## Case Report

# CHARGE Association with Schizencephaly in a Newborn Infant: A Case Report

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## ABSTRACT

CHARGE association is an increasingly recognized non-random clustering of congenital malformations.
We present a baby with readily recognizable clinical features that lead to a prompt diagnosis of CHARGE association. The baby also had a schizencephaly which makes us ponder that this could very well be a neural crest migratory disorder stressing the need for an expanded classification of "neurocrestopathies".
The recently recommended diagnostic criteria of CHARGE association are also reviewed.

KEY WORDS: CHARGE, choanal atresia, coloboma, neonatal, schizencephaly

## INTRODUCTION

The CHARGE association is a rare disorder that arises during early development and affects multiple organ systems[1]. It is a non-random occurrence of congenital malformations that occurs together more frequently than one would expect on the basis of chance[2,3]. There are certain diagnostic signs which enable a clinician to clinch the diagnosis and involve a multidisciplinary team in the management of this unique condition[3,4].

## CASE REPORT

A single live preterm, small-for-date, girl baby was born a $P^{0+0}$ Bangladeshi mother at 39 +4 weeks by an emergency lower segment Cesarean section due to fetal distress and bradycardia. The cord was around the neck once. The mother was 33 years of age and the father was 40 years old. The parents were non-consanguineous. The mother had primary infertility for about 10 years. She had regular antenatal care at the local polyclinic and was referred to the hospital only at the time of labor. There was no history of any malformations in the family.

The baby's Apgar Score was 3, 7 and 8 at one, five and ten minutes respectively. An endotracheal intubation was done immediately and intermittent positive pressure ventilation was performed. The baby responded to the resuscitation and had spontaneous breathing at about ten minutes of age. The baby became cyanosed immediately on extubation and had to be re-ventilated again.

A nasogastric tube could not be passed through both the nostrils. The weight was 1436 g, length was 43 cm and the head circumference was 28.5 cm, and they were all below the 3rd centile.

The baby had dysmorphic features. She had the distinctive 'CHARGE' facies (Fig. 1). A square facial appearance with a broad forehead with asymmetry and malar flattening was present. The philtrum was long, the nasal columella were prominent and the nostrils had a 'pinched' appearance. There was a high arched palate.

The ears were small, simple, asymmetrical, lowset and posteriorly rotated. There was increased width and decreased length of the ears. The ear lobes were absent, the antihelices were prominent and the conchae were triangular in shape (Fig. 2).

There was hyperteleorism and the palpebral fissures were short. The baby had clenched hands and a short sternum. The labia majora appeared hypoplastic. The cardiovascular system and the abdomen were normal.

A nasal fibroendoscopic examination revealed bilateral posterior bony choanal atresia with a deflected septum. This was confirmed by a CT scan of the nasopharyx (Fig. 3) which revealed narrowing of the internal nostrils with no contrast passage into the nasopharynx due to osteo choanal atresia.

Under general anaesthesia the posterior bony septa formed by the vomer were removed. A 3 mm size 'U' shaped stent was positioned and repeated suction was performed to maintain the patency.

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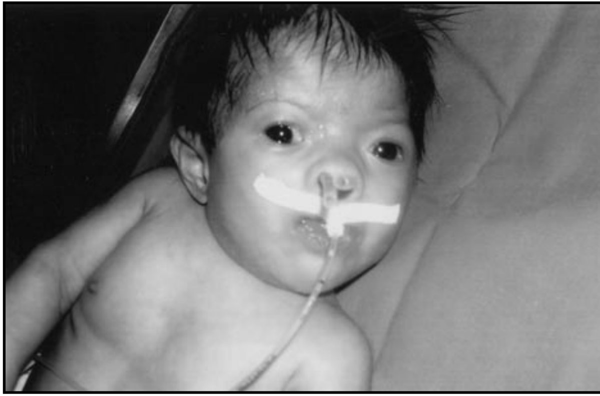

