Perinatal Diagnostic Approach to Fetal Skeletal Dysplasias: Six Years Experience of a Tertiary Center

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Skeletal dysplasias (SDs) constitute a group of heterogeneous disorders affecting growth morphology of the chondro-osseous tissues. Prenatal diagnosis of SD is a considerable clinical challenge due to phenotypic variability. We performed a retrospective analysis of the fetal autopsies series conducted between January 2006 and December 2012 at our center. SD was detected in 54 (10%) out of 542 fetal autopsy cases which included; 11.1% thanatophoric dysplasia (n = 6), 7.4% achondroplasia (n = 4), 3.7% osteogenesis imperfect (n = 2), 1.9% Jarcho-Levin Syndrome (n = 1), 1.9% arthrogryposis (n = 1), 1.9% Dyggve-Melchior-Clausen syndrome (n = 1), 72.1% of dysostosis cases (n = 39). All SD cases were diagnosed by ultrasonography. In 20 of the cases, amniocentesis was performed, 4 cases underwent molecular genetic analyses. Antenatal identification of dysplasia is important in the management of pregnancy and in genetic counseling. Our data analysis showed that SD is usually detected clinically after the 20th gestational week. Genetic analyses for SD may provide early diagnosis and management.

Keywords: skeletal malformations, genetic, fetal autopsy

INTRODUCTION

In general, skeletal dysplasias (SDs) constitute a group of heterogeneous disorders affecting growth morphology of the chondro-osseous tissues [1]. Since the 1960s numerous new entities have been identified by the expansion of the knowledge of the osteochondrodysplasias [2]. It is well known that the classification of skeletal dysplasias has evolved from that based on clinical-radiologic-pathologic features to that which includes the underlying molecular abnormality for conditions in which the genetic defect is known [3].

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The overall prevalence of skeletal dysplasias among perinatal deaths was 9.1 per 1000 cases [4]. Estimated prevalence of SDs is 2.4 to 4.5 per 10,000 births [1, 5]. Despite the recent advances in imaging, it is still difficult to diagnose certain subtypes of SD in utero due to large number of SDs and their phenotypic variability with overlapping features. For this reason, integrated clinical, pathological and genetic approach is needed. Prenatal diagnosis is easier when a positive family history is present [1]. SD is usually suspected in ultrasonographic evaluation when a shortened and/or dysmorphic long bone or abnormal skeletal findings are observed [6]. In addition, delineating the differential diagnosis to recognize the lethality of the case is important [1].

International nomenclature of constitutional bone diseases was initially formulated in 1972 and regularly revised by international working group on Constitutional Diseases of Bone [7]. The international nomenclature of constitutional (intrinsic) bone disease was adopted by European Society of Pediatric Pathology in 1977. Afterward, the nomenclature was modified in 1983, 1992 and 1997. In 1999, International Skeletal Dysplasia Society (ISDS) was established and revisions of nosology have been delegated to an expert group. In 2001, genetic dysostoses-osteochondrodysplasias was added [8]. Last revision was made in 2006 and 372 conditions have been listed in 37 groups defined by molecular biochemical and/or radiological criteria according to ISDS Statutes and Guidelines [7]. In 2010, categorization of the skeletal abnormalities was revised using clinical, radiologic, pathologic and molecular information. Therefore, revised 456 disorders are recognized within the 40 total nosology groups [9]. And nowadays, genetic counseling is given to families [2]. SD occurs singly or associated with other abnormalities. Widespread disturbance of bone growth, beginning during the early stages of fetal development causes SD and evolves throughout life due to active gene involvement [8].

Prenatal diagnosis of SD is a considerable clinical challenge due to phenotypic variability. Our study provides information regarding the frequency of perinatal skeletal dysplasias and encourages multidisciplinary working teams for accurate diagnosis and outlines the autopsy findings of the affected patients. The aim of this study is to discuss the (including associated anomalies) the findings of skeletal dysplasias, including associated anomalies, in our center in the south coast of Turkey. We expect that our preliminary findings will lead us to perform the meta-analyses if more skeletal dysplasia autopsy cases are reported.

METHODS

In this study, the fetal autopsy records were retrospectively examined at Akdeniz University, Prenatal Pathology Department between the period for January 2006 and December 2012. Our institution is a tertiary center on the south coast of Turkey which has an important consultation practice on perinatology and perinatal pathology. The analysis was performed by identifying the maternal and gestational ages, macroscopic assessments, baby-gram findings, the type of SD-associated abnormalities and clinical findings for each case in the data set.

Among 542 fetal autopsies, 54 cases had SD diagnosis by prenatal ultrasonography. Among them 20 cases underwent amniocentesis, one case underwent chorionic villous sampling. Twenty cases underwent cytogenetic analysis and four cases underwent molecular genetic analyses.

