

Atypical CHARGE Syndrome with Auditory Neuropathy and Vestibulocochlear Nerve Aplasia: A Case Report

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ABSTRACT

The CHARGE syndrome represents a rare congenital disorder characterised by a constellation of ocular, auditory, vestibular, craniofacial, and developmental anomalies, most commonly linked to pathogenic variants in the *CHD7* gene. The phenotypic spectrum is notably wide, and advances in molecular diagnostics have increasingly revealed incomplete and atypical presentations. This report describes a 17-month-old male child presenting with developmental delay, ocular coloboma, inner ear malformations, vestibulocochlear nerve aplasia, and Auditory Neuropathy Spectrum Disorder (ANSD), alongside absence of choanal atresia, cardiac, or renal anomalies. Whole exome sequencing identified a pathogenic *CHD7* mutation, confirming atypical CHARGE syndrome. This case is notable for the rare coexistence of ANSD with unilateral vestibulocochlear nerve aplasia in genetically confirmed atypical CHARGE syndrome. The absence of classical features such as choanal atresia, cardiac, and renal anomalies further emphasises the expanding phenotypic spectrum. Radiological-audiological discordance underscores the importance of detailed neuroimaging in children with unexplained hearing loss. This report highlights the critical role of whole exome sequencing in diagnosing incomplete presentations of CHARGE syndrome and guiding multidisciplinary management.

Keywords: Congenital coloboma, Cranial nerve aplasia, Developmental delay, Inner ear malformations, Whole exome sequencing

CASE REPORT

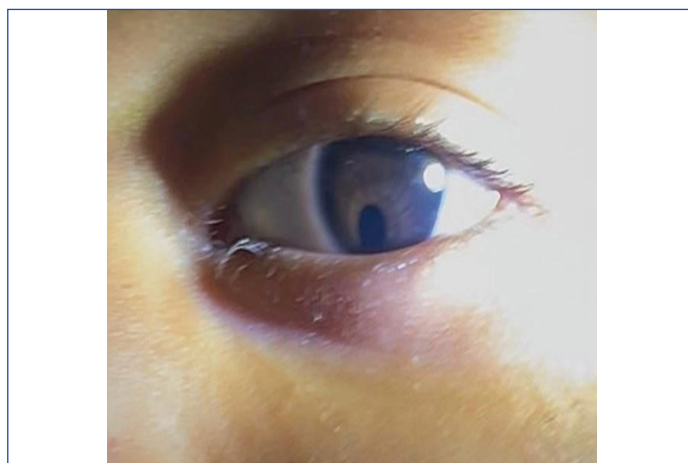
A 17-month-old male child, second born to non-consanguineous parents, presented with global developmental delay noticed by the mother since six months of age to the paediatric outpatient department. According to the mother, the child has been delayed in achieving developmental milestones compared to peers across multiple domains. She first noticed the delay at around six months of age, when the child did not attain expected milestones such as head control and rolling over. As the child grew, he failed to achieve age-appropriate milestones, including sitting without support, standing, walking, and development of meaningful speech. The elder sibling, a four-year-old sister, exhibited no similar complaints. She is a developmentally normal school going child. The child was born by normal vaginal delivery at 38 weeks gestational age with a birth weight of 2.7 kg. The mother reported no co-morbidities, chronic drug intake, radiation exposure, or substance abuse. The perinatal period remained uneventful, with no history of birth asphyxia, neonatal intensive care admission, feeding difficulty, or recurrent respiratory infections.

On general physical examination, the child appeared alert and haemodynamically stable, with vital parameters: Heart rate 110/min, respiratory rate 28/min, blood pressure 90/60 mmHg in the right upper limb in supine position, temperature 36.9°C, and SpO₂ 98% in room air. Anthropometric measurements proved appropriate for age. Facial examination revealed mild dysmorphic features including ocular prominence and a short philtrum; no facial asymmetry or orofacial cleft was noted. No choanal obstruction existed, and the oral cavity appeared normal [Table/Fig-1].

