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Comprehensive neuroimaging findings in charge syndrome: A case report of a 6-month-old female infant with congenital sensorineural hearing loss

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Abstract
Background: CHARGE syndrome is a rare genetic disorder characterized by multiple congenital anomalies with an estimated incidence of 1 in 10,000 live births. We present comprehensive neuroimaging findings in a 6-month-old female infant with CHARGE syndrome, demonstrating the full spectrum of central nervous system, temporal bone, and craniofacial abnormalities.
Case Presentation: A 6-month-old female with congenital bilateral sensorineural hearing loss underwent comprehensive neuroimaging evaluation. Multimodality imaging including CT of the head, paranasal sinuses, temporal bones, and MRI of the brain revealed characteristic features of CHARGE syndrome including bilateral semicircular canal agenesis, cochlear hypoplasia, choanal atresia, bilateral ocular colobomas, optic nerve hypoplasia, olfactory bulb aplasia, and cerebellar abnormalities, confirming the diagnosis.
Conclusion: This case demonstrates the importance of comprehensive neuroimaging in the evaluation of CHARGE syndrome, highlighting both classic and less commonly reported findings that contribute to diagnosis and management planning in patients with congenital sensorineural hearing loss.

Keywords: CHARGE syndrome, neuroimaging, sensorineural hearing loss, coloboma, choanal atresia

Introduction
CHARGE syndrome is a complex genetic disorder first described in 1979, with an estimated incidence of 1 in 10,000 live births [1]. The acronym represents the cardinal features: Coloboma, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital abnormalities, and Ear anomalies [1]. Approximately 60-70% of cases are caused by de novo mutations in the CHD7 gene located on chromosome 8q12.1 [2].
The diagnosis of CHARGE syndrome has evolved from the original clinical criteria to incorporate imaging findings, particularly temporal bone abnormalities. According to Verloes' updated criteria, the three major features include coloboma, choanal atresia, and hypoplastic semicircular canals [3]. The temporal bone abnormalities, particularly semicircular canal dysplasia, have emerged as one of the most consistent findings, present in up to 100% of cases [4, 5]. Congenital sensorineural hearing loss, present in 90-100% of patients, is often the presenting feature that prompts initial medical evaluation [6].
Neuroimaging plays a crucial role in diagnosis, particularly in identifying temporal bone dysplasias, cranial nerve abnormalities, and central nervous system malformations that may not be clinically apparent [7, 8]. The combination of CT and MRI provides complementary information essential for diagnosis, surgical planning, and prognostication [9].

Case Report
Clinical Presentation
A 6-month-old female infant presented to our institution for evaluation of congenital bilateral sensorineural hearing loss identified on newborn hearing screening. The patient was born at term following an uncomplicated pregnancy to non-consanguineous parents. Birth weight was 2.8 kg (10th percentile). Initial auditory brainstem response testing confirmed profound bilateral sensorineural hearing loss with absent responses at 90 dB. Physical examination revealed characteristic facial features including a broad forehead, hypertelorism, and low-set ears. Developmental assessment showed mild gross motor delay. Given the constellation of

findings and suspicion for CHARGE syndrome, comprehensive neuroimaging was performed.

Imaging Findings

Computed Tomography Findings

High-resolution computed tomography of the head and paranasal sinuses revealed multiple craniofacial abnormalities. The most striking finding was complete bony atresia of the left posterior choana, measuring 3 mm in thickness, with associated pooling of secretions in the left nasal cavity (Figure 1). The right choana was patent but mildly narrowed. The nasal septum showed mild rightward deviation. Bilateral ocular abnormalities were evident, with posterior globe defects consistent with chorioretinal colobomas involving the optic disc regions bilaterally. The globes appeared small for age, measuring 16 mm in anteroposterior diameter (normal for age: 18-19 mm).

