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ORIGINAL ARTICLE

Prenatal diagnosis and associated anomalies of congenital hand malformations

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ABSTRACT

Objective: Congenital hand malformations (CHM) are prevalent congenital anomalies in the prenatal period. We aimed to assess the prenatal features of CHM, associated genetic syndromes, and postnatal prognosis.

Material and Methods: Ultrasound findings, associated anomalies, genetic results, and postnatal course were evaluated in ten cases with CHM in two centers over three years.

Results: The mean gestational age at diagnosis was 22.8±2.7 weeks. CHM was isolated in four cases and accompanied by associated anomalies in six fetuses. It was bilateral in six cases. Polydactyly was the most common type of hand malformation. Termination of pregnancy was performed in four fetuses. There was no genetic etiology in isolated cases, and the postnatal course was favorable. Hand malformations with associated anomalies and a genetic syndrome carried a high risk, and the prognosis was poor.

Conclusion: Prenatal diagnosis of CHM should prompt a detailed anatomical scan and a comprehensive genetic work-up. In isolated cases, the likelihood of a genetic cause is relatively low. In fetuses with multiple congenital anomalies, genetic etiology is common, and the prognosis is poor.

Keywords: Genetic, hand, limb, malformation, ultrasonography.

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INTRODUCTION

Congenital hand malformations (CHM) are common defects and include various entities such as polydactyly, syndactyly, oligodactyly, transverse reduction defects, or ectrodactyly. Upper limb anomalies constitute 10–20% of all congenital anomalies, and the estimated prevalence is 5–27/10,000 in live births.[1]

The embryonic development of upper limbs is complex, and different genes and proteins are involved. The limb bud consists of mesoderm and ectoderm and begins forming around the 4th week of gestation. By the 8th week, hand formation is complete. Upper limbs develop in a proximodistal fashion.[2] Several mediators are responsible for upper limb development, including fibroblast growth factor (FGF), sonic hedgehog protein (SHH), and wingless-type mouse mammary tumor virus integration site family (Wnt7a).[3]

The etiology of CHM is diverse, and chromosomal aberrations, copy number variations, and Mendelian diseases may be responsible. Additionally, viral infections, medications, and disruptive conditions such as amniotic band syndrome can cause hand deformities. Unfortunately, the exact origin remains unknown in many cases.[4]

A detailed fetal anomaly scan should be performed on every pregnant woman in the second trimester, particularly between 18–22 weeks of gestation. The International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) and several national organizations advise checking all long bones, hands, and feet. However, it has been highlighted that counting fingers or toes is not necessary during the standard mid-trimester scan.[5] Nevertheless, in many cases, fingers can be counted, and movements can be examined. Additionally, 3D ultrasound allows for a comprehensive analysis of the hands.

The objective of our study is to assess the prenatal and postnatal features of 10 fetuses with CHM in two referral centers between 2020 and 2023.

MATERIAL AND METHODS

We evaluated the records of ten cases with CHM detected in our centers between January 2020 and June 2023. Research involving human subjects complied with all relevant national regulations and institutional policies, in accordance with the tenets of the Helsinki Declaration (as revised in 2013), and was approved by the authors' Institutional Review Board (Van Yüzüncü Yıl University, Decision number 2024/08-16). Data on fetuses and postnatal outcomes were retrieved from our database systems. The following variables were assessed: maternal age, gestational age at diagnosis, fetal sex, location of hand malformation, other system anomalies, karyotype and/or chromosomal array analysis, neonatal diagnosis, and short-term outcomes.

The evaluation of patients was conducted by a multidisciplinary team, including maternal-fetal medicine specialists and genetic specialists. Families were consulted by a hand surgeon before birth. Ultrasound examinations were performed with high-quality ultrasound equipment (Voluson E6, Voluson E8, GE Healthcare, Milwaukee, USA). Hands, feet, and all long bones were examined for their presence. The count and configuration of digits were assessed in each fetus. A standard anatomical protocol for targeted ultrasound evaluation of the upper extremities was followed: five hyperechoic, cylindrical metacarpal bones; five independent digits of different lengths; three hyperechoic phalanges (two for thumbs); and normal-length radius and ulna.