Ophthalmological examination confirmed bilateral iris coloboma [Table/Fig-2] with optic disc coloboma. Neurological examination revealed global developmental delay, with delayed gross motor (sitting with support, no independent standing), fine motor (absence of pincer grasp), and language milestones (no babbling or meaningful words). Muscle tone was normal in all four limbs, with no evidence of hypo- or hypertonia. Deep tendon reflexes were elicitable,



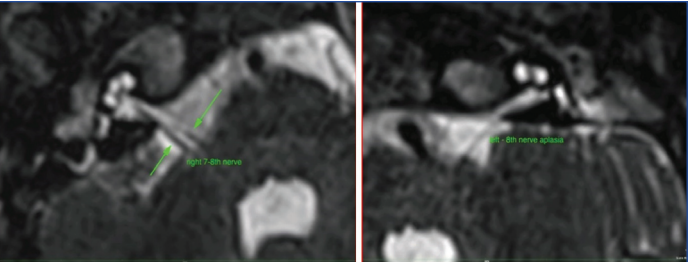
[Table/Fig-1]: Photograph of the child with mild dysmorphic features and a short philtrum; no facial asymmetry or orofacial cleft was noted.



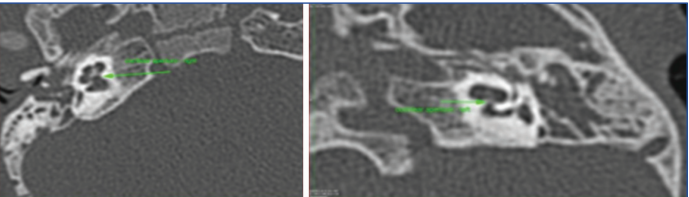
[Table/Fig-2]: Clinical photograph of the child demonstrating a visible inferonasal defect of the iris consistent with iris coloboma.

symmetric, and appropriate for age, with bilateral flexor plantar responses. There were no clinical signs of pyramidal, extrapyramidal, or cerebellar dysfunction. Cranial nerve examination was grossly normal, except for auditory deficits. Cardiovascular, respiratory, abdominal, genitourinary, and skeletal system examinations proved unremarkable.

Magnetic Resonance Imaging (MRI) of the brain and temporal bones revealed bilateral small vestibules with dysplastic semicircular canals, consistent with vestibular and semicircular canal dysplasia. The left vestibulocochlear (VIII cranial) nerve was not visualised [Table/Fig-3], suggestive of left-sided aplasia, with a corresponding narrowed internal auditory canal and hypoplastic cochlear aperture measuring 0.5 mm [Table/Fig-4]. The right internal auditory canal was preserved, with a cochlear aperture measuring 1.6 mm and grossly normal cochlear size and morphology. No other structural inner ear abnormalities were identified.



[Table/Fig-3]: High-resolution axial MRI images of the internal auditory canals demonstrating a normally visualised vestibulocochlear (VIII cranial) nerve on the right and non-visualisation on the left, consistent with left vestibulocochlear nerve aplasia.



[Table/Fig-4]: Axial T2-weighted MRI temporal bone images showing hypoplastic cochlear aperture on the left-side (right panel, arrow) with relative preservation on the right-side (left panel).

There was minimal fluid opacification of the bilateral middle ear cavities and mastoid air cells, with intact and normally configured middle ear ossicles. The cerebral parenchyma demonstrated normal grey-white matter differentiation with no evidence of structural brain malformations. The pituitary gland and sella turcica appeared normal, with no imaging evidence of hypothalamic–pituitary axis abnormality. Cranial nerve VII (facial nerve) appeared intact on imaging, with no clinical evidence of facial palsy or asymmetry.

Audiological evaluation demonstrated absent behavioural responses to sound. Oto acoustic emissions were observed to be present in both ears in frequencies, 1, 1.5,2,3,4 kHz, suggestive of normal outer hair cell function in both ears. Peak V could not be obtained at 80 dBnHL using click stimuli with a repetition rate of 11.1/sec in rarefaction, condensation and alternating polarities. These findings were consistent with bilateral ANSD in the child. In the context of associated unilateral cochlear nerve aplasia, the ANSD profile is likely attributable to dysfunction in the contralateral

ear with an intact cochlear nerve, highlighting the importance of careful ear-specific interpretation. Conditioned play audiometry was deferred at initial assessment due to developmental limitations precluding task participation; however, serial audiological follow-up with reassessment for age- and development-appropriate behavioural testing has been planned. Cochlear microphonics was not assessed during the evaluation, which represents a limitation in further electrophysiological characterisation.