Dedicated high-resolution temporal bone CT demonstrated severe bilateral inner ear malformations. The most prominent finding was the complete absence of all three semicircular canals bilaterally, with no identifiable lateral, superior, or posterior canal structures (Figure 2). The vestibules were severely dysmorphic and hypoplastic, appearing as small, irregular cavities measuring approximately 2 mm in maximum dimension. The internal auditory canals were narrowed, measuring 2.8 mm in diameter (normal: 4-8 mm) (Figure 3).The cochleae showed bilateral dysplasia characterized by hypoplastic middle and apical turns, with only the basal turn normally formed, consistent with incomplete partition type II (Mondini deformity)(Figure 4). The modiolus was deficient bilaterally. Additional temporal bone findings included bilateral stenosis of the oval windows with absent or hypoplastic stapes footplates, and dysmorphic ossicular chains with malformed incus and malleus (Figure 5). The facial nerve canals appeared normal in caliber throughout their course.

Magnetic Resonance Imaging Findings

MRI of the brain with high-resolution T2-weighted sequences confirmed and expanded upon the CT findings. At the skull base, the left choanal atresia was redemonstrated with high T2 signal fluid accumulation in the obstructed left nasal cavity extending to the nasopharynx. Coronal T2-weighted images revealed complete absence of the olfactory bulbs (Figure 6) and sulci bilaterally, with no identifiable olfactory structures along the cribriform plate. The gyrus rectus appeared to extend to the cribriform plate without intervening olfactory structures.

Evaluation of the orbits demonstrated bilateral micro-ophthalmia with dysmorphic globes. The posterior globe defects were better characterized on MRI, showing bilateral chorioretinal colobomas extending from the optic disc region inferiorly, creating a characteristic "morning glory" appearance (Figure 7). The right optic nerve showed moderate hypoplasia, measuring 2.5 mm in diameter (normal: 3.5-4 mm), while the left optic nerve was severely hypoplastic, measuring only 1.5 mm. The optic chiasm was present but small. Additional ocular findings included a dysmorphic left ciliary body with irregular configuration and an abnormally shaped left lens with posterior displacement.

High-resolution T2-weighted CISS (Constructive Interference in Steady State) sequences of the temporal bones confirmed the complete absence of all semicircular canals and severe vestibular hypoplasia. Critically, no vestibulocochlear nerves could be identified in either internal auditory canal on axial or sagittal oblique reconstructions, with only the facial nerves visible bilaterally. The cochlear nerve apertures were absent bilaterally (Figure 8). The endolymphatic sacs were not identified.

Brain parenchymal evaluation revealed mild to moderate ventriculomegaly with lateral ventricular frontal horn width measuring 12 mm. The third and fourth ventricles were normal in size. There was no evidence of hydrocephalus or transependymal CSF seepage. The corpus callosum was intact but mildly thin. Posterior fossa structures showed hypoplasia of the inferior vermis (Figure 9). The cerebellar tonsils were normally positioned. The brainstem appeared normal in morphology and signal intensity. No areas of abnormal enhancement were identified following gadolinium administration.

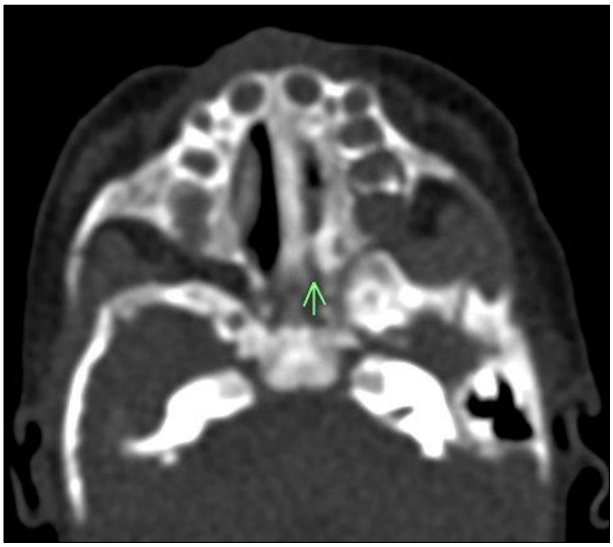

Fig 1: Axial CT skull base shows left choanal atresia (arrow) with retained secretions in the nasal cavity.