Three-dimensional sonography (3D USG) was routinely used for primary diagnosis, improved visualization, and characterization of hand malformations. 3D USG analyses were performed using surface rendering and skeletal mode. All cases underwent a meticulous anatomical assessment and fetal echocardiography, adhering to the guidelines provided by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG).[5]

Following an extensive genetic counseling session, the parents of all cases were given the option to undergo a prenatal diagnostic test. Chromosome preparations from amniotic fluid after amniocentesis were performed according to standard procedures. Conventional chromosome analysis was conducted via Giemsa banding, with a median resolution at the 500–550 band level for numerical and structural analysis. Array comparative genomic hybridization was performed to detect microdeletions and duplications. It was routinely used as an adjunct tool in fetuses with congenital anomalies and normal karyotypes. Genomic DNA was extracted from long-term cultures of the cases, and labeling, hybridization, and analysis were performed according to the manufacturer's protocols.

The process of diagnostic confirmation and outcome assessment involved a meticulous review of pediatric patient records and pathology reports. Additional information about cases was obtained through telephone interviews with parents and consultations with plastic and reconstructive surgeons.

Statistical Analysis

Statistical analysis was performed using a software package (SPSS 14.0; SPSS, Chicago, IL). Descriptive parameters are expressed as mean or median (±SD), where appropriate. Frequencies are given as the number of cases or percentages.

RESULTS

Between January 2020 and June 2023, ten fetuses with CHM were detected over three years. The mean maternal age was 27.4±4.2 years, and the mean gravida was 2.9±1.3. The mean gestational age at diagnosis was 22.8±2.7 weeks. The hand anomaly was bilateral in six cases and unilateral in the remaining fetuses. In six cases, the hand anomaly was associated with other system anomalies, and among those fetuses, four pregnancies were terminated. The clinical, genetic, and postnatal results of the cases are summarized in Table 1, and various CHMs are shown in Figures 1, 2, 3, and 4.

Polydactyly was the most common hand anomaly in our cohort. Three cases (cases 2, 3, and 10) had polydactyly, and in all of them, both hands were affected. Case 2 had isolated bilateral polydactyly, and no additional anomaly was detected either prenatally or postnatally. The baby was born healthy. In case 3, short long bones and a narrow chest were detected in addition to polydactyly. This case was suspected to have short rib-polydactyly syndrome, and termination of pregnancy (TOP) was offered to the family. However, they decided to continue the pregnancy, and the fetus was delivered at

Table 1: Ultrasonographic, clinical and genetic features and postnatal outcomes of 10 cases

C	GA at dia.	Hand anomalies	Associated anomalies	Karyotype or chr. array	Prognosis
1	19+3	Unilateral oligosyndactyly	Radius and ulna hypoplasia	Normal	Alive
2	22+1	Bilateral Postaxial polidactyly	No associated anomaly	Normal	Alive
3	23+1	Bilateral postaxial polidactyly	Short ribs, short long bones	Normal	Short rib polydactyly syndrome Neonatal ex
4	18+4	Unilateral oligosyndactyly	No associated anomaly	Normal	Alive
5	17+5	Unilateral transverse reduction	No associated anomaly	Normal	Alive
6	18+4	Bilateral transverse reduction	No associated anomaly	Normal	TOP
7	29+5	Bilateral brachydactyly	Rhizomelia, macrocephaly	Normal	Achondroplasia Alive
8	19+4	Unilateral Clenched hand	İnlet VSD, ventriculomegaly, bilateral renal pelvis dilatation, IUGR	Trisomy 18	TOP
9	24+5	Bilateral Split hand	Bilateral split food	Normal	TOP
10	20+3	Bilateral postaxial polidactyl	Bilateral polycystic kidney and encephalocele	Normal	Meckel-Gruber syndrome TOP

C: Case; GA: Gestational age; dia: Diagnosis; chr: Chromosomal; VSD: Ventricular septal defect; IUGR: Intrauterine growth restriction; TOP: Termination of pregnancy.