Autopsy Analysis
In our institution, all fetal autopsies are performed on fresh materials. Before starting the autopsy, we check the autopsy permission of the parents and the type of consent.
given, the identity of the infant and consult the clinicians, to determine the questions that have to be answered by the autopsy. A radiograph of the whole body in mammography dose called baby-gram is performed on all fetuses. Macroscopic photos of fetus are taken. Measurements of crown heel, crown rump, head circumference, foot length and weight are taken for comparison with standard charts. Wigglesworth provides weights and measurements for stillborn and live born infants by using data from the Women & Infants Hospital, Providence, Rhode Island, USA [10]. Foot length is used to determine gestational age, which can then be compared with chronological age. The external examination is systematically performed on all fetuses regardless of gestational age. We use a standard autopsy protocol form of Turkish Federation of Pathology Societies, Perinatal and Pediatric Pathology study group [11]. Timing of the fetal death is determined by the degree of maceration. Standard fetal autopsy procedures were performed [12]. In SDs, in addition to baby-gram findings, the growth zone of femur and humerus are sampled for histopathological examination.

RESULTS

Within this retrospective autopsy series, 54 (10%) of 542 fetal and perinatal autopsy cases with diagnosis of skeletal dysplasia were evaluated. Twenty-one (38.9%) of 54 cases were female, 33 (61.1%) of 54 cases were male. Mean of maternal age is 27.81 ± 5.73 and mean of gestational age is 21.17 ± 5.43. Among 54 cases, 6 cases of thanatophoric dysplasia (TD, 11.1%) (Figure 1), 4 cases of achondroplasia (ACH, 7.4%) (Figure 2), 3 cases of osteogenesis imperfecta (OI, 5.5%) (Figure 3), 1 case of Jarcho-Levin Syndrome (JLS, 1.9%) (Figure 4), 1 case of arthrogryposis (1.9%), one case of Dyggve-Melchior-Clausen Syndrome (DMCS, 1.9%) and 38 cases of dysostosis (unclassified) (70.4%) were terminated.

Some of the cases (ACH, OI and TD) were screened for mutation analysis. ACH cases had shortened extremities, narrowed growth zone in baby-gram (Figure 1) and disordered chondrocytes in growth zone. Only one case was screened for FGFR3 gene mutations, and no mutation was detected. Three cases (case 5, 38, 39) were type 2 OI, characterized by intrauterine multiple rib and long bone fractures, and broad long bones (Figure 2). None of the cases had mutations. Among TD cases, one of the cases had heterozygous p.Arg248Cys and the other had heterozygous p.Gly370Cys missense mutations at the FGFR3 gene. All of the cases had bilateral rhizomelic extremities, bowed femur which is given in Figure 3.

From the clinical view, one case of JLS had segmentation anomalies of vertebral bones (hemivertebrae, absent vertebrae, fused vertebrae, sickle-shaped vertebrae), costal defects (posterior fusion of the ribs and absent, irregular and bifid ribs) and pulmonary hypoplasia (Figure 4). The arthrogryposis case (case 7) had multiple joint contractures in upper and lower extremities associated with agenesis of cerebellum, dilatation of bilateral cerebral ventricles and hypoplasia of psoas muscle.

Interestingly, one of the cases (case 8) which had Trisomy 18 had multiple anomalies such as hyperplasia of radius, long fourth finger of bilateral hands and feet, hyperplastic fifth finger of bilateral feet, omphalocele, cleft-lip and palate, dysplastic ears and this case was terminated at gestational age of 14 weeks. Besides, the other case (case 9) which had Trisomy 13 also had multiple anomalies; bilateral agenesis of 11th and 12th ribs, bone defect of vertex, rocker-bottom foot, polycystic kidney disease, uterus bicornis, clitoromegaly, microgastria, low-set ears and this case was terminated at gestational age of 24 weeks (Table 1).

Three of the cases (case 4, 33 and 40) had specific gene mutations as following: p.Gly370Cys and p.Arg248Cys, heterozygous missense mutations at fibroblast growth factor receptor (FGFR3) gene (NM_000142) and homozygous c.1878delA/c.1878delA
Figure 1. Baby-gram of thanatophoric dysplasia.

Figure 2. (a) Baby-gram of achondroplasia. (b). Growth zone, chondrocyte columnization is absent and cartilaginous spicules in the metaphysis are reduced, small and distorted in the femoral physeal growth zone of a fetus with achondroplasia.
mutation at *dymeclin* gene (*DYM*; NM_017653). In all of the cases, ultrasonographic findings were detected at gestational ages of 20th and 25th weeks. Fetus (case 40) which was terminated at 16 weeks gestation had a *dymeclin* gene formation, also had a sibling with Dyggve-Melchior-Clausen syndrome (DMCS; OMIM 223800).

