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Fetal Hand Anomalies: 18 Cases Diagnosed Between 2020-2022 from a Single Tertiary Care Center

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ABSTRACT

Objective: The aim of this study was to present and investigate fetal cases with hand anomalies by discussing their antenatal and postmortem findings.

Materials and Methods: This retrospective review re-evaluates fetal cases identified antenatally with hand anomalies including polydactyly, syndactyly, reduction defects, and oligodactyly. The following data were collected from the patients' medical records: Demographic information, family histories, X-ray images, photographs, and cytogenetic/molecular findings. The study also performed a chromosome analysis, array-comparative genomic hybridization (CGH), and Sanger sequencing of *FGFR2* and *GLI3* genes.

Results: This study involved 18 cases with hand anomalies, all of which were diagnosed antenatally. Three cases were diagnosed with Greig cephalopolysyndactyly, Apert Syndrome, and triploidy, respectively.

Conclusions: Fetal ultrasonography is the most valuable tool for providing prenatal diagnosis. Prenatal detection of hand anomalies causes great anxiety for parents; therefore, making an accurate diagnosis list is important for the prenatal period. Prenatal diagnosis and management of hand anomalies must involve a multidisciplinary team composed of a perinatologist, a clinical geneticist, and a hand surgeon.

Keywords: Polydactyly, syndactyly, prenatal diagnosis

INTRODUCTION

The prevalence of upper limb congenital anomalies is 5.25-27.2 in 10,000 live births among the various populations. Hand anomalies are included in upper limb anomalies, with polydactyly being an extremely common type of hand anomaly, followed by transverse reduction defects, syndactyly, and oligodactyly (1, 2).

Upper limb development occurs between the 4th-8th week of gestation from the mesoderm and ectoderm. The temporal and spatial expressions of different gene families are involved in limb formation. Homeobox (HOX) transcription factors regulate the position of the limbs along the craniocaudal axis. The upper limb bud develops on the ventrolateral wall of the embryo on the 26th day of gestation. The apical ectodermal ridge (AER) is a thickened ectoderm layer at the apex of the limb bud and produces the fibroblast growth factors (FGFs) that control the development of the underlying mesoderm. The zone of polarizing activity (ZPA) occurs in the posterior border of the limb bud and produces the Sonic hedgehog (SHH) protein, which regulates the anteroposterior development of the limbs. Dorsal ectoderm controls limb dorsalization through the secretion of WNT7a, which induces the transcription factor LMX1 in the underlying dorsal mesoderm (3-5).

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The etiology of limb anomalies is very complex and can occur due to chromosomal abnormalities, single gene disorders, or disruptive conditions. However, the cause in many cases is still unknown. Polydactyly is a condition in which extra fingers form on the hands or toes. It usually occurs as a sixth digit, with the extra finger on the radial, ulnar or central side, respectively known as preaxial, postaxial, or mesoaxial polydactyly. Polydactyly affects the right hand more than the left hand and may appear isolated (non-syndromic) or combined with other anomalies (syndromic) as part of a syndrome (6). Isolated polydactyly is mostly passed from parent to child through the genes associated with non-syndromic polydactyly. Syndactyly, or congenital webbing, is characterized by containment of the skin, soft tissues, or osseous interconnections between adjacent digits at an estimated incidence rate of 1 in 2,000–3,000 live births and is more common in males than females (7). Syndactyly is assumed to arise as a failure of interdigital apoptosis, which falls under the control of bone morphogenetic proteins (BMPs) and is associated with FGFs in the AER. It can appear isolated or as part of a syndrome (8).

Because hand anomalies may be syndromic, the clinician should evaluate for other findings associated with polydactyly and consider other syndromic presentations. Case diagnoses of fetal hand anomalies are complicated. Detailed dysmorphological assessment of the fetus should be performed to detect additional minor anomalies or facial dysmorphism. In terms of preliminary and differential diagnoses, options such as karyotype, array-CGH, single gene sequencing, and whole exome sequencing (WES) should be offered to the family. This study aimed to investigate the types of 18 antenatally diagnosed fetal cases with hand anomalies and to discuss the genetic etiopathogenesis.