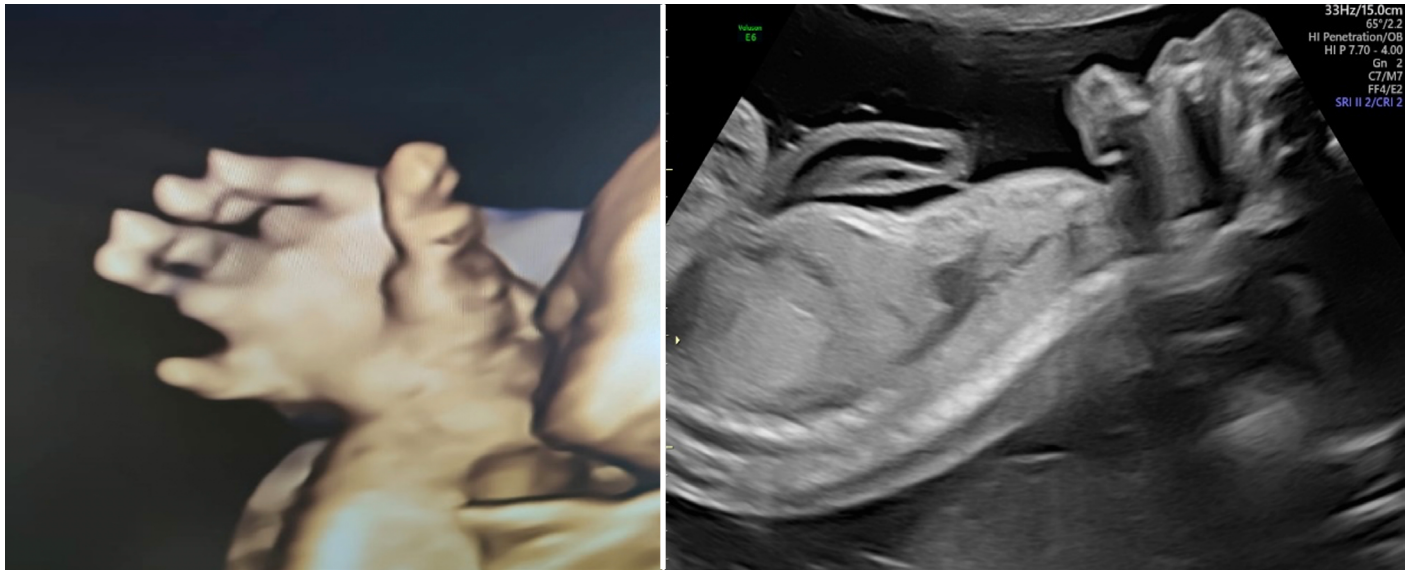

Figure 1: Polydactyly in 22 weeks of gestation demonstrated by 3-D surface rendering with short rib-polydactyly syndrome. A narrow thorax due to short ribs was shown in 2-D ultrasonography.

38 weeks by cesarean section. The baby was admitted to the neonatal intensive care unit (NICU) and died postnatally on the fourth day. Case 10 had anhydramnios, bilateral hyperechogenic large kidneys, and a posterior encephalocele. The combination of polydactyly and these anomalies led to a diagnosis of Meckel-Gruber syndrome. The parents were informed about the very poor prognosis, and they accepted TOP.

Cases 1, 4, and 5 had unilateral hand anomalies. A detailed anatomical scan showed no additional anomalies in these cases, and they were delivered at term. All three cases were well after birth and were followed up by a hand surgeon.

Case 6 was particularly challenging for both the medical team and the family. Bilateral reduction defects in the hands were detected, with no accompanying anomalies. Amniocentesis was performed, and chromosomal array analysis was normal. Due to severely diminished hand function, TOP was offered and accepted by the family.