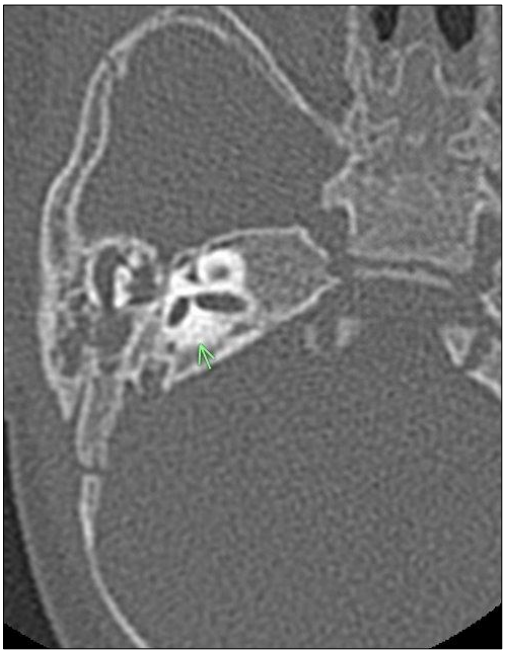

Fig 2: Axial CT of the temporal bones shows a complete absence of semicircular canals.

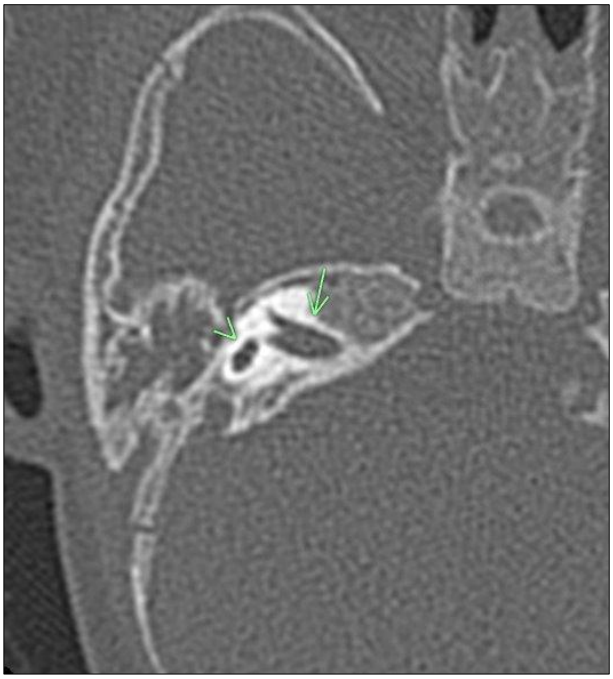

Fig 3: Axial CT of temporal bones shows severely dysmorphic and hypoplastic vestibule (arrowhead). The internal auditory canal is narrowed (arrow).

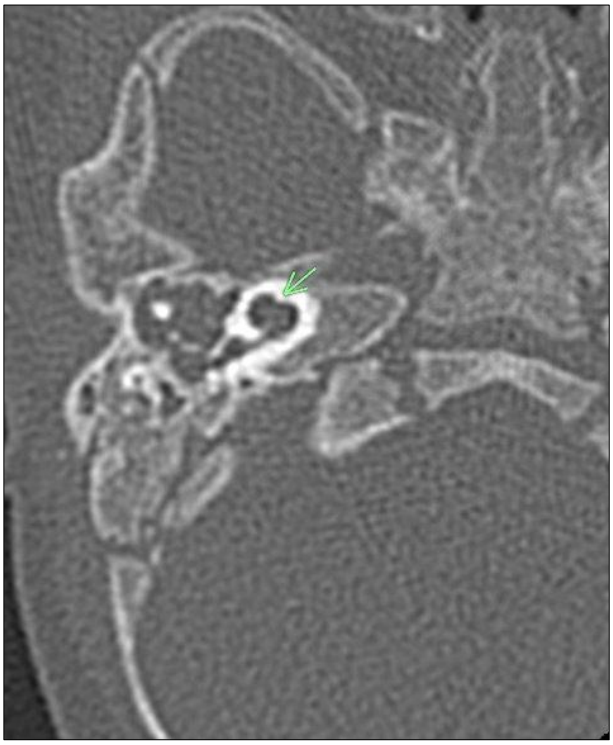

Fig 4: Axial CT of temporal bones shows dysplasia of cochlea characterized by hypoplastic middle and apical turns, with only the basal turn typically formed (arrow), consistent with incomplete partition type II (Mondini deformity).