Despite radiological evidence of vestibular dysplasia, formal vestibular function testing, including caloric testing, video Head Impulse Test (vHIT), and videonystagmography was not performed at the time of evaluation due to the child’s young age and limited cooperation. Clinically, no overt balance abnormalities could be reliably assessed, as independent standing and walking had not yet been achieved. The observed motor delay may, in part, reflect underlying vestibular dysfunction.

Serial developmental and vestibular follow-up was planned, with periodic assessment of posture, gait, and balance as motor milestones emerge, along with consideration of age-appropriate vestibular function testing.

Baseline laboratory evaluation, including complete blood count, renal and liver function tests, serum electrolytes, thyroid function tests (including TSH), and morning serum cortisol levels, was within normal limits for age, with no biochemical evidence of endocrine dysfunction despite the normal-appearing pituitary gland and sella turcica.

Echocardiography showed a structurally normal heart, and ultrasonography of the abdomen revealed normal kidneys and other abdominal organs. No genital anomalies were noted.

In view of the combination of ocular coloboma, characteristic inner ear malformations, cranial nerve involvement, and developmental delay, a syndromic diagnosis was suspected. The differential diagnoses considered included CHARGE syndrome, Kabuki syndrome, VACTERL association, and isolated coloboma-deafness syndromes. Kabuki syndrome was considered due to the presence of coloboma and developmental delay; however, the absence of characteristic facial features and the presence of typical inner ear malformations favoured CHARGE syndrome. VACTERL association was unlikely due to the absence of vertebral, cardiac, tracheoesophageal, renal, and limb anomalies. Isolated coloboma–deafness syndromes were excluded based on the presence of vestibular and semicircular canal dysplasia, cranial nerve involvement.

Whole exome sequencing identified a heterozygous pathogenic non-sense variant in the *CHD7* gene (NM_017780.4: c.7957C>T; p.Arg2653Ter). This stop-gain variant introduces a premature termination codon leading to predicted protein truncation and loss of function, an established disease mechanism in CHARGE syndrome [Table/Fig-5]. The variant has previously been reported in individuals with CHARGE syndrome and is classified as pathogenic in ClinVar. Prior literature supporting this variant includes Lalani SR et al., who described the spectrum of *CHD7* mutations in CHARGE syndrome [1].

Parental genetic testing was not performed; therefore, it could not be determined whether the variant arose de novo or was inherited. Given that most *CHD7* mutations are de novo this remains the most likely possibility, although germline transmission cannot be excluded.

Gene and Transcript	Exon/Intron Number	Variant Nomenclature	Zygosity	Classification	OMIM Phenotype	Inheritance
CHD7 (NM_017780.4)	Exon 36/Exon 38 –	c.7957C>T p.Arg2653Ter [34x /64x]	Heterozygous	Pathogenic	CHARGE syndrome, Hypogonadotropi c hypogonadism 5 with or without anosmia	Autosomal dominant

[Table/Fig-5]: Whole exome sequencing report showing a heterozygous pathogenic nonsense variant in the *CHD7* gene (NM_017780.4), c.7957C>T resulting in p.Arg2653Ter, consistent with autosomal dominant CHARGE syndrome.

Clear genotype-phenotype correlation for this specific variant is limited in the literature. However, truncating variants in *CHD7* are generally associated with a broad phenotypic spectrum, including ocular coloboma inner ear malformations, cranial nerve abnormalities, and developmental delay, as observed in this child, albeit with an atypical presentation lacking major cardiac or choanal anomalies.

Genetic counselling was provided to the family, explaining the autosomal dominant inheritance pattern, the uncertainty regarding de novo versus inherited status, and the implications for recurrence risk. The recurrence risk was discussed as low in the case of a de novo mutation but up to 50% if one parent is a carrier. The option of parental testing and prenatal diagnosis in future pregnancies was also discussed.

The estimated recurrence risk was discussed in the context of either a *de novo* or an inherited (50% risk) scenario, and the option of prenatal genetic testing in future pregnancies was outlined. The long-term prognosis was explained, emphasising the likelihood of persistent hearing loss, vestibular dysfunction, and developmental delay, along with the need for multidisciplinary follow-up.