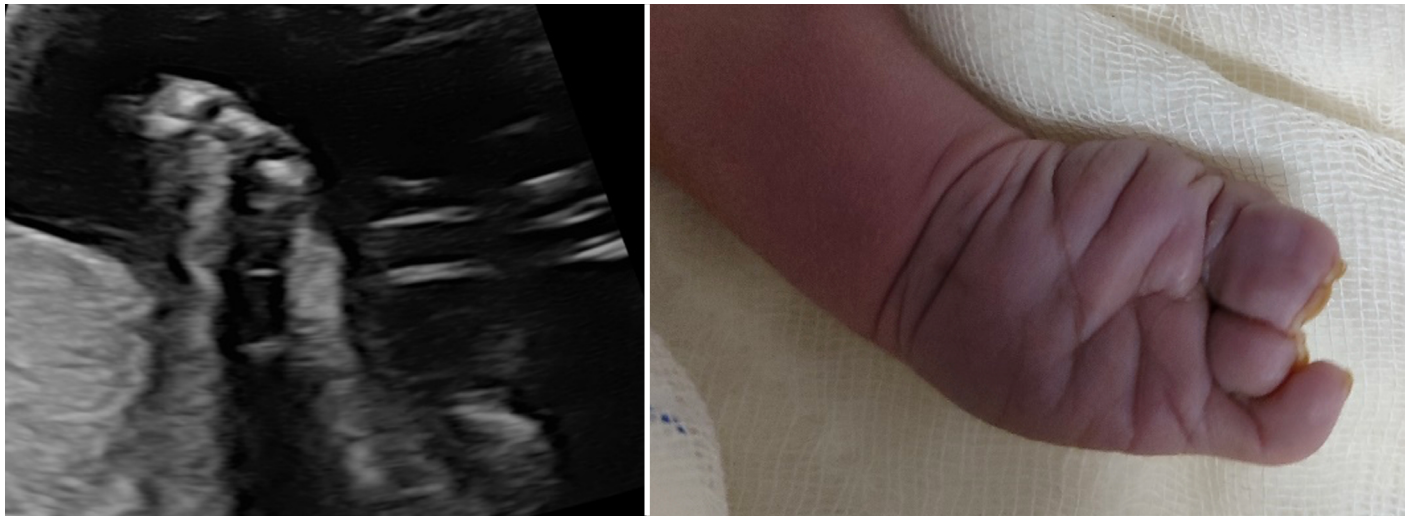

Figure 2: Oligo syndactyl in a fetus at 19 weeks of gestation and postnatal appearance of CHM.