**Fig.1:** The distinctive 'CHARGE facies'

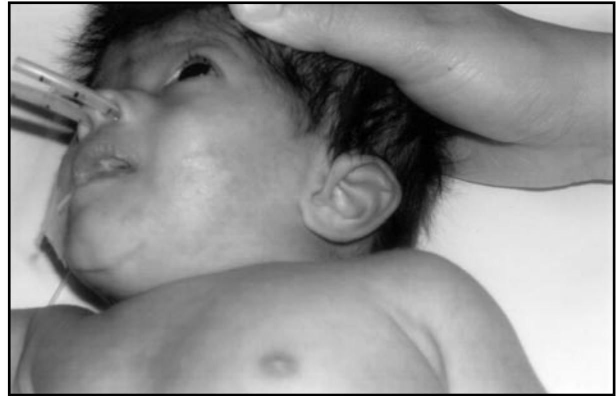

**Fig.2:** The characteristic 'CHARGE ear'.

The baby had assisted ventilation for about five weeks. The baby subsequently had broncho-pulmonary dysplasia and was gradually weaned off the oxygen.

The baby had sucking and swallowing difficulties due to velopharyngeal in-coordination.

**Pertinent investigations**

CT scan of the nasopharynx (Fig. 3) showed narrowing of the internal nostrils with no contrast passage into the nasopharynx due to osteomembranous choanal atresia. MRI Brain (Fig. 4) showed atrophy involving the left parietal lobe. There was a prominent schizencephalic cleft in the left parietal lobe extending into the left frontal lobe.

CT scan of the petrous temporal bone showed defective development of the bony part of the anterior wall of the external auditory canal. The tympanic membrane was not adequately visualized. The ossicular chain of the middle ear was deformed and seemed to be attached to the anterior wall of the middle ear cavity.

On ophthalmologic examination, there was no evidence of any coloboma.

A chromosomal study revealed XX Chromosome and the integrity of the chromosomes was preserved.

A chest skiagram and an ECG were normal. An echocardiography showed the heart to be normal. An ultrasound of the abdomen showed no renal anomalies.

The baby had severe sucking and swallowing difficulties and had to be fed by gavage feeds. There was a global developmental delay. There was microcephaly. The head circumference was 30 cm at about three months of age and this was well below the 3rd centile. There was severe growth retardation.

Thus, this infant had a combination of congenital anomalies, *viz*, a distinctive CHARGE facies, bilateral posterior choanal atresia, characteristic ear abnormalities, retardation of growth and development, swallowing problems (velopharyngeal in-coordination due to cranial nerve IX/X dysfunction), small labia, central nervous system malformation namely schizencephaly and the abnormal ossicular chain which is consistent with a diagnosis of CHARGE syndrome.

**DISCUSSION**

The CHARGE association is a non-random clustering of congenital malformations.

Although it was first described by Hall[1] in 1979, it was Pagon *et al*[2] in 1981 who first coined the acronym CHARGE association, the features of which were coloboma, heart defects, atresia choanae, retardation of growth, genital anomalies and ear anomalies. Pagon *et al*[2] proposed that to make a confident diagnosis of CHARGE association, four of the six major features included in the acronym have to be present and these should include either coloboma or choanal atresia or both[2].

The CHARGE association has an estimated prevalence of 1:10,000[3].

In recent times, several consensus diagnostic criteria have been proposed which incorporate both major and minor features for CHARGE association both to enhance clinical diagnosis and facilitate research efforts[3].

Blake *et al*[3] have proposed that CHARGE association should be considered, if there are one or two major characteristics and several minor characteristics.

The major criteria are coloboma, choanal atresia, cranial nerve involvement and characteristic ear abnormalities.

The minor characteristics occur less frequently or are less specific to CHARGE association. They are a distinctive characteristic facies, genital hypoplasia, cardio-vascular malformations, short stature, orofacial clefting and developmental delay. Our patient had three major characteristics namely bilateral bony posterior choanal atresia,

