Case Report

Indian Journal of Trauma and Emergency Pediatrics
Volume 7 Number 1, January - March 2015

Charge Syndrome

Liza Bulsara*, Sunil Mhaske, Bipin Rathod*****

Abstract

The CHARGE association was first described in 1979 by Hall *et al*., in 17 children with multiple congenital anomalies who were ascertained by choanal atresia. In the same year, Hittner reported this syndrome in 10 children with ocular colobomas and multiple congenital anomalies, hence the syndrome is also called Hall-Hittner syndrome .Pagon *et al*., in 1981 first coined the acronym CHARGE association (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness) as a non-random association of anomalies occurring together more frequently than one would expect on the basis of chance. The original diagnostic criteria required the presence of four out of six of the CHARGE characteristics. Over the past 15 years the specificity of this pattern of malformations has reached the level that many clinicians now consider it to be a recognizable CHARGE syndrome.

Keywords: Charge Syndrome; Choanal Atresia; Coloboma.

Introduction

CHARGE syndrome was initially defined as a non-random association of anomalies (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies / deafness). In 1998, an expert group defined the major (the classical 4C's: Choanal atresia, Coloboma, Characteristic ears and Cranial nerve anomalies) and minor criteria of CHARGE syndrome. Individuals with all four major characteristics or three major and three minor characteristics are highly likely to have CHARGE syndrome. However, there have been individuals genetically identified with CHARGE syndrome without the classical choanal atresia and Coloboma. The reported incidence of CHARGE syndrome ranges from 0.1–1.2 / 10,000 and depends on professional recognition. Coloboma mainly affects the retina. Major and minor congenital heart defects (the commonest cyanotic heart defect is tetralogy of Fallot) occur in 75–80% of patients. Choanal atresia may be membranous or bony; bilateral or unilateral. Mental retardation is variable with intelligence quotients (IQ) ranging from normal to profound retardation. Under-development of the external genitalia is a common finding in males but it is less apparent in females. Ear abnormalities include a classical finding of unusually shaped ears and hearing loss (conductive and / or nerve deafness that ranges from mild to severe deafness). Multiple cranial nerve dysfunctions are common. A behavioral phenotype for CHARGE syndrome is emerging. Mutations in the *CHD7* gene (member of the chromodomain helicase DNA protein family) are detected in over 75% of patients with CHARGE syndrome. Children with CHARGE syndrome require intensive medical management as well as numerous surgical interventions. They also need multidisciplinary follow up. Some of the hidden issues of CHARGE syndrome are often forgotten, one being the feeding adaptation of these children, which needs an early aggressive approach from a feeding team. As the child develops, challenging behaviors become more common and require adaptation of educational and therapeutic services, including behavioral and pharmacological interventions.

Case Report

3year old female child presented with chief complaint of head injury since 8 days back and vomiting ,projectile ,non bilious also complain of loose motion.On further examination ,we found that she has squint in left eye,nystagmus and webbed neck

Author Affilation: *Resident, **Head & Professor, ***Resident**,** Department of Paediatrics, P.D.V.V.P.F's Medical College, Ahmednagar, India.

Reprint request: Reprint request: Liza Bulsara, Resident, Dept. of Paediatrics, Dr. Vikhe Patil Memorial Hospital, Viladghat, Post-MIDC, Vadagaon Gupta, Ahmednagar-414111.

E-mail: liza.bulsara@gmail.com

also her developmental milestone was delayed. Otherwise, the perinatal and developmental history was normal.