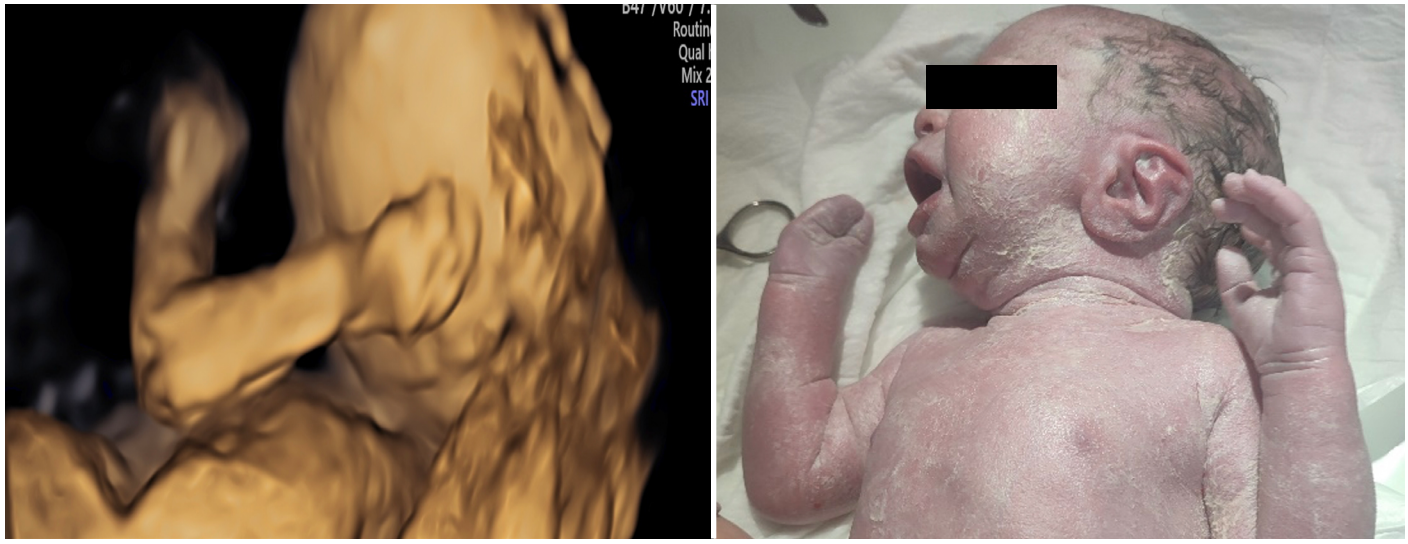

Figure 3: Unilateral oligo syndactyly in a fetus at 22 weeks demonstrated by 3-D surface rendering and postnatal confirmation.

In case 7, bilateral brachydactyly, rhizomelia, and macrocephaly were detected in the third trimester. Cordocentesis revealed an FGFR3 gene mutation associated with achondroplasia.

In case 8, overlapping fingers were observed in both hands. Additionally, a cardiac defect, severe ventriculomegaly, bilateral hydronephrosis, and fetal growth restriction (FGR) were detected. Amniocentesis confirmed trisomy 18, and TOP was performed.

Case 9 had severe polyhydramnios, and both hands and feet had a claw-like appearance. These findings were associated with ectrodactyly-ectodermal dysplasia syndrome, and the pregnancy was terminated.

DISCUSSION

The evaluation of fetal hands during prenatal assessment varies depending on the physician's level of expertise and knowledge. Most national and international organizations advise checking and documenting the presence of arms, legs, hands, and feet. However, none of the guidelines recommend counting the fingers or evaluating the anatomy of the hands. Although the guidelines do not mandate the diagnosis of hand anomalies, the postnatal diagnosis of these anomalies can cause significant distress and anxiety for families. To date, only a few studies have been published on the prenatal diagnosis of hand anomalies. Therefore, our study aimed to investigate the prenatal characteristics of CHM and associated genetic and structural anomalies.

In our series, the most common anomaly was polydactyly, which was consistent with the literatüre.[6,7] Polydactyly is characterized by the presence of supernumerary digits, which can occur in isolation or as a feature of a genetic syndrome. The prevalence of polydactyly is estimated to be around 1 in 500 to 1,000 live births, with potential variations in incidence based on ethnicity.[8] When polydactyly is detected on prenatal ultrasound (USG), the most important prognostic marker is whether it is isolated or not. In most instances, polydactyly is identified as an isolated finding, exhibiting autosomal dominant transmission and a favorable prognosis.[9] However, in fetal series,

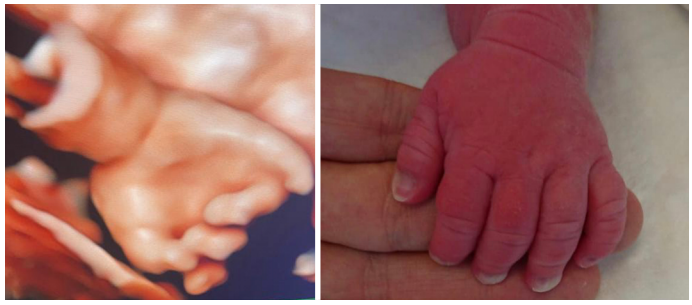

Figure 4: Bracydactyl in a fetus with achondroplasia at 29 weeks of gestation and postnatal appearance.