MATERIALS AND METHODS

The study involved the antenatally diagnosed fetal cases of intrauterine fetal demise (IUFD) or termination of pregnancy (ToP) with hand anomalies that have been referred to postmortem examination at Istanbul Faculty of Medicine, Department of Medical Genetics clinic at Istanbul University between 2020-2022; 18 fetal cases among 2,342 patients who had been evaluated by the multidisciplinary team for major congenital anomalies were included in the study as a result of additional anomalies accompanying the hand anomalies. The study was reviewed and approved by the institutional review board, and written informed consent (No: 17.10.2022-1316113) was obtained from all parents of the patients included in the study. The study retrospectively reviewed the clinical, radiological, and genetic results. Chromosome analysis was performed using standard cytogenetic Giemsa-Pancreatin-Leishman (GPL) banding technique in long term cultures on cells obtained from the chorionic villus biopsy in five cases (Cases 4, 5, 10, 13, 18), amniocentesis in four cases (Cases 6, 7, 11, 12), and fetal blood in eight cases (Cases 1, 2, 3, 8, 9, 14, 15, 17). To rule out other submicroscopic chromosomal abnormalities, a array-CGH test was performed for the available 11 cases (Case 3, 5, 6, 7, 8, 11, 15, 17). Genomic DNA was extracted from the long-term cultures of the cases, as well as peripheral blood from the parents for Cases 3 and 18 using commercial kits according to manufacturer's instruction (Mammalian Blood and Cells and Tissue DNA Isolation Kit/High Pure Kit, Roche Diagnostics GmbH, Mannheim Germany). Primers for the *FGFR2* (NM_000141.5) and *GLI3* (NM_000168.6) genes were designed to cover all the coding exons and deep exon intron boundaries. Sanger methods on an ABI 3500 Genetic Analyzer (Applied Biosystems, ThermoFisher Scientific, Foster City, CA, USA) and electropherograms in the Sanger sequencing were analyzed using SeqScape software (SeqScape Version 3.0; Applied Biosystems, Calsbad, CA, USA). The human genome GRCh37/hg19 was used as the reference version for alignments of the variants. The variants were investigated in the dbSNP ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) and HGMD (http://www.hgmd.cf.ac.uk/ac/) databases. These are classified according to the comments from the American College of Medical Genetics and Genomics (ACMG, 2015) standards (9).

RESULTS

This study involved a total of 18 fetal cases (5 females and 13 males) from unrelated families that had been diagnosed with hand anomalies. TOP was performed at a median gestational age of the 23rd week of gestation (GW; range = 15th-31st GW). The pregnancies had ended in an IUFD during the 34th GW in Case 7 and the 32nd GW in Case 16. Case 5 had bilateral syndactyly of the 3rd and 4th digits and was diagnosed as triploidy. The karyotype analyses of the remaining cases were normal except for Case 16, as her parents refused the invasive procedure. In cases where a single-gene disease was considered in the preliminary diagnosis, the diagnosis was made by performing the sequence analysis related to that disease. The clinical, cytogenetic and molecular results of the cases are summarized in Table 1, and hand anomalies are shown in Figure 1.

Polydactyly was found in five cases with syndromic features (Cases 1, 3, 9, 13, and 18), while one case (Case 2) was identified with a co-occurrence of neural tube defects (NTD) and polydactyly. Meckel-Gruber syndrome was evaluated in the preliminary diagnosis due to occipital encephalocele in two of three cases (Cases 13 and 18), with renal findings accompanying the polydactyly. Short-rib polydactyly syndrome (SRPS) was considered in one case with a narrow thorax (Case 9). Greig cephalopolysyndactyly syndrome was confirmed with the detection of the c.958_959insA (p.Ile320Asnfs*4) novel variant in the *GLI3* gene, which was the predicted pathogenic in Case 3 that had broad thumbs and halluces accompanying postaxial polysyndactyly in the upper extremity and preaxial polysyndactyly in the lower extremity. According to the ACMG criteria, this truncating variant received scores for PVS1 and PM2 and has been determined as the likely pathogenic. Case 6 had acrosyndactyly in the upper/lower extremity with severe craniosynostosis. Apert syndrome has been diagnosed through molecular testing, with a heterozygous c.755C>G (p.Ser252Trp) pathogenic variant being identified in the *FGFR2*

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Table 1. Clinical and cytogenetic/molecular findings of fetal cases with hand anomalies.