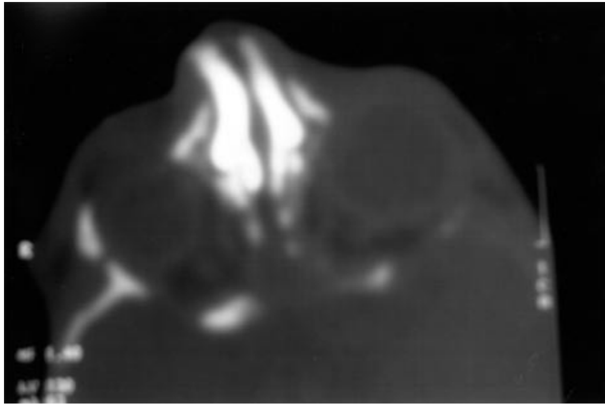

**Fig.3:** Contrast CT nasopharynx: bilateral choanal atresia

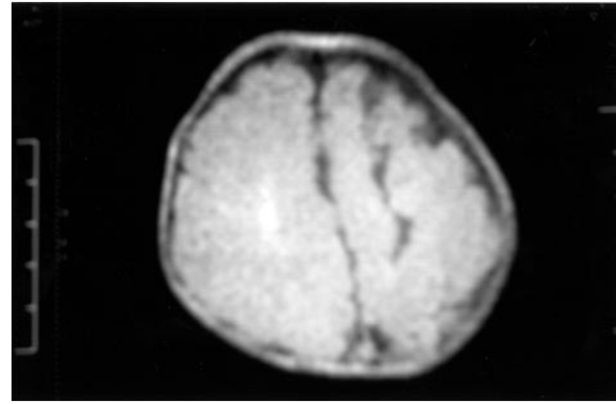

**Fig.4:** MRI Brain.Schizencephalic cleft left parietal lobe

characteristic ear anomalies and severe sucking and swallowing problems due to velopharyngeal dysfunction caused by the involvement of the IX and X cranial nerves. She also had the distinctive facies, developmental delay and growth retardation as minor criteria. The labia majora appeared hypoplastic but this finding is unreliable in the neonatal period.

Bilateral posterior choanal atresia is an uncommon congenital anomaly (one case in 5000 - 8000 live births)[3] and it should always alert pediatricians to the possibility of CHARGE association[3,4]. Choanal atresia is seen in about 50 - 60% of patients with CHARGE association[3,4]. Our patient had bilateral bony posterior choanal atresia.

Eye malformations in the form of coloboma of the iris, retina, choroid or disc occur in more than 80% of patients with CHARGE[3]. Our patient did not have any eye abnormalities.

Distinctive ear anomalies have been reported in 90% of patients with CHARGE association[3]. The characteristic ear is small with increased width and decreased length, asymmetrical with a prominent antihelix and a distinctive triangular concha. The ear lobe is absent. This pattern of ear anomalies is so distinctive that a preliminary diagnosis of CHARGE association can often be made on the basis of the ear shape alone[3,5]. Our patient had the distinctive external ears seen in classical CHARGE association.

Computed tomography of the temporal bone is often helpful in defining structural ossicular and / or inner ear anomalies[3,6,7].

A computed tomography of the petrous bone in this baby revealed defective development of the bony part of the anterior wall of the external auditory canal. The tympanic membrane was not adequately visualized. The ossicular chain of the middle ear was attached to the anterior wall of the middle ear cavity.

Cranial nerve dysfunction is seen in about 70 - 90% of patients with CHARGE association[3,8,9]. There could be anosmia (cranial nerve I) facial palsy (cranial nerve VII), sensorineural hearing loss (VIII) and severe swallowing difficulties (IX, X). Our baby had severe swallowing difficulties due to velopharyngeal in-coordination and needed gavage feeds throughout the period of hospitalization.

A characteristic distinctive facies is seen in 80% of patients with CHARGE association[3,5,9].

The most frequent facial findings consist of a broad forehead, square face, high nasal bridge, full nasal tip, small mouth, facial asymmetry, ptosis, arched eyebrows and laterally protruding ears[3,9,10]. Our baby had the distinctive characteristic face seen in CHARGE association.

Congenital heart defects are seen in 75 - 80% of the patients with the CHARGE association[3]. Conotruncal and aortic arch anomalies are seen most commonly[3,10,11]. Our patient did not have any structural malformation of the heart.

Developmental delay was seen in 100% of the patients with CHARGE association[3]. Our baby had not attained head control till the age of four months.

There was severe growth retardation. The head circumference was well below the 3rd centile and had grown only one cm in four months. Microcephaly is one of the parameters predictive of poor intellectual outcome[12]. The other two parameters that are predictive of poor intellectual outcome are extensive bilateral ocular coloboma and brain malformations[12].