isolated polydactyly has been reported rarely, with most cases being syndromic. Associated syndromes include Meckel-Gruber syndrome, Bardet-Biedl syndrome, Smith-Lemli-Opitz syndrome, and skeletal dysplasias.[10]

Filges et al.[11] reviewed 24 fetuses with polydactyly and found that in ten cases (42%), polydactyly occurred in a familial or nonsyndromic context. In seven cases (28%), polydactyly was associated with aneuploidies, mainly trisomy 13 and trisomy 18. In these cases, polydactyly was accompanied by multiple congenital anomalies. In the remaining seven cases, polydactyly was a feature of genetic syndromes such as Smith-Lemli-Opitz syndrome or VACTERL association.

In our series, two out of three polydactyly cases were associated with genetic syndromes, namely Meckel-Gruber syndrome and short rib-polydactyly syndrome. Moreover, in these cases, polydactyly was a key feature in the differential diagnosis. We emphasize that in cases involving renal or skeletal anomalies, a comprehensive evaluation of the hands and fingers is crucial, and counting the digits is essential.

Extremity reduction defects are congenital anomalies characterized by the absence or severe hypoplasia of skeletal structures in the limbs. Various factors, such as Mendelian inheritance disorders, chromosomal abnormalities, established associations, sequences, teratogenic exposures, and presumed vascular disruption defects, have been identified as potential causes of extremity reduction defects. Nonetheless, in numerous cases, the underlying cause remains unknown. Reduction defects affecting a single limb are less likely to have a genetic cause compared to those affecting multiple limbs.[12,13]

Bergman et al.[14] analyzed data from the EUROCAT Northern Netherlands database, including 391 fetuses and children with extremity reduction defects born between 1981 and 2017. Their findings indicated that an etiological diagnosis was made three times more often when an extremity reduction affected multiple limbs compared to a single limb. Additionally, no genetic disorders were detected in isolated cases involving only one affected extremity. Furthermore, if associated anomalies were present, a genetic disorder was identified in 16% of cases.

In our series, one case of an extremity reduction defect involved a single limb, with no additional organ system anomalies. Karyotype and chromosomal microarray analysis were normal, and the child was born healthy. In another case, both extremities were affected, but no genetic cause was identified. The family opted for TOP.

The ascertainment of the underlying cause has become a crucial diagnostic step in the workup of a fetus with CHM. CHM may serve as the first clue of an underlying syndrome in the fetus, making the establishment of an etiological diagnosis essential for accurate prognosis assessment and counseling.[15]

Carli et al.[16] analyzed genetic data from 487 cases with upper limb anomalies and found that a genetic etiology was identified in 199 (41%) patients. Chromosomal aneuploidy was detected in 13 cases, whereas 186 fetuses were diagnosed with a single-gene disorder. Cases with involvement of the lower limbs, anomalies in other organ systems, and facial dysmorphism were significantly more frequent among those with a genetic origin. Additionally, central defects were markedly higher in patients with a genetic etiology.

Aslanger et al.[17] presented 18 cases with hand anomalies, including oligodactyly, syndactyly, reduction defects, and polydactyly. They reported triploidy in one case, while karyotype analysis was normal in the remaining fetuses. Furthermore, they identified single-gene disorders in more than half of the cases, including ciliopathies, Nager syndrome, and Apert syndrome. In these fetuses, multiple congenital anomalies were present, and hand malformations were predominantly bilateral. The authors emphasized that the identification of hand anomalies should prompt a detailed anatomical survey, and the diagnosis should be confirmed through advanced cytogenetic and molecular analyses conducted by a multidisciplinary team consisting of perinatologists, clinical geneticists, and hand surgeons.