Case	Hand anomalies	Other anomalies	Karyotype Results	Diagnosis & Molecular Results
Case 1	Bilateral postaxial polydactyly of hands and toes	Bilateral polycystic renal disease, absence of renal corticomedullary differentiation	46, XY	MCA R/O: Ciliopathies
Case 2	Postaxial rudimentary polydactyly on the left hand, bilateral camptodactyly on the 4th and 5th fingers	Meningomyelocele, hydrocephaly, kyphoscoliosis, hemivertebra	46, XY	MCA R/O: Neural tube defect plus polydactyly
Case 3	Bilateral postaxial polydactyly on the hands and syndactyly on 3rd and 4th fingers and preaxial polydactyly on the foots and syndactyly on 1st and 3rd toes, bilateral broad halluces and thumbs	Polyhydramnios, overgrowth Macrocephaly, facial dysmorphism Cavum velum interpositum cysts Interhemispheric cyst	46, XY	Greig cephalopolysyndactyly heterozygote c.958_959insA (p.Ile320Asnfs*4) in the *GLI3* gene
Case 4	Partial cutaneous syndactyly on 3rd and 4th Thumbs hypoplasia on the left Bilateral clinodactyly on the 5th fingers	Anhidramnios, pericardial effusion, tricuspid regurgitation, PEV, forearm hypoplasia on the left	46, XX	MCA
Case 5	Bilateral syndactyly of 3rd and 4th of hands	Alobar HPE, cleft palate, VSD, PA, IUGR, anal atresia	69, XXX	Triploidy
Case 6	Bilateral acrosyndactyly, bilateral broad distal phalanx of thumbs	Craniosynostosis, cleft palate, segmental intestinal dilatation	46, XY	Apert syndrome c.755C>G (p.Ser252Trp) in the *FGFR2* gene
Case 7	Oligodactyly and ectrodactyly on right hand Camptodactyly of the 4th fingers on the right hand, bilateral 5th clinodactyly	Polyhydramnios, VSD, pulmonary stenosis, fallot tetralogy, facial dysmorphism	46, XX	MCA
Case 8	a single digit on the right hand, brachydactyly on the left hand	severe ulnar hypoplasia	46, XY	MCA R/O: Cornelia de Lange syndrome
Case 9	Bilateral postaxial polydactyly on hands and toes	Unilateral cleft lip and palate, labiogingival frenulum, short ribs with narrow trunk, rhizo-meso-acromelic shortness	46, XY	MCA R/O: Short-Rib Polydactyly syndrome
Case 10	Bilateral partial cutaneous syndactyly on 3rd-5th fingers	Bilateral renal agenesis, oligohydramnios, hyperechogenic bowel, facial dysmorphism	46, XY	MCA R/O: Fraser syndrome
Case 11	Oligodactyly (with preserved thumb) and syndactyly on 3rd and 4th enlarged fingers (macrodactyly) on the left hand	Facial dysmorphisim, lower limb hypoplasia on the right	46, XY	MCA R/O: Segmental overgrowth
Case 12	Oligodactyly (single finger on both hands)	Facial dysmorphism, bilateral severe mesomelia with elbow webbing, single bone (ulna?) on the forearm	46, XY	MCA R/O: Radial longitudinal deficiency
Case 13	Bilateral postaxial polydactyly on hands and toes	Occipital encephalocele, polycystic renal disease, omphalocele, bilateral PEV	46, XX	MCA R/O:Meckel-Gruber syndrome
Case 14	Bilateral thumb agenesis, camptodactly Clinodactyly and brachydactyly on hands	Facial dysmorphism, bilateral elbow contractures, bilateral mesomelic shortness	46, XX	MCA R/O: Nager syndrome
Case 15	Terminal amputation and constriction rings of the 2nd, 3rd and 4th digits on the left Constriction rings of the 1st digit on the right and total cutaneous syndactyly between 2nd and 5th digits on the right	Facial dysmorphism, cleft lip and palate, borderline ventriculomegaly, cavum velum interpositum cysts, suspected aortic coarctation and corpus callosum dysgenesis	46, XY	MCA A/O: Amniotic Band Sequence + congenital cardiac and brain abnormalies+ cleft lip and palate