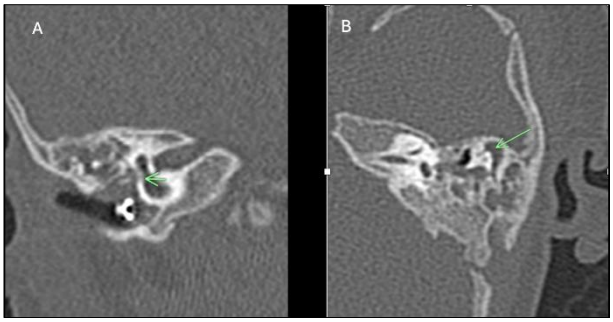

Fig 5: (A) Coronal CT of the temporal bone shows a stenotic bivalve window with a hypoplastic stapes footplate. (B) Axial CT of the temporal bone shows dysmorphic ossicular chains.

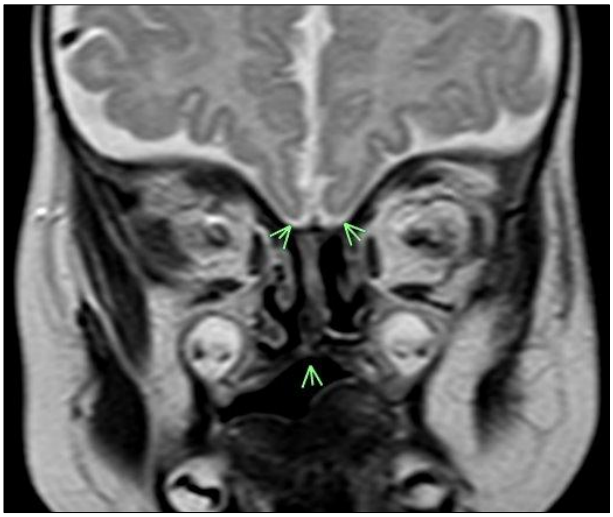

Fig 6: Coronal T2 weighted MR image shows complete absence of the olfactory bulbs and sulci bilaterally, with no identifiable olfactory structures along the cribriform plate. Note is made of high arched palate.

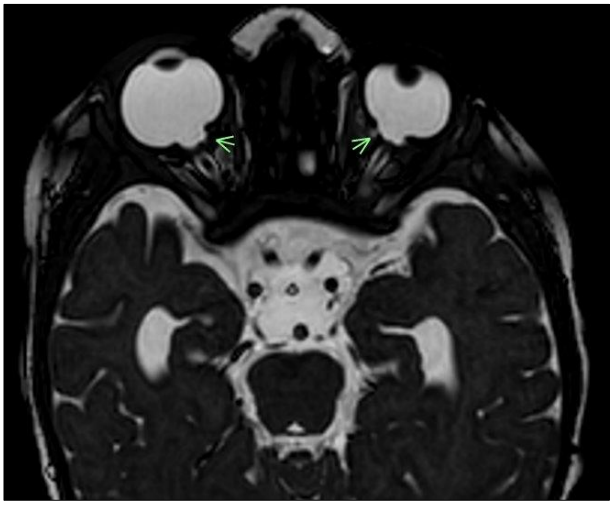

Fig 7: Axial CISS image at the level of the orbits demonstrates focal outpouching of the posterior globes at the optic disc, consistent with bilateral colobomas (arrows).

