WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Co-Occurrence of Neonatal Familial Cleidocranial Dysplasia with Carrier Phenotype of CFTR Gene: A Case Report from Iran

Mohammad Ali Zamani[1], Amir Ali Zamani[2], Hamideh Seifi[3], Zeinab Jannat*[4]

[1]. MD, Neonatologist, Department of Pediatrics, Division of Neonatology, School of Medicine, Tehran University of Medical Sciences, Tandis Hospital, Tehran, Iran.
drzamanii@yahoo.com
[2]. MD, School of Medicine, Iran University of Medical Sciences, Tandis Hospital, Tehran, Iran.
zamani.amirali@icloud.com
[3]. MD, Department of Pediatrics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tandis Hospital, Tehran, Iran.
Hamideh_s80@yahoo.com
[4]. MSN, Department of Neonatal Intensive Care Nursing and Midwifery, Tehran University of Medical Sciences, Tandis Hospital, Tehran, Iran.
Jannat1365@yahoo.com

ABSTRACT

Introduction*:* The cooccurrence of cleidocranial dysplasia (CCD) and cystic fibrosis (CF), with two distinct genetic etiologies and inheritance patterns, is theoretically possible in large chromosomal deletion syndromes, although it has not been previously reported. Reporting a very rare case of genetic concurrence in a neonate presenting with respiratory distress highlights the importance of multidisciplinary consultations and enriches the systematic statistical data.

Case*:* The case presented is a 36-week-old male neonate born with a low Apgar score following maternal abruption and spotting, admitted to the NICU with a diagnosis of respiratory distress. On physical examination, both the anterior and posterior fontanelles were found to be very wide, and failure of the two ends of the right clavicle to connect at the midline was noted. The clinical history revealed similar manifestations in the neonate's father, and genetic testing confirmed the diagnosis of cleidocranial dysplasia with deletion of exons 4 and 5 of the RUNX2 gene in both the father and neonate. Additionally, the neonate carried the carrier phenotype for the c.1521_1523del variant of the CFTR gene, which had been previously identified in the parents. This co-occurrence necessitates further specialized investigations, including complete genome sequencing and evaluation of chromosomal deletion syndromes in the family members.

Conclusion*:* Neglecting clinical genetics results in undetected rare diseases and hinders the advancement of medical support for affected populations. Multilateral and specialized collaboration within the treatment team enables timely identification and necessary interventions.

Keywords: Neonate, Cleidocranial Dysplasia, Phenotype, Cystic Fibrosis

Introduction:

Cleidocranial dysplasia (CCD) is a rare autosomal dominant genetic disorder caused by mutations in the RUNX2 gene(1). It has a global prevalence of 1:1,000,000, with an estimated 100 cases in Iran's 88 million population(2). The exact comprehensive epidemiological studies of its incidence in Iran is unknown due to a lack of regional data, its resemblance to other growth disorders, variable access to genetic specialists, and insufficient attention to clinical findings in remote regions.
The prevalence in Iran depends on family genetic patterns and access to diagnostic facilities. Common symptoms in Iranian patients include delayed fontanelle closure, absent or incomplete clavicles, dental issues, and short stature. Patients typically have normal cognitive skills and can achieve a good quality of life with supportive care(3).

Cystic fibrosis (CF) is a progressive autosomal recessive genetic disorder caused by CFTR gene (cystic fibrosis transmembrane conductance regulator) mutations. It has a global prevalence of 1 in 3,000–4,000 live births in European populations and an estimated 1 in 5,000–10,000 in Iran (4). CF is characterized by decreased ciliary function in mucosal tissues, leading to secondary infections and reduced mucosal function.

This case emphasizes the importance of early clinical diagnosis, lifelong multidisciplinary care, and systematic data collection in rare disease registries.

Case Presentation:

A male neonate, born prematurely at 36 weeks and 2 days via C-section with a birth weight of 2440 g and low APGAR Score (4/7/8/9), was admitted to

the NICU for respiratory distress following placental abruption. He required intubation because of severe respiratory acidosis and lung involvement. Physical examination revealed wide fontanelles and short, broad fingers, and chest X-ray showed right clavicular hypoplasia (Figure 1), which was confirmed by an orthopedic specialist. Cardiology consultation revealed a large patent ductus arteriosus (PDA), dilated pulmonary artery (PA), and elevated pulmonary pressure. Brain sonography was normal, and cranial CT was not performed because of the infant's unstable condition. The other abdominal organs were normal.