Table 1. Clinical and cytogenetic/molecular findings of fetal cases with hand anomalies. (continued)

Case	Hand anomalies	Other anomalies	Karyotype Results	Diagnosis & Molecular Results
Case 16	Constriction rings of the 2nd and 3rd digits on the right and 1st and 3rd digits on the left Terminal amputation and constriction rings of the 2nd, 4th and 5th on the left	Constriction rings of the 2nd and 4th on the right, terminal transvers deficiency on the right hallux, tibial and fibular bowing on the right	N/D	MCA R/O: Amniotic Band Sequence + tibial bowing
Case 17	Terminal amputation and constriction rings of the 2nd, 4th digits on the left with distal swelling Terminal amputation and constriction rings of the 2nd, 3rd and 4th digits on the left	Unilateral PEV, polyhydramnios	46, XY	MCA R/O: Amniotic Band Sequence
Case 18	Bilateral postaxial polydactyly on hands and toes	Occipital encephalocele, polycystic renal disease, omphalocele, bilateral PEV	46, XY	MCA R/O:Meckel-Gruber syndrome

MCA, Multiple Congenital Anomalies; R/O, Rule out diagnosis; PEV, Pes EquinoVarus; HPE, Holoprosencephaly; VSD, Venticular Septal Defects; PA, Pulmonary Atresia; IUGR, IntraUterin Growth Retardation; N/D, Not Done