Laboratory investigation

Hb-9.3gm%

TLC-8600

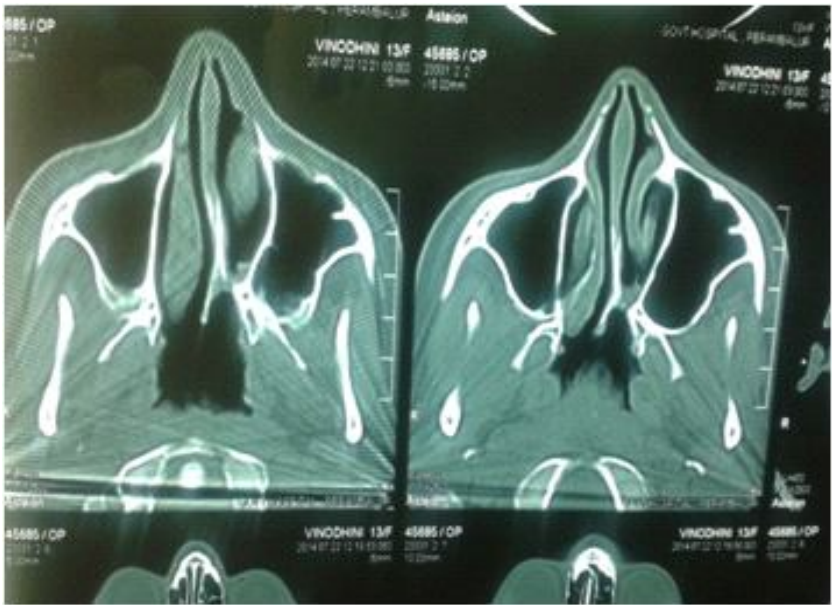
N31,L52,E16 ,M01 ,B00

Platelet-0.23 lacs

On examination unilateral choanalatresia, sensorineural hearing loss on both side. Eye examination revealed left eye micro cornea with typical Coloboma choroid involving optic disc and iris, squint, spontaneous nystagmus, loss of left eye vision. General examination of the patient showed facial asymmetry, polydactyly systemic examination revealed, wide fixed split on auscultation, abdominal land respiratory systems are normal.

Child was investigated. Diagnostic nasal endoscopy showed complete choanal atresia on left side. Severe sensorineural hearing loss on both sides on Pure Tone Audiogram.CT PNS and temporal bones showed posterior Coloboma left eye ,left osseous choanal atresia (Figure 1).

Fig. 1: CT PNSshowing choanal atresia (L).



Discussion

The CHARGE association was first described in 1979 by Hall*etal*.,min 17 children with multiple congenital anomalies who were as curtained by choanal atresia[1][2]. In the same year, Hittner reported this syndrome in 10 children with ocular Colobomas and multiple congenital anomalies [3] hence the syndrome is also called Hall-Hittner syndrome[4]. Pagon *et al*. ,in 1981 first coined the acronym CHARGE association[5], (coloboma, heartdefect, atresiachoanae,retardedgrow thanddevelopment, genitalhypoplasia, Earanomalies / deafness) asanon- randomassociation of anomalies occurring together more frequently than one would expecton the basis of chance. The original diagnostic criteria required the presence of four out of six of the CHARG Echaracteristics.Overthepast15 years the specificity of this pattern of malformations has reached the level that many clinicians now consider it to be a recognizable CHARGE syndrome.

Clinical Description

- Coloboma This feature may be unilateral orbilateral and may affect only.There is or extend to involve the retina, or only the retina. Vision may be normal or impaired [7].
- HeartDefect Congenital heart defects anomalies are patent ductus arteriosus, double outlet right ventricle with atrioventricularcanal, ventricular septal defect and atrial septal defect with or without cleft mitral valve. Vascular rings and more complex heart defects need to be anticipated[8]-[11].
- ChoanalAtresia Choanal atresia is an arrowing orablock age of the passages between the nasal cavity and then aso-pharynx. It represents a primary feature with a high index of suspicion for CHARGE syndrome and it should focus attention on other organ systems such as the eye

and heart. Choanal atresia may be membranous or bony; bilateral or un-ilateral. Bilateral posterior choanal atresia(BPCA) was shown to be associated with increased neonatal mortality ,especially if associated with major cardiac malformations+\" tracheoesophageal atresia[8]. However, the Canadian epidemiological study data suggests that an individual from this population with a more severe clinical presentation of CHARGE features generally survive[9]. Polyhydramnios in pregnancy is seen commonly in in-dividuals with bilateral posterior choanalatresia, and may also be present without BPCA, probably due to an insufficient swallowing mechanism. Chronic middle ear infections and deafness can be associated complications of choanal atresia[12].

- Retardationof GrowthandDevelopment rowth and developmental retardation become more obvious as the child matures .At birth, children with CHARGE syndrome usually have normal weights and lengths[13]. When growth deceleration is due to cardiac a nd respiratory problems, there may be catch up growth, and normal height can be obtained [14]. However, the influence of feeding problems on growth in infancy should not be under estimated. Early and continue dinterven-tion for feeding difficulties is vitally important [15]; occasionally there is growth hormone deficiency. Feeding with solids and lumpy foods, and risk of aspiration may still exist .Mental retardation is variable with intelligence quotients(IQ) ranging from near-normal to profound retardation. Behavioral issues and an autism-like spectrum disorder are now being recognized as features of the syndrome[16][17].

GenitourinaryProblems

Under-development of the external genitalia is a common finding in males but it is more difficult to recognize in females. Microphallus, penile agenesis, hypospadias, chordee, cryptorchidism, bifidscrotum, atresia of uterus, cervix and vagina, hypo plastic labia and clitoris are reported genital anomalies in this syndrome. Reported renal anomalies include solitary kidney, hydronephrosis, renal hypoplasia, duplex kidneys and vesicoureteral reflux. Hypogonado-trophic hypogonadism has been reported and is associated with delays in puberty or pubertal arrest [18][19].