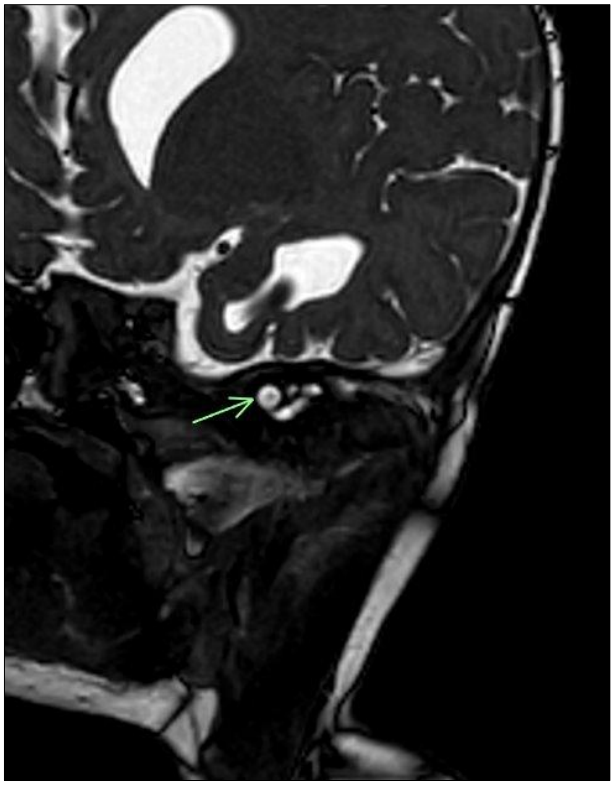

Fig 8: Sagittal Oblique CISS image at the level of the IAC demonstrates the presence of the facial cranial nerve. The vestibulocochlear nerves were not identified.

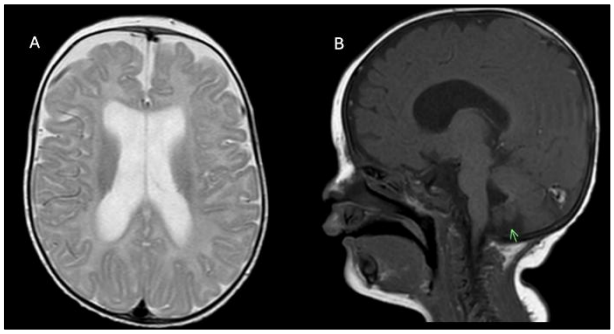

Fig 9: (A) Axial T2-weighted MR image shows mild to moderate ventriculomegaly without transependymal CSF resorption. (B) Sagittal T1-weighted MR images show severely hypoplastic inferior vermis.

Discussion

This case exemplifies the characteristic neuroimaging spectrum of CHARGE syndrome, demonstrating multiple major and minor diagnostic criteria through comprehensive multimodality imaging in an infant presenting with congenital sensorineural hearing loss.

Temporal Bone Abnormalities and Hearing Loss

The complete absence of semicircular canals observed in our patient represents the most specific imaging finding in CHARGE syndrome, with a reported prevalence of 90-100% [4,5]. This finding has been elevated to a major diagnostic criterion due to its high specificity and near-universal presence [3]. The semicircular canal agenesis in CHARGE syndrome reflects arrested development at the 6th week of gestation, before semicircular canal formation begins [10]. The associated vestibular hypoplasia contributes to the balance difficulties and delayed motor milestones commonly observed in these patients.

The cochlear dysplasia in our patient, characterized by incomplete partition type II (Mondini deformity), occurs in approximately 80% of CHARGE syndrome cases [5]. This malformation, resulting from arrested development at the 7th week of gestation, typically preserves the basal turn while the middle and apical turns remain underdeveloped. The bilateral absence of vestibulocochlear nerves, demonstrated on MRI in our case, is reported in 60-90% of CHARGE syndrome patients and represents a critical finding for cochlear implant planning [6, 11]. The absence of cochlear nerves contraindicates traditional cochlear implantation and necessitates consideration of alternative approaches such as auditory brainstem implants.

Olfactory System Abnormalities and Cranial Nerve Deficits

The complete bilateral absence of olfactory bulbs and sulci observed in our patient is increasingly recognized as a cardinal feature of CHARGE syndrome, present in 80-100% of cases [12]. This finding has been proposed as an additional major diagnostic criterion. The olfactory aplasia correlates with hypogonadotropic hypogonadism, which manifests later in life, reflecting the shared developmental pathway of GnRH neurons that migrate from the olfactory placode to the hypothalamus. The combination of anosmia and hypogonadism in CHARGE syndrome overlaps with Kallmann syndrome, suggesting common pathophysiological mechanisms.