The mother had hypothyroidism and a history of two unsuccessful in vitro fertilization (IVF) attempts. The father reported a personal history of open fontanelles, short stature, mild cranial deformity, recurrent jaw and dental defects, clavicular instability, and pelvic surgery. Owing to the family history, amniocentesis and genetic counseling were performed. DNA analysis revealed a deletion in exons 4 and 5 of the RUNX2 gene in both the father and fetus, confirming the diagnosis of CCD. Additionally, CFTR gene analysis showed a heterozygous genotype for the variant c.1521_1523del (carrier) and a homozygous normal genotype for the variant c.3850A>T. After two days, at the request of the family, the neonate was transferred to another medical center under non-invasive positive pressure ventilation (NIPPV) for continued care. Informed consent was obtained from the family to introduce the newborn.

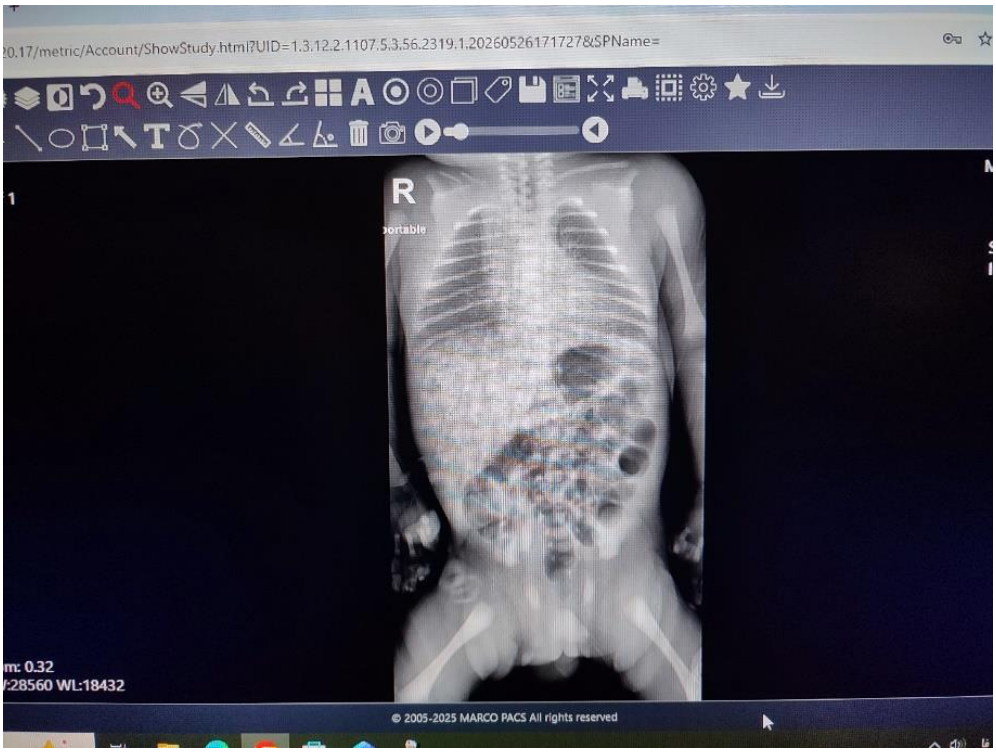


Figure 1. Right Clavicle Dysplasia in this case. The clavicle is completely separated in the middle, and its difference from a fracture is the rounded edge of the bone on both sides.

Discussion:

This case describes a preterm male infant diagnosed with CCD and a carrier of CF, with clinical and genetic manifestations also present in the father. The autosomal dominant inheritance pattern of the RUNX2 gene explains the diagnoses of the father and infant. Genetic counseling is crucial for families with a history of CCD.

Most cases of CCD are diagnosed in adulthood, often after the onset of clinical problems. Owing to its rarity and the cost of genetic testing, definitive diagnosis is often delayed, particularly in low-income regions. In newborns, CCD symptoms can resemble other developmental and skeletal issues, making early diagnosis challenging. Common neonatal signs include abnormal skeletal features, such as wide fontanelles, incomplete skull fusion, absent or incomplete clavicles (a pathognomonic sign), short stature, abnormal chest shape, respiratory problems, and broad fingers(5). The patient in the present case exhibited wide fontanelles and an incomplete right clavicle. Dental and jaw deformities typically appear after the age of one year(6).

CCD generally has a good prognosis, is not life-threatening, and most affected individuals lead normal lives(7). The infant's father, aged 31 years, received supportive treatment for bone, dental, jaw, and pelvic defects and had a good quality of life. Common challenges include dental malocclusion, shoulder drooping, and difficulties in carrying heavy loads.

Pelvic problems in women with CCD can complicate childbirth, requiring specialized obstetric care(8). Follow-up is essential to prevent complications, such as pulmonary valve stenosis, hearing loss, and neuro-respiratory issues, in older infants.

