and oedema of the nasal turbinate, bilateral arytenoids, and vocal cords, highlighting the airway abnormalities associated with this condition.

Bronchoscopy was repeated on day 48 of life, revealing improved laryngeal oedema, although mild vocal cord oedema persisted [Table/Fig-3]. To address this, the infant received dexamethasone applied

directly to the vocal cords via direct laryngoscopy for five days following reintubation. At four months, the infant underwent laparoscopic gastrostomy and fundoplication, resulting in improved muscle tone and weight gain. Treatment for upper airway oedema included dexamethasone and nasal ciprofloxacin. Repeat bronchoscopy and microlaryngoscopy demonstrated improved vocal cord mobility and reduced oedema [Table/Fig-4]. The infant was discharged on room air at 4.6 months and continues to receive follow-up care for otolaryngology.



[Table/Fig-3]: Flexible laryngoscopy findings in a 48-day-old infant with CHARGE Syndrome (CS). Improved laryngeal oedema, although mild vocal cord oedema persisted.



[Table/Fig-4]: Repeat microlaryngoscopy at 4.2 months of age with CHARGE Syndrome (CS) showing improved vocal cord mobility and reduced oedema following intervention.

At six months, a follow-up otolaryngoscopy examination revealed continued improvement in vocal cord mobility and resolution of upper airway oedema. The infant's weight gain and muscle tone remained stable and he continued to thrive on room air. Ongoing follow-up care will ensure the infant's continued progress and address any potential concerns that may arise.

This case highlights the complexities of CS, emphasising the importance of multidisciplinary care and genetic testing in diagnosis and management.

DISCUSSION

The CS is a rare genetic disorder characterised by a distinct set of physical and developmental abnormalities [1]. The condition typically results from spontaneous mutations in the CHD7 gene, which codes for chromodomain helicase DNA-binding protein 7, located on chromosome 8q12, and follows an autosomal dominant inheritance pattern [1,2]. This gene plays a crucial role in regulating the transcription of tissue-specific genes involved in various developmental stages [2]. The syndrome's name, CHARGE, serves as a mnemonic device, encompassing its primary features: coloboma (eye defects), heart defects, atresia choanae (nasal passage obstruction), retarded growth and development, genital hypoplasia (underdeveloped reproductive organs), and ear anomalies/deafness [1]. Clinical diagnostic criteria for CS were first established in 1998 by Blake KD et al., and later revised in 2005 by Verloes A [3,4].

The presented case of a seven-day-old male infant was reported with respiratory distress and dysmorphic features, ultimately diagnosed with CS, highlighting the importance of early diagnosis and multidisciplinary management of CS. This case presents unique clinical manifestations, complex airway management challenges and associated conditions, underscoring the need for comprehensive evaluation and genetic testing.

Early diagnosis of CS is vital for timely multidisciplinary care. However, diagnosis is challenging due to phenotypic variability and overlap with conditions like 22q11.2 deletion, Kallmann syndrome, Treacher Collins syndrome and VACTERL syndromes, which share features such as genital hypoplasia, cleft palate and heart defects [5]. CS is a complex genetic disorder characterised by multiple congenital anomalies and remarkable variability. The full scope of its clinical features was only fully elucidated after the discovery of the underlying causative gene in 2004. This condition results from autosomal dominant mutations in the CHD7 gene [6]. In the present case, genetic testing was conducted that confirmed a pathogenic variant of the CHD7 gene, revealing CS.

The condition typically occurs sporadically, with rare familial cases [7]. No family history of inherited diseases was reported in present case. Furthermore, the diagnosis is based on a combination of major and minor criteria, including structural and functional abnormalities, which expand upon the original CHARGE acronym [7]. In this case, the patient presented with several features suggestive of the condition. Major criteria include Congenital Heart Defects (CHD), specifically a Patent Ductus Arteriosus (PDA) causing heart failure and retardation of growth and development, evidenced by generalised increased tone, brisk deep tendon reflexes and feeding difficulties. Additionally, ear anomalies and deafness were noted, with bilateral profound conductive and neurosensory hearing loss. Minor criteria include dysmorphic ear features, retromicrognathia, cranial nerve anomalies with an immobile right vocal cord and developmental delay. Other significant findings comprise respiratory distress, noisy breathing, laryngeal and vocal cord oedema and gastrointestinal issues, including gastroesophageal reflux and feeding difficulties [8].