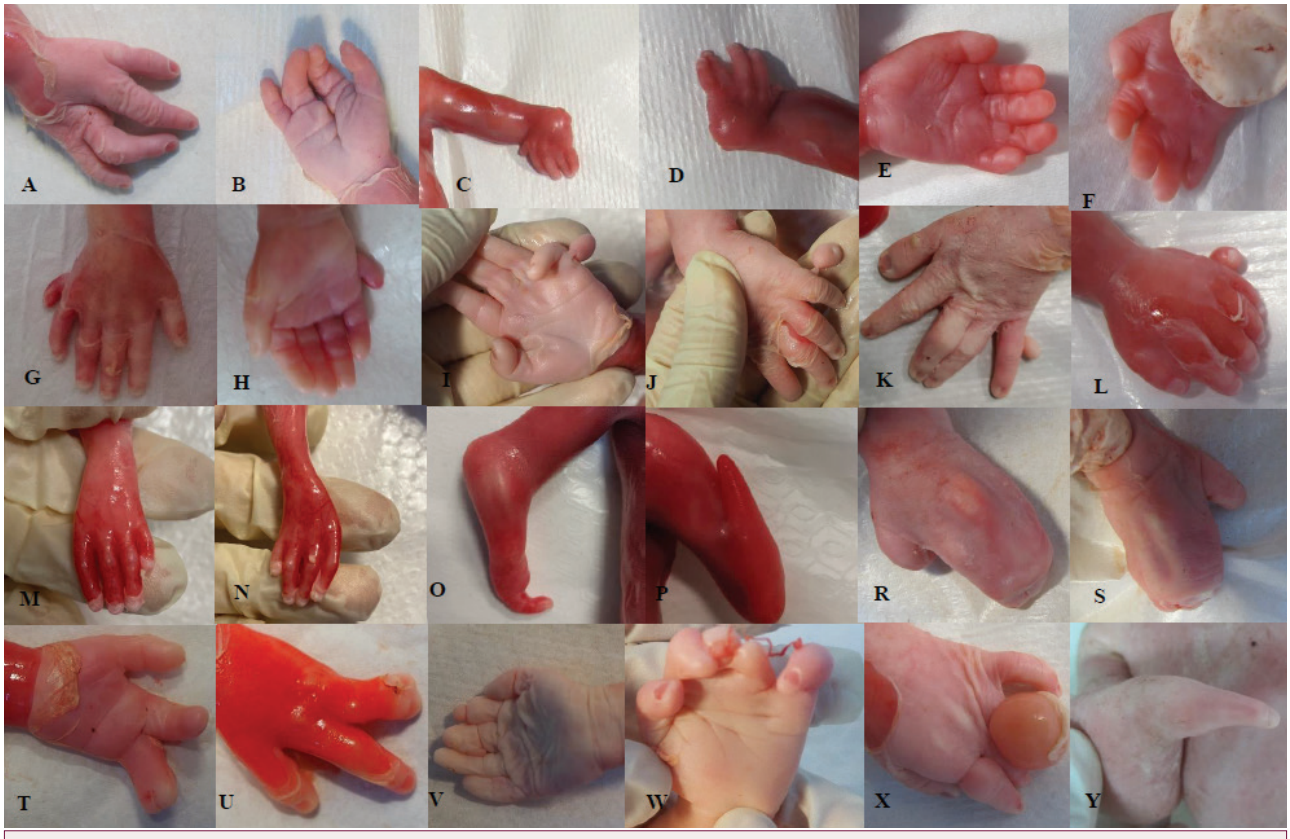

Figure 1. Clinical features of our cases.

A-B = Ectrodactyly in Case 7. **C-D =** Thumbs hypoplasia in Case 4. **E-F =** Partial cutaneous syndactyly in Case 10 with preliminary diagnosis of Fraser syndrome. **G-L =** Postaxial polydactyly in Case 1 (G-H), in Case 2 (I-J), in Case 3 with bilateral syndactyly of the 3rd and 4th digits with Greig cephalopolysyndactyly (K), and in Case 9 with a preliminary diagnosis of SRPS (L). **M-N =** Thumb hypoplasia in Case 14. **O-P =** Single finger on both hands in Case 12. **R-S =** Mitten-like acrosyndactyly in Case 6 with Apert syndrome. **T-U =** Segmental overgrowth in Case 11. **V-X** = Amniotic band sequence in Cases 16, 15, and 17. **Y =** Severe ulnar hypoplasia of the forearm with only a single digit in Case 8 with a preliminary diagnosis of CdLs.

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gene. No variant was found in parents and with the clinical significance of this variant pathogenic being determined according to the ClinVar database. Three cases were considered in the differential diagnosis to involve Nager syndrome (Case 14), Cornelia de Lange syndrome (CdLS; Case 8), and Fraser syndrome (Case 10).

DISCUSSION

Congenital hand anomalies involve complex disorders such as polydactyly, syndactyly, reduction defects, or amniotic band sequence (ABS). Generally, cases detected around 20. GW should be carefully evaluated in terms of other structural abnormalities. These anomalies were first classified by Swanson according to the morphology of limb development and surgical procedures, with such classifications as 1) failure of formation (transverse deficiency (terminal arrest) or longitudinal (radial/ ulnar longitudinal deficiency, central cleft of the hand)), 2) failure of differentiation (syndactyly, camptodactyly, clinodactyly), 3) duplications (preaxial/ thumb duplications, postaxial/5th finger duplications, mesoaxial polydactyly), 4) overgrowth (macrodactyly), 5) undergrowth (thumb hypoplasia, brachydactyly), 6) amniotic band syndrome, and 7) generalized skeletal syndromes (4,10). Since 2012, the International Federation of Societies for Surgery of the Hand (IFSSH) has recommended the Oberg-Manske-Tonkin (OMT) classification system as the new classification system for all congenital upper extremity anomalies (11). This embryology-based classification system includes malformations, deformities, dysplasias, and syndromes along the three axes of limb development. Malformations are divided in three subgroups: axis formation/differentiation of the entire upper limb, hand plate, or unspecified axis with respect to the proximal-distal, radial-ulnar (anteroposterior), and dorsal-ventral axes. Deformations mostly involve constriction rings. Dysplasias consist of segmental overgrowth or hypertrophy of the fingers (macrodactyly) and/or unilaterally upper limb or tumoral growth. Approval has been given to the independent classification of syndromes. Recent publications have classified their cases according to the OMT system (3, 11,-14), which this study has done as well. Three syndromic cases were definitively diagnosed as having Greig cephalopolysyndactyly (Case 3), triploidy (Case 5), and Apert Syndrome (Case 6). Furthermore, seven cases were preliminary diagnosed, with ciliopathies in Case 1, Meckel-Gruber syndrome in Cases 13 and 18, SRPS in Case 9, Nager syndrome in Case 14, Fraser syndrome in Case 10, and CdLS in Case 8. Case 11 was presented with segmenter overgrowth complicated by macrodactyly and oligodactyly, which can be classified in the group of dysplasia. Case 12 with isolated hand anomaly was considered a radial longitudinal deficiency and classified as a malformation. Meanwhile, Cases 2, 4, and 7 were evaluated as multiple congenital anomalies because of major anomalies accompanying the hand anomalies. Three cases (Cases 15, 16, and 17) were affected by ABS.