Genital hypoplasia is seen in 70 - 80% of these children. Boys have micropenis and cryptorchidism and girls have hypoplastic labia[3].

Tracheo-esophageal fistula and orofacial clefting are seen in 15 - 20% of the patients with CHARGE association[3]. However, these were not seen in our patient.

Renal anomalies are seen in 25% of children with CHARGE association[3]. These anomalies include horseshoe kidneys, hydronephrosis, renal hypoplasia, solitary or duplex kidneys and

ureteropelvic obstruction. This baby did not have any renal anomaly.

Central nervous system malformations in children with the CHARGE association have been well described in the literature[13]. About 55% of these children have definite central nervous system malformations such as arrhinencephaly, holoprosencephaly and other defects. The presence of central system malformations is most strongly associated with choanal atresia[13]. This baby had a prominent shizencephalic cleft in the left parietal lobe extending into the left frontal lobe.

The term 'schizencephaly' designates the presence of clefts in the cortical hemispheres which result from flawed development of the cortical mantle during cell migration in the first trimester of pregnancy[14].

The etiology of CHARGE association remains speculative. A teratogenic causation was initially thought of but this has not been substantiated.

There is a crucial stage of embryogenesis, when failure to rupture the primitive bucconasal membrane (35$^{th}$ to 38$^{th}$ day) brings about choanal atresia. Conotruncal anomalies result from aberration in cephalic neural crest cell migration during the 4$^{th}$ and 5$^{th}$ weeks after conception. The cochlear duct begins to develop around the 36$^{th}$ day and the eyes develop between days 34 and 44 days post conception, which is also the time during which many cranial nerves are developing. All these malformations in CHARGE association occur early, during the first trimester[3,15].

Another interesting postulate is that CHARGE association seems to result from abnormalities in the development, migration and interaction of the cells of the cephalic neural crest and could belong to a class of the neurocrestopathies[14,15,16].

Interestingly, our baby had schizencephaly which is an important aftermath of a flawed development of the cortical mantle, a cell migratory disorder[14].

Thus, as many of the pathognomonic features of CHARGE association seem to arise secondary to an aberration in cephalic neural crest migration, this area needs to be explored further in establishing the aetiology of this interesting condition.

Most cases of CHARGE syndrome have been sporadic occurrences in an otherwise normal family. There have been chromosomal imbalances seen in some patients[17]. The chromosomal study in our patient was normal.

Tellier *et al*[18] noticed a significant increase in the mean paternal age at birth of patients with CHARGE association as compared with the normal population suggesting the possible role of a dominant mutation or a subtle chromosomal abnormality. Incidentally, our patient's paternal age was forty years.

Infants with CHARGE association who survive early infancy have a better prognosis of growth and mental development[19]. Extensive bilateral coloboma, microcephaly and brain malformations are predictive of poor intellectual outcome[12].

Aspiration is common during infancy due to incoordination of swallowing and gastro-esophageal reflux causing recurrent chest infection leading to increased respiratory morbidity and mortality[20].

Wyse *et al*[11] found that survival was poor with more than one of the following features, *i.e.* cyanotic heart disease, bilateral choanal atresia and tracheo-esophageal fistula.

Tellier *et al*[21] have proposed several criteria for poor survival including male gender, central nervous system and/or esophageal malformations and bilateral choanal atresia.

Since CHARGE association is a multisystem disorder involving various vital organs, a multidisciplinary approach involving specialists from different fields is mandatory in the proper management of these patients[22, 23].

## CONCLUSION

CHARGE association is a chronic and complex anomaly. The diagnosis should be considered in any neonate with bilateral choanal atresia, ocular coloboma, the classic CHARGE 'ears' and the distinctive characteristic CHARGE facies[2,3,4,6,9].

The recently recommended several diagnostic major and minor criteria should also be borne in mind and applied in establishing a diagnosis of CHARGE association[3-6,9,10].

The presence of a neural crest migratory disorder should alert the clinician to examine for the classic presentation of CHARGE association [12-15].

The management of this condition involves a multidisciplinary approach[3,22,23].

Early identification and prompt referral for medical, therapeutic and educational consultative services, regular follow up and a comprehensive intervention program would greatly enhance the morbidity and mortality in this multi-featured disorder characterized by a unique combination of diverse abnormalities[3,22,23].

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