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LETTER TO THE EDITOR

A unique case of CHARGE syndrome with craniosynostosis

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Dear Editor:

In this article, we would like to report a unique case of CHARGE syndrome and craniosynostosis in a child heterozygous for CHD7 mutation. CHARGE syndrome has been associated with multiple congenital abnormalities; however, to the best of our knowledge, an association between genetically confirmed CHARGE and craniosynostosis has not been previously reported. We believe that this unique phenotype serves as an exciting illustration of the interrelation of CHARGE syndrome with other syndromes exhibiting overlapping phenotypes, occasionally including craniosynostosis.

This baby boy was born by spontaneous vaginal delivery at 34 weeks of gestation and was clinically diagnosed with CHARGE syndrome shortly after birth. Following transfer to our hospital, he underwent successful surgical repair of esophageal atresia. Postnatal examination also revealed evidence of delayed visual maturation, severe left hearing loss, global developmental delay, hypotonia, micropenis, and athymic severe combined immune deficiency.

CT and MR imaging revealed bilateral dysplastic cochleae accompanied by aplasia of the semi-circular canals (Fig. 1). The left cochlear nerve was absent, but the right cochlear nerve and vestibular nerves were preserved. The right vestibular aqueduct was enlarged and the vestibules appeared hypoplastic. There was also hypoplasia of the brainstem and cerebellum and underdevelopment of the inferior cerebellar vermis.

Cranial deformity was observed in the first months of life, raising the possibility of underlying craniosynostosis. CT at 18 months confirmed the presence of bicoronal craniosynostosis as well as premature synostosis of the left lambdoid and squamous sutures resulting in a turricephalic appearance of the cranial vault (Figs. 1 and 2). There was also left choanal atresia and a narrow right nasal cavity accompanied by rightward deviation of the nasal septum, as well as right paramedian cleft involving the lip and palate. No abnormalities of the ossicular chain were identified.

It is worth noting that this combination of developmental abnormalities and craniosynostosis presents a challenge for health professionals in medicine and audiology managing the child's hearing loss and rehabilitation for any balance and vestibular deficits. The combination of inner and middle ear dysfunction, the potential of deterioration of cochlear hearing levels in the context of a widened vestibular aqueduct and the challenging hearing aid compliance due to craniosynostosis, contribute to challenging audiological management.

Genetic analysis revealed a heterogeneous mutation in the CHD7 gene (c.3106C>T, p.(Arg1036*) (HGVS : CHD7: c.[3106C>T; [=]; p.[(Arg1036*)];[(=)]. Genetic screening including the most common mutations associated with craniosynostosis in the FGFR1, FGFR2, FGFR3, TWIST, MSX2, ALX1, ALX3, ALX4, RUNX2, and EFNB1 genes revealed no pathogenic variant.

CHARGE syndrome incorporates a diverse phenotype characterized by colobomas, heart defects, choanal atresia, retardation of growth or development, genital abnormalities, and ear abnormalities [1]. However, to the best of our knowledge, no case of genetically proven CHARGE and craniosynostosis has been previously reported. Collective data of current research on CHD7 function supports its regulatory role in complex pathways involved in neural crest (NC) and craniofacial development [2]. The latter association links CHARGE with other chromatinopathies and neurocristopathies sharing overlapping phenotypic characteristics and interestingly, occasionally associated with craniosynostosis. This group of disorders includes but is not limited to DiGeorge syndrome, Treacher Collins syndrome (TCS), Kabuki syndrome (KS), and Mowat-Wilson syndrome (MWS) [2].

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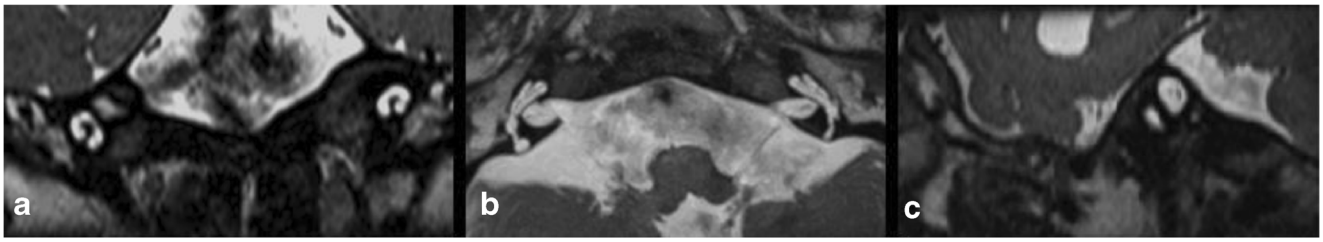