Ear,Olfactory and OtherCranialNerve Anomalies

Ear abnormalities include a classical finding of unusually shaped ears. Lack of cartilage to the outer ear with deficient 7th nerve innervations to intrinsic ear muscles produces a prominent lop-orcup-shaped ear with a hy-poplastic lobule .Hearing loss, conductive and/or nerve deafness, ranges from mild to severe. Ear anomalies were reported in 80%-100% of cases indifferent series [10][20] .Facial nerve palsies were noted to be a reliable predictor of sensorineural hearingloss. The characteristic abnormalities demonstrated by temporal bone computerized tomography(CT) or magnetic resonance imaging(MRI) scan include hypoplastic incus,de-creased numbers of turns to the cochlea (mondinidefect), and, in particular ,absent semicircular canals. These distinctive radiological findingsareclassical for CHARGE syndrome and can aid diagnosis in a suspected case[21].For this reason, a neonatal CT scan to look at the choanae and temporal bones can be extremely useful [22].

Management

Children with CHARGE syndrome require intensive medical Management as well as numerous surgical inter-ventions. The most common neonatal emergencies in CHARGE syndrome involve cyanosis due to bilateral posterior choanal atresia and/or congenital heart defects, or the less common presentation of tracheoesophageal fistula. The primary foci of management should be airway Stabilization and circulatory support All patients suspected of having CHARGE syndrome should have a cardiology consultation. If the infant has Restrictive pulmonary blood flow and is dependent on a patent ductus arteriosus, the administration of prostagland into maintain ductal patency may saving. Some children require tracheostomy to manage chronic Airway problems and/or gastroesophageal reflux and aspiration.

Children with CHARGE syndrome require aggressive Medical managemen t of their feeding difficulties, often needing gastrostomy and jejunostomy feeding tubes. Gastro oesophageal fundoplication may be required for GER that does not respond to medical management. As intubation can be difficult in children with CHARGE syndrome, a pediatric anesthesiologist or pediatric Otolaryngologist should be present for planned surgical Pro-cedures.

Any infant suspected of having CHARGE syndrome should have a complete eye examination by an ophthal-mologist ,with follow-up every three to six months thereafter, depending on the eye involvement. Photophobia is often a significant problem that can be ameliorated with tinted

spectacles or by wearing a caporvisor with a dark brim. In the presence of facial palsy, patients should avoid corne scarring by usin artificial tears.

Hearing aids should be used as soon as hearin gloss is documented. Frequent re-molding of the ear pieces is necessary as the ear canals can be initially very small and ear cartilage may be insufficient to support a hearing aid. Cochlear implantations have been successfully performed in CHARGE syndrome patients .Children with CHARGE syndrome who undergo cochlear implantation should be allowed to continue with their sign language in parallel with their expressive speech training[23]. Adapted educational and therapeutic services to deal with dual auditory and visual sensory impairment should be proposed early in the child's life[23]-[25]. However, this population is unique with respect to their aberrant cranial nerve pathways and problems with expressive language.

In terms o f endocrine issues ,sex steroid therapy has been used for penile growth and descent of testes in males with CHARGE syndrome. The main use for testosterone is for delayed and in complete male puberty dur-ing adolescence. Females often require hormone replacement at puberty[18]. Sex hormon e replacement is also indicated for prevention of osteoporosis[19].

Conclusion

The acronym "CHARGE" denotes the non random association of coloboma, heartanomalies , choana-latresia, retardation of growth and development, andgenital and ear anomalies, which are frequently present in various combinations and varying degrees in individuals with CHARGE syndrome.