Overall, 31 (57.4%) of the cases were associated with at least one additional congenital anomaly which is given in Table 2. Twenty-two (42.6%) cases had only skeletal abnormalities (Table 3).

**DISCUSSION**

To our knowledge, there is very limited number of reports about the associated anomalies for skeletal dysplasia, focused on perinatal autopsy cases all over the world [13–16]. This study reviews all skeletal dysplasia cases and summarizes the six years experience at a tertiary care center on the south coast of Turkey. Unfortunately, most of the published reports are case reports or case series from Turkey, and no comparative data is available. There has been only two meeting reports focused on skeletal dysplasia by Basbug et al. in 2007 and our preliminary report by Toru et al. in 2013 from Turkey [17, 18].

In 2007, Basbug et al. reported 27 fetuses with skeletal dysplasia, and emphasized that most common type was Roberts syndrome (18.5%) [17]. It is known that Roberts syndrome (OMIM 268300), a kind of dysostosis, is a rare autosomal recessive condition caused by mutations in the *ESCO2* gene which is characterized by long bone deficiencies associated with cleft lip-palate [19]. However, our series did not contain any cases.
with Roberts syndrome. Mean gestational age at diagnosis was found as 26.5 (range 15–35) in Basbug et al.’s study [17]. In our series, mean gestational age was $21.17 \pm 5.43$, with an earlier prenatal diagnosis compared to published reports.

To date, there have been two reports on fetal autopsy from Hatay and Cukurova regions which are located on the southern east of Turkey. Based on Hakverdi et al.’s report, 36 of 274 cases (22.5%) were associated with musculoskeletal anomalies [20]. In Acikalin et al.’s study, 2150 fetal autopsies were reported and 97 of 2150 (8.3%) cases had musculoskeletal anomalies [21]. Thus, as there is no available data to compare the frequencies of SDs, our series is limited on the skeletal dysplasias, and discusses intensive genetic, radiologic and morphologic features.

Skeletal dysplasia is a group of disorders of the skeleton; defined as derangement of growth, development and/or differentiation of the skeleton [7]. Accurate prenatal diagnosis of SD is still a clinical challenge due to phenotypic variability and lack of a precise molecular diagnosis in many cases. Moreover, the phenotypic characteristics of some skeletal disorders are not manifested until later in pregnancy. In 1988, Spranger classified hypochondroplasia, ACH and thanatophoric dysplasias (TD-I and TD-II) in the family of dysplasias, denominated generically as SDs. All of the dysplasias display common phenotypic characteristics with different grades of severity [22].

**Figure 4.** Baby-gram of Jarcho-Levin syndrome.
Table 1. Associated anomalies in Turkish skeletal dysplasias.

| SD type (n)                  | Associated anomalies                                                                 |
|-----------------------------|---------------------------------------------------------------------------------------|
| Achondroplasia (3)          | Immature lungs and kidneys, depressed nasal bridge, low-set ears, Cleft-lip and palate, dysplastic ears, immature lungs |
| Thanatophoric dysplasia (1) | Pulmonary hypoplasia, immature kidneys                                                |
| Osteogenesis imperfecta (1) | Cliteromegaly, immature kidneys                                                       |
| Jarcho-Levin syndrome (1)   | Pulmonary hypoplasia                                                                  |
| Arthrogryposis (1)          | Agenesis of cerebellum, dilatation of bilateral cerebral ventricles, hypoplasia of psoas muscle |
| Dysostosis (24)             | Abdominal wall: Omphalocele, gastroschisis                                             |
|                            | Craniofacial: cleft-lip and palate, dysplastic ears, micrognathia, low-set ears, depressed nasal bridge, agenesis of external auditory channel, agenesis of the nose, agenesis of right eye-lid. |
|                            | Genitourinary system: Polycystic kidney disease, renal agenesis, immature kidneys, ureteropelvic dilatation of kidneys, bilateral adrenal gland agenesis, bladder agenesis, uterus bicornis, agenesis of uterus and vagina, cliteromegaly, agenesis of external urethral ostium, distal located penis, localized cystic disease of right kidney, hydroureteronephrosis |
|                            | Central Nervous system: Neural tube defect, pachygyria, hydrocephalus, dolicocephaly |
|                            | Gastrointestinal system: Imperforate anus, anal atresia, fibrous bant of ileocecal valve |
|                            | Respiratory system: Pulmonary hypoplasia, hypolobulated right lung                    |
|                            | Cardiac anomaly: Hypoplastic left heart, ventricular septal defect, single cardiac outlet, agenesis of truncus pulmonalis, hypoplastic right heart |
|                            | Others: Single artery in umbilical cord, early involutions in thymic gland, hydrops fetalis, Sacrococcygeal teratoma |