Whole-exome sequencing (WES) is a next-generation sequencing method that focuses on exons, which contain >85% of genetic variants associated with human disease phenotypes.[18] Lord et al.[19] demonstrated that WES had a diagnostic yield of 15.4% (10/65) in fetuses with skeletal anomalies and normal karyotype and chromosomal microarray (CMA) results. In a cohort of 28 chromosomally normal fetuses with extremity anomalies, Liu et al.[20] revealed that 75% (21/28) of cases had mutations in genes related to skeletal diseases, detected through WES. WES has a high diagnostic rate for extremity anomalies, improving clinical management during pregnancy and providing families with better-informed reproductive decisions.

In our series, a genetic etiology was identified in four cases. One case with multiple congenital anomalies was diagnosed with trisomy 18. In the remaining three cases, single-gene disorders were observed, including achondroplasia, Meckel-Gruber syndrome, and short rib-polydactyly syndrome. We recommended WES analysis for all fetuses with normal chromosomal arrays; however, none of the families consented to WES due to its high cost.

A comprehensive workup, including a detailed anatomical scan, fetal echocardiography, and genetic counseling, is essential for the antenatal evaluation of CHM to determine its genetic cause. It is crucial to emphasize that expert ultrasound evaluation, including fetal echocardiography, is warranted, as a significant proportion of these cases involve associated major and minor anomalies that may be detected by an experienced sonologist. Furthermore, the presence of associated anomalies may completely alter the prognosis of cases initially thought to be isolated.

Paladini et al.[21] analyzed 100 fetuses with upper limb anomalies and found that 12 cases were isolated, whereas the remaining 88 cases had additional organ anomalies. The researchers highlighted

the importance of ultrasound in detecting specific upper extremity anomalies, which led to an accurate diagnosis in 27% of fetuses.

In recent years, three-dimensional (3D) ultrasonography has been widely used in prenatal diagnosis. Several studies have demonstrated that the implementation of 3D ultrasonography facilitates the recognition of acral malformations, enables the assessment of extremities in the coronal plane, and allows for a clearer visualization of digit positioning in cases of clenched hands or polydactyly. Moreover, the use of surface-rendering images has played a crucial role in enhancing communication with expectant couples regarding the diagnosis.

In our series, CHM was a key ultrasound finding that contributed to an exact etiological diagnosis in three (30%) cases.

Prenatal counseling is the most critical aspect of perinatal care in cases of CHM. In syndromic cases or those with multiple organ defects, postnatal prognosis is generally poor, making counseling relatively straightforward. However, perinatal counseling becomes more challenging in isolated cases.

A multidisciplinary team approach is essential and should include a geneticist, a neonatologist, a hand surgeon, and a psychologist. A genetic counselor should provide pre- and post-test genetic counseling, offering detailed information about appropriate genetic tests such as karyotyping, chromosomal microarray, or whole-exome sequencing. The neonatologist should assess the neonate to rule out additional anomalies, the hand surgeon should plan potential surgical reconstruction, and the psychologist should provide emotional support to the family.[22,23]

In our study, all cases were evaluated prenatally by a geneticist and a hand surgeon, ensuring that families received comprehensive counseling regarding CHM.

CONCLUSION

The identification of CHM should prompt a detailed anatomical scan, followed by advanced cytogenetic and molecular genetic testing. In isolated cases, the likelihood of a genetic cause is relatively low. However, in fetuses with multiple anomalies, the risk of an underlying genetic syndrome is high, and the pattern of hand malformation may serve as a key diagnostic clue.

Statement

Ethics Committee Approval: The Van Yüzüncü Yıl University Non-Interventional Clinical Research Ethics Committee granted approval for this study (date: 05.08.2024, number: 2024/08-16).

Author Contributions: Concept – GT, ZB; Design – GT, ZB; Supervision – GT; Resource – GT, OK; Materials – GT, ZB; Data Collection and/or Processing – GT; Analysis and/or Interpretation – GT, OK; Literature Search – GT, ZB; Writing – GT; Critical Reviews – GT, OK.

Conflict of Interest: The authors have no conflict of interest to declare.

Informed Consent: Written, informed consent was obtained from the patients' families for the publication of this this study and the accompanying images.

Use of AI for Writing Assistance: Not declared.

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