References

1. Blake, K.D., Davenport, S.L.H., Hall, B.D., Hefner, M.A., Pagon, R.A., Williams, M.S., Lin, A.E. and Graham Jr., J. M. (1998) CHARGEAssociation: An Update and Review for the Primary Pediatrician. *Clinical Pediatrics*, 37,159-173.
2. Hall, B.D.(1979) Choanal Atresia and Associated Multiple Anomalies. *Journal of Pediatrics*,95,395-398.
3. Hittner, H., Hirsch, N., Kreh, G. and Rudolph, A. (1979) Colobomatous Microphthalmia, Heart Disease, HearingLoss, and Mental Retardation: A Syndrome. *Journal of Pediatric Ophthalmology and Strabismus*, 16, 122-128.
4. Graham Jr., J.M.(2001) A Recognizable Syndrome within CHARGE Association: Hall-Hittner Syndrome. *American Journal of Medical Genetics*, 99, 120-123.
5. Pagon, R.A., Graham Jr., J.M., Zonana, J. and Young, S.L. (1981) Coloboma ,Congenital Heart Disease, and Choanal Atresia with Multiple Anomalies: CHARGE Association. *Journal of Pediatrics*, 99, 223-227.
6. Russell-Eggitt, I.M., Blake, K.D., Taylor, D. and Wyse, R.K. (1990) The Eye in CHARGE Association. *British Journal of Ophthalmology*,74, 421-426.
7. Mc Main, K., Robitalle, J., Blake, K., Wood, E., Smith, I., Temblay, F., Johnston, J. and Beis, J.(2005) Eyein Charge.
8. Blake, K. D., Russell-Eggitt, I. M., Morgan, D.W., Ratcliffe, J.M. and Wyse, R.K.H. (1990) Who'sin CHARGE? Mul-tidisciplinary Management of Patients with CHARGE Association. *Archives of Diseasein Childhood*, 65, 217-223.
9. Lin, A.E., Siebert, J.R. and Graham Jr., J.M. (1990) Central Nervous System Malformations in the CHARGE Association. *American Journal of Medical Genetics*, 37, 304-310.
10. Tellier, A.L., Cormier-Daire, V., Abadie, V., Amiel, J., Sigaudy, S., Bonnet, D., deLonlay-Debeney, P., Morrisseau-Durand, M.P., Hubert, P., Michel,J .L., Jan, D., Dollfus, H., Baumann, C., Labrune, P., Lacombe, D., Philip, N., LeMerrer, M., Briard,M .L., Munnich, A. and Lyonnet, S. (1998) CHARGE Syndrome: Report of 47 Cases and Review. *American Journal of Medical Genetics*, 76,402-409.
11. Cyran, S.E., Martinez, R., Daniels, S., Dignan, P .S.J. and Kaplan, S. (1987) Spectrum of Congenital Heart Disease in CHARGE Association. *Journal of Pediatrics*, 110, 576-580.
12. Keller, J.L. and Kacker, A. (2000) Choanal Atresia, CHARGE Association, and Congenital Nasal Stenosis. *Otolaryn-gologic Clinics of North America*, 33, 1343-1351.
13. Blake, K.D., Kirk, J.M. and Ur, E. (1993) Growth in CHARGE Association. *Archives of Disease in Childhood*, 68,508-509.
14. Searle, L. and Blake, K.D. (2005) CHARGE Syndrome from Birth to Adulthood: An Individual Reporte don from 0 to 33 Years. *American Journal of Medical Genetics Part A*, 133,344-349.
15. Dobbelsteyn, C., Marche, D.M., Blake, K.D. and Rashid, M. (2005) Early Oral Sensory Experiences and Feeding Developmentin Children with

CHARGE Syndrome: A Report of Five Cases. *Dysphagia*, 20, 89-100.

16. Smith, I.M., Nichols, S.L., Issekutz, K. and Blake, K. (2005) Behavioral Profiles and Symptoms of Autism in CHARGE Syndrome: Preliminary Canadian Epidemiological Data. *American Journal of Medical Genetics PartA*, 133, 248-256.
17. Hartshorne, T.S., Grialou, T.L. and Parker, K.R. (2005) Autistic-like behavior in CHARGE syndrome. *American Journal of Medical Genetics PartA*, 133, 257-261.
18. Blake,K.D.,Salem-Hartshorne, N., Abi Daoud, M. and Gradstein, J. (2005) Adolescent and Adult Issues in CHARGE Syndrome. *Clinical Pediatrics*, 44, 151-159.
19. Forward, K., Cummings, E. and Blake, K. (2005) Bone Health in Adolescents and Adults with CHARGE Syndrome. i. In Press.
20. Lalani, S.R., Safiullah, A.M., Fernbach, S.D., Harutyun yan, K.G., Thaller, C., Peterson, L.E., Mc Pher son, J.D., Gibbs, R.A., White, L.D., Hefner, M., Davenport, S.L., Graham, J.M., Bacino, C.A., Glass, N.L., Towbin, J.A., C raigen, W.J., Neish, S.R., Lin, A.E. and Belmont, J.W. (2006) Spectrum of *CHD*7 Mutationsin 110 Individuals with CHARGE Syndrome and Genotype-Phenotype Correlation. *The American Journal of Human Genetics*, 78, 303-314.
21. Amiel,J.,Attiee-Bitach, T., Marianowski, R., Cormier-Daire, V., Abadie, V., Bonnet, D., Gonzales, M., Chemouny, S., Brunelle, F., Munnich, A., Manach, Y. and Lyonnet, S. (2001) Temporal Bone Anomaly Proposed as a Major Criterion for Diagnosis of CHARGE Syndrome. *American Journal of Medical Genetics*, 99, 124-127
22. Verloes, A. (2005) Updated Diagnostic Criteriafor CHARGE Syndrome: A Proposal. *American Journal of Medical Genetics Part A*, 133A,306-308.
23. Blake, K.D. and Brown, D. (1993) CHARGE Association Look in gatthe Future—The Voiceofa Family Support Group.*Child*:*Care*,*Health and Development*,19,395-409.