Ocular and Visual Pathway Abnormalities

The bilateral chorioretinal colobomas in our patient represent a major diagnostic criterion, occurring in 70-90% of CHARGE syndrome cases [13]. Colobomas result from failure of the embryonic fissure to close during the 5th to 7th week of gestation. The associated optic nerve hypoplasia, more severe on the left in our case, occurs in approximately 50% of patients and correlates with the severity of the coloboma. The micro-ophthalmia observed bilaterally reflects global ocular underdevelopment and is reported in 20-30% of cases. The asymmetric involvement with more severe left-sided abnormalities, including ciliary body and lens dysmorphy, exemplifies the variable expressivity characteristic of CHARGE syndrome.

Central Nervous System Abnormalities

The cerebellar hypoplasia involving the inferior hemispheres and vermis in our patient aligns with increasingly recognized posterior fossa abnormalities in CHARGE syndrome, reported in 30-50% of cases [7]. While not part of the classic diagnostic criteria, cerebellar abnormalities contribute significantly to the neurodevelopmental phenotype, including motor delays, coordination difficulties, and cognitive impairment. The vermian hypoplasia may contribute to the behavioral and autism spectrum features observed in some CHARGE syndrome patients.

The ventriculomegaly observed in our case, present in approximately 40% of CHARGE syndrome patients, may be secondary to white matter underdevelopment or represent a primary developmental abnormality. The thin corpus callosum, though not severely hypoplastic in our case, is reported in 20-30% of patients and may contribute to cognitive and behavioral manifestations.

Choanal Atresia and Airway Implications

The unilateral left-sided complete bony choanal atresia in our patient represents one of the original major criteria for CHARGE syndrome, occurring in 35-65% of cases [14]. While bilateral atresia is more common and presents as a neonatal emergency, unilateral atresia, as in our case, may remain asymptomatic or present with unilateral nasal obstruction and discharge. The complete bony atresia demonstrated on CT has important surgical implications, as bony atresia typically requires drilling for surgical repair, with higher rates of restenosis compared to membranous atresia.

Genetic and Developmental Considerations

The constellation of imaging findings in our patient strongly supports the diagnosis of CHARGE syndrome, warranting genetic testing for CHD7 mutations. CHD7 encodes a chromodomain helicase DNA-binding protein crucial for chromatin remodeling during embryonic development [2]. The protein is expressed in the developing ear, eye, olfactory epithelium, and neural crest cells, explaining the characteristic distribution of anomalies. The timing of developmental arrests evident in our patient's imaging (semicircular canals at 6 weeks, cochlea at 7 weeks, eye at 5-7 weeks) suggests a critical role for CHD7 in mid-embryonic organogenesis.

Clinical Management Implications

The comprehensive neuroimaging findings have several critical implications for clinical management:

1. **Hearing Rehabilitation:** The absence of vestibulocochlear nerves bilaterally precludes conventional cochlear implantation. Auditory brainstem implants should be considered, though outcomes are generally less favorable than cochlear implants [11].
2. **Visual Optimization:** The asymmetric visual impairment necessitates aggressive management of refractive errors and amblyopia prevention in the better-seeing right eye.
3. **Airway Management:** While the unilateral choanal atresia may not require immediate intervention, monitoring for respiratory difficulties during upper respiratory infections is essential.
4. **Developmental Support:** The multisensory deficits (profound hearing loss, anosmia, visual impairment) combined with cerebellar abnormalities necessitate intensive early intervention services.
5. **Endocrine Monitoring:** Given the olfactory aplasia, monitoring for hypogonadotropic hypogonadism and growth hormone deficiency is indicated [12].

Conclusion

This case demonstrates the value of comprehensive multimodality neuroimaging in evaluating infants with congenital sensorineural hearing loss suspected of having CHARGE syndrome. The combination of complete semicircular canal agenesis, cochlear dysplasia, absent vestibulocochlear nerves, olfactory aplasia, bilateral colobomas, optic nerve hypoplasia, choanal atresia, and cerebellar abnormalities provides definitive radiological evidence for the diagnosis. Recognition of these imaging patterns is crucial for early diagnosis, appropriate management planning, and genetic counseling. The severity and bilateral nature of the cranial nerve deficits, particularly the absent cochlear nerves, significantly impact rehabilitation options and prognosis. This case emphasizes the importance of systematic evaluation of all potentially affected structures in suspected CHARGE syndrome cases and highlights the role of neuroimaging in guiding clinical management decisions [15].

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