Just as in the literature, polydactyly here was also the most common type of hand anomaly in our case series. Occasionally, an extra finger including a fingernail was connected to the hand with a small skin tag. When polydactyly is accompanied by a polycystic or dysplastic kidney anomaly, ciliopathies should be considered. Ciliopathies include primary ciliary dyskinesia, cystic kidney disease, nephronophthisis, retinitis pigmentosa, Bardet-Biedl syndrome, oral-facial-digital syndrome, SRPS, Joubert syndrome, and Meckel-Gruber syndrome, which involve genetic mutations regarding the encoding proteins involved in cilia function (15). Meckel-Gruber syndrome should be on the differential diagnosis list, especially in the presence of occipital encephalocele (16). The remaining cases were evaluated in the ciliopathy group, and WES was planned as a case with a preliminary diagnosis of SRPS. Common syndromic craniosynostosis syndromes including Crouzon, Pfeiffer, and Saethre-Chotzen are caused by mutations in the *FGFR2* gene and can have similar clinical manifestations. Mutations in the *FGFR2* comprise the majority of known mutations in syndromic forms of craniosynostosis. Our case with the syndactyly craniosynostosis diagnosed as Apert with mitten-like acrosyndactyly involved a wide abdominal circumference, segmental intestinal dilated colon, and rectum anomaly. Intestinal findings of the case where no postmortem autopsy had been conducted were found to be consistent with other intestinal findings such as intestinal malrotation, obstruction, and atresia, which in the literature are reported more frequently in the general population in patients with FGFR-related craniosynostosis syndrome (17).

ABS is a disruptive condition which surrounds the limbs or any part of the fetal body by the congenital constriction rings formed by fibrous bands of the amniotic sac. Constriction bands can cause permanent or transient disruption of the tissues under pressure. ABS is classified within the spectrum ranging from mild to severe as: 1) simple constriction rings, 2) rings with distal soft tissue deformity with or without lymphedema, 3) distal bone syndactyly, and 4) terminal amputation. In our case series, Cases 15, 16 and 17 were affected by ABS. Interestingly, Case 16 with ABS was complicated by tibial bowing, which is difficult to predict for *in-utero* ABS. However, the literature does contain some ABS reports with tibial bowing. A transient constriction by an amniotic band *in utero* may cause congenital bowing of the tibia (18). However, ABS should be distinguished from symbrachydactyly and transverse deficiency. Symbrachydactyly is an anomaly of the hand caused by Poland sequence or other similar anomalies of vascular disruption that affects all fingers unilaterally. Unlike ABS, the nail structure is present because ectodermal development is not affected in symbrachydactyly (19, 20). Fetal cases involving hand abnormalities should be referred to a perinatologist and clinical geneticist for further evaluation and counselling (21). These cases should be carefully evaluated for other structural abnormalities. If chromosomal abnormalities are suspected, invasive tests such as chorionic villus sampling and amniocentesis should be recommended, and if the karyotype analysis returns normal, an array-CGH should be performed.

The identification of hand anomalies should prompt a careful and detailed anomaly survey for any other structural

abnormality. After careful evaluation, the diagnosis should be made by advanced cytogenetic and molecular tests with a multidisciplinary team consisting of perinatologists, clinical geneticists, and a hand surgeon.

Providing families with the right genetic counseling is very important in terms of the treatment, prognosis, and recurrence risks of such diseases.

Ethics Committee Approval: This study procedure was approved by the relevant animal experimental local ethics committee of Istanbul University (E-29624016-050.99-52402).

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