As of 2024, the co-occurrence of CCD and CF in a single patient has not been definitively documented in the medical literature. The RUNX2 gene (CCD)

is located on chromosome 6p21 (autosomal dominant)(9), whereas the CFTR gene (CF) is located on 7q31.2 (autosomal recessive)(10). These genes are located on different chromosomes and affect distinct biological processes (bone formation versus chloride ion channels). Although both can cause respiratory symptoms, their origins are typically independent. Simultaneous occurrence is likely to occur only in rare large chromosomal deletion syndromes affecting both genes, which have not yet been reported. Given the genetic findings in this case, further specialized genetic counseling, including whole exome or genome sequencing and investigation of chromosomal deletion syndromes, should be considered for the family.

Acknowledgments:

The authors would like to thank the involved family who tightly collaborated with this report.

Conflict of Interest:

In this study, the authors have no conflict of interest.

Declaration:

We acknowledge the use of [Paperpal AI; https://edit.paperpal.com/] in writing of the manuscript to improve the language and readability].

Conclusion:

In populations with similar genetic backgrounds, multidisciplinary counseling and interprofessional collaboration are essential for screening, identifying the disease, determining its underlying cause, and recognizing its overlap with other genetic conditions to improve patient quality of life and symptom management.

REFERENCES:

1) Motaei, Jamshid, Arash Salmaninejad, Ebrahim Jamali, et al. "Molecular Genetics of Cleidocranial Dysplasia." *Fetal and Pediatric Pathology* 40, no. 5 (2021): 442–54. https://doi.org/10.1080/15513815.2019.1710792.
2) https://www.orpha.net/en/disease/detail/1452?name=Cleidocranial%20dysplasia&mode=name
3) "Retraction: Omid Daneshjoo, Pirooz Ebrahimi, Leila B. Salehi, Antonio Pizzuti, Masoud Garshasbi (2020). Identification of a Novel RUNX2 Gene Mutation and Early Diagnosis of CCD in a Cleidocranial Dysplasia Suspected Iranian Family. *Clin Case Rep* . 2020; 1-8." *Clinical Case Reports* 8, no. 8 (2020): 1596–1596. https://doi.org/10.1002/ccr3.3178.
4) Hammoudeh, Samer, Sarah Aqel, Farha Mukthar, Prem Chandra, and Ibrahim A. Janahi. "A Systematic Review of the Epidemiology of Cystic Fibrosis in Arab Countries: An Update." *Clinical Epidemiology and Global Health* 28 (July 2024): 101697. https://doi.org/10.1016/j.cegh.2024.101697.
5) Zhao, Shimeng, Tongtong Wang, Haipeng Yang, and Riyan Huang. "Neonatal Familiar Cleidocranial Dysplasia: A Case Report." *American Journal of Case Reports* 26 (December 2024). https://doi.org/10.12659/AJCR.946322.
6) Giri, Akash Kumar, Barsha Thapa, and Manisha Chaudhary. *Cleidocranial Dysplasia: A Case Report Highlighting Dental, Craniofacial, and Skeletal Complexity*. n.d.
7) Hoover-Fong, Julie, Cheryl Anderson-Cermin, Frank Artinian, et al. "Diagnosis, Treatment, and Management Recommendations for Cleidocranial Dysplasia: A Modified Delphi Panel." *Journal of Bone and Mineral Research*, January 8, 2026, zjag004. https://doi.org/10.1093/jbmr/zjag004.
8) Nishio, Yumiko, Teruyuki Hiraki, Hiroko Taniguchi, and Kazuo Ushijima. "Anesthetic Management during a Cesarean Section in a Patient with Cleidocranial Dysplasia: A Case Report." *JA Clinical Reports* 4, no. 1 (2018): 2. https://doi.org/10.1186/s40981-017-0141-2.
9) Jamali, Ebrahim, Department of Genetics, School of Basic Science, Tonekabon Branch, Islamic Azad University, Tonekabon, Iran, Raziyeh Khalesi, et al. "Identification of a Novel Splice Site Mutation in RUNX2 Gene in a Family with Rare Autosomal Dominant Cleidocranial Dysplasia." *Iranian Biomedical Journal* 25, no. 4 (2021): 297–302. https://doi.org/10.52547/ibj.25.4.297.
10) Nami, Amin Hosseini, Mahboubeh Kabiri, Fatemeh Zafarghandi Motlagh, et al. *Genetic Attributes of Iranian Cystic FIbrosis Patients: The Diagnostic Efficiency of CFTR Mutations in over a Decade*. n.d.