The child was managed with a multidisciplinary approach involving paediatrics, ENT, audiology, ophthalmology, genetics, physiotherapy, and early intervention services. Audiological rehabilitation was initiated with a trial of hearing amplification, with close monitoring of benefit. In view of the underlying ANSD and imaging evidence of vestibulocochlear nerve aplasia, alternative communication strategies and candidacy for cochlear implantation or other assistive modalities were discussed, recognising that outcomes may be variable.

Developmental intervention, including physiotherapy and early stimulation programs, was initiated to address global developmental delay, with particular focus on motor and communication skills. Regular follow-up has been planned at multidisciplinary clinics to monitor hearing, speech-language development, motor milestones, and emerging balance/gait functions, with periodic reassessment for age-appropriate audiological and vestibular testing.

The family received detailed genetic and prognostic counselling regarding CHARGE syndrome, including the likelihood of persistent hearing impairment, possible vestibular dysfunction, and developmental challenges. The importance of early intervention, long-term rehabilitation, and structured follow-up was optimised. Parents were also counselled regarding realistic expectations, communication options, and the need for ongoing supportive care to optimise functional outcomes and quality of life.

DISCUSSION

CHARGE syndrome is a rare congenital disorder most commonly caused by heterozygous pathogenic variants in the *CHD7* gene, which encodes a chromatin-remodelling protein involved in embryonic development. Disruption of *CHD7* function results in a broad multisystem phenotype involving the eyes, inner ear, cranial nerves, central nervous system, cardiovascular system, and endocrine system [2-4]. Most affected individuals have de novo pathogenic variants, although *CHD7*-related disorder follows an autosomal dominant inheritance pattern and familial transmission has been described [2]. The estimated incidence of CHARGE syndrome is approximately 1 in 8,500–15,000 live births, although milder and atypical presentations may remain under-recognised [4,5].

Following the identification of *CHD7* as the major genetic cause of CHARGE syndrome, the recognised phenotypic spectrum has expanded considerably. The term *CHD7*-related disorder encompasses individuals with the classical CHARGE phenotype as well as those with milder or incomplete presentations [4,6,7]. Pathogenic *CHD7* variants are identified in approximately 70–90% of clinically suspected cases, with higher detection rates among individuals fulfilling established clinical diagnostic criteria [6,8].

Importantly, the absence of individual classical features does not exclude a *CHD7*-related disorder. Individuals with predominantly cochleovestibular abnormalities and other limited manifestations have also been described [6]. In the present case, child similarly lacked choanal atresia and major cardiac or renal anomalies but had ocular coloboma, characteristic inner-ear abnormalities, vestibulocochlear nerve aplasia, developmental delay, and a pathogenic *CHD7* variant.

Semicircular canal dysplasia is one of the characteristic radiological abnormalities associated with CHARGE syndrome and may be particularly useful in patients with incomplete clinical presentations [9]. Green GE et al., demonstrated *CHD7* mutations in patients with semicircular canal dysplasia and identified cochlear nerve abnormalities in affected individuals, supporting an association between *CHD7* abnormalities and combined cochleovestibular malformations [9]. More recently, predominantly cochleovestibular presentations of *CHD7* disorder have been described, emphasising the importance of temporal-bone imaging in patients with unexplained hearing loss and inner-ear malformations [6]. In the present case, bilateral vestibular and semicircular canal dysplasia together with unilateral vestibulocochlear nerve aplasia may have contributed to delayed acquisition of gross motor milestones. However, because formal vestibular testing was not performed, the contribution of vestibular dysfunction to the developmental delay remains presumptive.

The auditory phenotype in *CHD7*-related disorders is heterogeneous and may involve abnormalities of the cochlea, cochlear nerve, vestibular system, or central auditory pathways [6,8,10]. The present case demonstrated an unusual combination of preserved bilateral otoacoustic emissions and absent auditory brainstem responses. Preserved otoacoustic emissions indicate retained outer hair cell function, whereas absent auditory brainstem responses in this setting are compatible with an auditory neuropathy spectrum disorder phenotype [10]. Buchman CA et al., demonstrated that children with cochlear nerve deficiency may exhibit electrophysiological characteristics of auditory neuropathy, highlighting the importance of integrating electrophysiological findings with high-resolution imaging of the cochlear nerve [10].