Fig. 1 MR reconstructions demonstrating bilateral dysplastic cochleae and absence of the semicircular canals (**a** Coronal T2WI reconstruction. **b** Axial T2WI maximum intensity projection). There is also enlargement of the right vestibular aqueduct, a finding further complicating audiological management of this patient with severe left hearing loss (b). **c** Left parasagittal IAM T2WI illustrates absence of the left cochlear nerve with preserved vestibular nerves

KS is a "chromatinopathy" demonstrating high clinical overlap with CHARGE. KS is caused by mutations in KMT2D and KDM6A genes, and craniosynostosis has been reported in approximately 6% of KS cases [3]. DiGeorge syndrome also demonstrates significant phenotypic overlap with CHARGE and has been associated with craniosynostosis, although this is considered an atypical feature of the disorder [2]. MWS is another syndrome with overlapping phenotypic characteristics with CHARGE to the extent that in a recently reported series, Wenger et al. describe cases of MWS initially misdiagnosed as CHARGE [4]. MWS is caused by mutations or deletions of the zinc finger E-box-binding homeobox 2 (ZEB2) gene, and craniosynostosis has been reported in 1.9% of cases [4].

Research on the causative genetic and molecular basis of craniosynostosis has largely been based on investigations of syndromic forms of craniosynostosis, such as Pfeiffer, Crouzon, and Muenke. The most common causative mutations have been detected in genes encoding fibroblast growth factor receptors 1, 2, and 3 (FGFR-1, FGFR-2, and FGFR-3), MSX2 (muscle segment homeobox 2) and TWIST [5]. Our reported case, similar to previously reported neurocristopathies with craniosynostosis, was negative for the aforementioned mutations, although it is noted that other less frequent mutations have not been excluded.

It has been hypothesized that craniosynostosis in chromatinopathies and neurocristopathies probably reflects the pleiotropy of the associated defective genes leading to widespread impairment of gene transcription. The latter is in accordance with the findings of current research investigating the pathways of cranial neural crest cells in the normal development of the craniofacial complex, including normal growth and development of the calvarium [2].

Neurocristopathies and chromatinopathies are characterized by overlapping clinical features, including craniosynostosis.

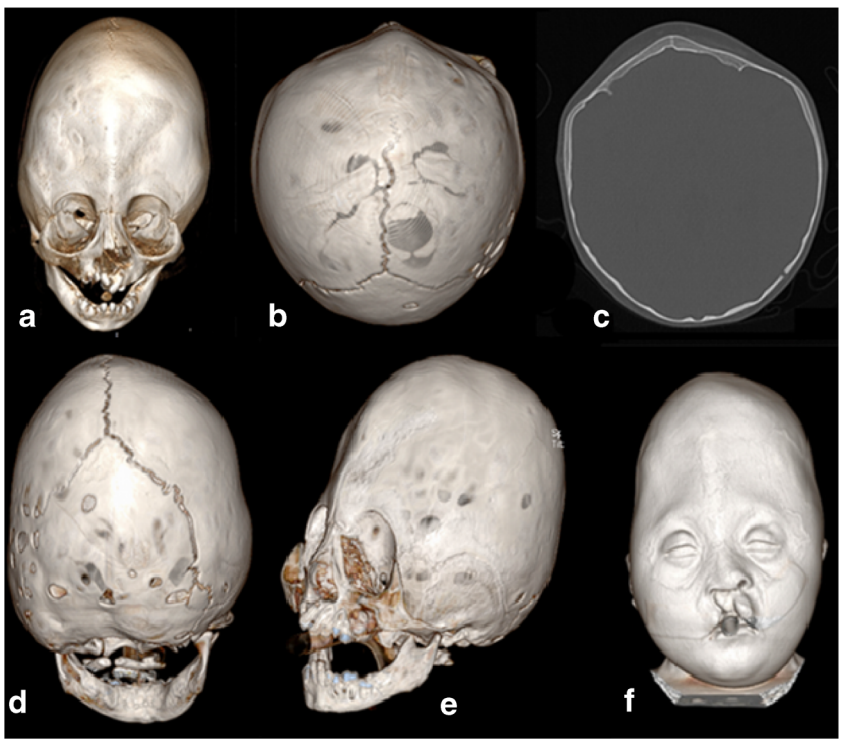

Fig. 2 CT study at 18 months of age. 3D Reconstructions (**a**, **b**) and axial image (**c**) illustrate features of bicoronal craniosynostosis as well as trigonocephaly suggestive of a premature closure of the metopic suture. CT reconstructions demonstrating fusion of the left coronal and partial fusion of the left lambdoid and squamous sutures (**d**, **e**) associated with appearances of turricephaly (e, f). The lip cleft is also noted (**f**)

This rare occurrence in a patient with CHARGE may reflect the syndrome's genetic pleiotropy; however, its pathogenesis remains indeterminate.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to disclose.

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