In another similar case reported by Lau CL et al., the infant presented with multiple anomalies, including dysmorphic features, abnormal ear shapes and a preauricular skin tag [9]. Ocular examination revealed a smaller left palpebral fissure, but otherwise normal ocular findings. Multiple lentigines were present on the trunk and back. Respiratory distress was evident, with inspiratory stridor and retraction of the chest wall. Cardiac examination revealed a soft systolic murmur at the left upper sternal border. Additional features included a deviated angle of the mouth, generalised hypertonia, and brisk deep tendon reflexes. Genital examination revealed a micropenis with a stretched penile length of 2.5 cm and a width of 0.5 cm, along with small testes. In the currently reported case, no abnormalities with respect to genitalia was reported. In a study reported by Jain S et al., a consistent pattern of major and minor criteria was observed [10]. Notably, all patients presented with coloboma and either hypoplastic or absent semicircular canals, except for one patient who had an abnormal right vestibular enlargement instead. Additionally, all patients exhibited rhombencephalic dysfunction, abnormalities of the middle or external ear and psychomotor delay. Furthermore, seven patients had malformations of mediastinal organs, including the heart and oesophagus, which varied in severity.

Nevertheless, Pagon's and Blake's criteria are previous diagnostic systems that were considered too restrictive. Later, Verloes A's proposed definition aimed to capture a wider range of symptoms and manifestations. The updated definition of CHARGE syndrome

broadens diagnostic criteria, enabling diagnosis in less typical patients. New categories, "partial" and "atypical" CHARGE, capture cases with mild or unclear symptoms. This expansion has increased diagnosis in borderline cases and reduced "possibly CHARGE" classifications. The revised definition aimed to improve diagnostic accuracy, awareness, and patient care for this rare genetic disorder [4].

Ear anomalies with deafness are a common feature of CS, affecting various components of the ear [11]. In this case, low-set ears, abnormal ear shapes, and a preauricular skin tag, along with bilateral profound conductive and neurosensory hearing loss, were found.

Patients with this condition often have external ear abnormalities (90%) and middle ear malformations (80%), leading to conductive hearing loss. Internally, Mondini defects (90%) cause sensorineural hearing loss, especially affecting high-frequency sounds. This results in complex mixed hearing loss [11]. The Mondini defect, a rare congenital anomaly, was first identified by Gaston Michel in 1863. It involves incomplete cochlear development, resulting in only 1.5 turns instead of the typical 2.5 turns, causing significant hearing loss [12]. Semicircular canal defects occur in 94% of cases, impacting balance and visual processing and contributing to delayed motor development [11].

Visceral malformations in CS frequently involve CHD, affecting 50-85% of cases. The majority of these defects, approximately 75%, are conotruncal in nature. Specifically, common conotruncal defects include Tetralogy of Fallot, which occurs in about one-third of cases, as well as atrioventricular canal defects, Ventricular Septal Defects (VSD), Atrial Septal Defects (ASD), aortic coarctation, and Patent Ductus Arteriosus (PDA) [13]. In the present case, PDA (1.3 mm) with heart failure was found.

Furthermore, aberrant subclavian arteries are also commonly observed. Notably, statistical analysis has revealed a significant association between CHD and other congenital anomalies, including tracheoesophageal fistula, renal malformations and cleft lip/palate, highlighting the complex interplay of developmental abnormalities in CS [13].

The significance of presenting the current case is essential for several reasons. Firstly, it contributes to the limited literature on CS, providing valuable insights into its clinical manifestations and management. Secondly, it highlights the importance of early diagnosis and multidisciplinary care in improving outcomes for affected individuals. Additionally, this case report emphasises the significance of genetic testing in confirming the diagnosis and guiding management decisions. Finally, sharing this case will raise awareness among healthcare professionals about the complexities of CS, ultimately enhancing recognition and care for individuals with this rare and complex condition. By disseminating the knowledge gained from this case, clinicians can better diagnose and manage similar cases, improving the quality of life for patients with CS and their families.

CONCLUSION(S)

This case report highlights the complexities and challenges associated with diagnosing and managing CS, a rare genetic disorder. The infant presented with respiratory distress, vocal cord paralysis and bilateral profound hearing loss, among other characteristic features. Early recognition and multidisciplinary management, including genetic testing, were crucial in improving the infant's outcome. This case underscores the importance of considering CS in the differential diagnosis of infants with congenital anomalies and emphasises the need for comprehensive evaluation and timely intervention.

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