An important feature of the present case was the radiological-audiological discordance. MRI demonstrated non-visualisation of the left vestibulocochlear nerve, with a narrowed internal auditory canal and hypoplastic cochlear aperture, whereas otoacoustic emissions were preserved bilaterally. Because the left cochlear nerve was anatomically absent, the left-sided structural abnormality alone cannot explain bilateral absent auditory brainstem responses. The findings therefore raise the possibility of abnormal auditory neural function in the contralateral ear despite preservation of the cochlear nerve on imaging. However, cochlear microphonics were not assessed, and ear-specific electrophysiological characterisation was limited; therefore, the precise mechanism and laterality of the auditory neuropathy phenotype cannot be definitively established. This limitation is important when interpreting the apparent discordance between structural and functional auditory findings. The findings also emphasise the importance of MRI in children with auditory neuropathy, particularly when cochlear nerve deficiency is suspected [10].

The combination of ocular coloboma, vestibular abnormalities, and cochlear nerve involvement in the absence of choanal atresia or major cardiac anomalies illustrates the phenotypic variability of *CHD7*-related disorders [6,7]. A recent case report described a de novo *CHD7* variant in a child with an atypical CHARGE phenotype, further supporting the value of molecular testing when clinical features are incomplete [11]. Similarly, the case series by Bedeschi MF et al., demonstrated considerable phenotypic variability and

emphasised the diagnostic value of temporal-bone imaging and ear abnormalities in patients with relatively nonspecific presentations [12]. The present case extends this spectrum by demonstrating the coexistence of ocular coloboma, bilateral vestibular dysplasia, unilateral vestibulocochlear nerve aplasia, and an auditory neuropathy phenotype in a genetically confirmed case.

The presence of auditory neuropathy and cochlear nerve aplasia has important implications for auditory rehabilitation. Children with auditory neuropathy may benefit from cochlear implantation in selected circumstances; however, cochlear nerve deficiency is an important consideration when counselling families regarding expected benefit [10,13]. In the present child, the unilateral absence of the vestibulocochlear nerve makes assessment of cochlear implant candidacy more complex and emphasises the importance of detailed preoperative neuroimaging. Alternative communication strategies and other assistive auditory modalities should therefore be considered as part of individualised rehabilitation. In children with confirmed cochlear nerve aplasia, auditory brainstem implantation may be considered in appropriately selected cases at specialised centres [14].

Early multidisciplinary management is essential in *CHD7*-related disorders and should include audiological, ophthalmological, developmental, vestibular, and genetic assessment [2,6,8]. Vestibular dysfunction may not be clinically obvious in early childhood and may become more apparent as independent standing and walking develop [6,9]. In the present child, formal vestibular function testing was deferred because of age and limited cooperation. Serial assessment of posture, gait, balance, and motor development, with age-appropriate vestibular testing when feasible, is therefore warranted.

Genetic counselling is an important component of management because *CHD7*-related disorders are inherited in an autosomal dominant manner, although most affected individuals have a de novo pathogenic variant [2]. Parental testing was not performed in the present case; therefore, the variant cannot be definitively classified as de novo. If a parent is found to carry the pathogenic variant, the recurrence risk in each pregnancy would be 50%. If the variant is confirmed to be de novo, the recurrence risk is substantially lower, although germline mosaicism cannot be completely excluded [2].

CONCLUSION(S)

Overall, this case highlights the expanding phenotypic spectrum of *CHD7*-related disorders and the importance of integrating clinical, radiological, audiological, and molecular findings. The coexistence of ocular coloboma, bilateral vestibular dysplasia, unilateral vestibulocochlear nerve aplasia, and an auditory neuropathy phenotype in the absence of choanal atresia or major cardiac

anomalies demonstrates the diagnostic complexity of incomplete presentations. Detailed temporal-bone and cranial-nerve imaging is particularly important in children with unexplained hearing loss because structural cochlear nerve abnormalities may substantially influence auditory rehabilitation and prognostication.

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