Categorizing SDs is important because some of them are lethal. ACH and hypochondroplasia dysplasias not only exhibit phenotypic but also genetic features. Ninety-nine percent of ACH dysplasias have two common FGFR3 gene mutations in p.Gly380Arg amino acid substitutions and, 10% of ACH is caused by p.Asn540Lys which is typical for hypochondroplasias [21]. However, 7% of hypochondroplasia cases are shown to have p.Gly380Arg mutation [23]. These findings indicate that there are overlapping phenotypic and genotypic characteristics for ACH and hypochondroplasias.

Thanatophoric dysplasia (OMIM 187600) is the most frequent sporadic lethal skeletal dysplasia with a prevalence of about 1 in 17 000–50 000 births [1]. Characteristic features of TD include markedly shortened limbs, narrow thorax with short ribs but normal trunk length, macrocephaly with frontal bossing, and low depressed nasal bridge [1, 24]. It has been shown that expected mutations in TD include p.Arg248Cys, p.Tyr373Cys and p.Lys650Glu mutations [23]. In our series, all TD cases had typical radiologic and morphologic features of TD. Only three cases underwent genetic analysis and two cases (case 4, 33) showed specific heterozygous mutations (p.Gly370Cys and p.Arg248Cys) at FGFR3 gene and case 34 did not have any mutations.

It is well known that ACH (OMIM 100800) is the most common type of human dwarfism as a result of decreased endochondral ossification and is prenatally characterized mainly by rhizomelic micromelia, macrocephaly with frontal bossing, and midface hypoplasia [25]. Both of our cases had typical findings of ACH, accompanied by prenatally ultrasonographic findings that also suggested ACH. Only one case under-
### Table 2. Clinical features of Turkish skeletal dysplasia patients associated with at least one anomaly.

| Case | Maternal age (years) | Gestational age (weeks) | Fetal gender | Genetic analysis | Skeletaldysplasia | Detailedskeletal anomalies | Associated anomalies |
|------|----------------------|-------------------------|--------------|------------------|-------------------|--------------------------|----------------------|
| Case 1 | 17 | 20 | M | ** *** | Achondroplasia | Rhizomelic extremities, narrowed epiphysis, disordered chondrocytes in the growth zone of the femur (microscopic) | Immature lungs and kidneys, depressed nasal bridge, low-set ears |
| Case 2 | 28 | 24 | F | ** *** | Achondroplasia | Rhizomelic extremities, narrowed epiphysis, disordered chondrocytes in the growth zone of the femur (microscopic) | Cleft-lip and palate |
| Case 3 | 29 | 20 | M | No FGFR3 gene mutation in exon 7 and 10. Chromosomal analyze was normal | Achondroplasia | Rhizomelic extremities, frontal bossing, mechanic bowing of distal radius | Depressed nasal bridge, dysplastic ears, immature lungs |
| Case 4 | 31 | 20 | M | p.Gly370Cys/+ mutation in FGFR3 gene | Thanatophoric dysplasia | Bilateral rhizomelic extremities, bowed femur, distorted growth zone of femur (microscopic) Pulmonary hypoplasia, immature kidneys | |
| Case 5 | 30 | 16 | F | Osteogenesis imperfecta | Broad and short long bones with broad and beaded ribs (macroscopic), multiple fractures and healing long bones and ribs (radiology) | Cliteromegaly, immature kidneys |
| Case 6 | 26 | 25 | M | Chromosomal analysis was normal | Jarcho-Levin syndrome | Segmentation anomaly of vertebral bones (hemivertebrae, absent vertebrae, fused vertebrae, block/wedge vertebrae, sickle shaped vertebrae), costal defects (posterior fusion of the ribs and absent, irregular and bifid ribs) | Pulmonary hypoplasia |
| Case 7 | 22 | 27 | F | Arthrogryposis | Multiple joint contractures in upper and lower extremities | Agenesis of cerebellum, dilatation of bilateral cerebral ventricles, hypoplasia of psoas muscle |
| Case 8+ | 44 | 14 | M | 47,XY, +18 | Dysostosis | Hyperplasia of radius, long 4th finger of bilateral hands and feet, hyperplastic Omphalocele, cleft-lip and palate, dysplastic ears |

(Continued on next page)
Table 2. Clinical features of Turkish skeletal dysplasia patients associated with at least one anomaly (Continued)

| Case   | Maternal age (years) | Gestational age (weeks) | Fetal gender | Genetic analysis | Skeletal dysplasia | Detailed skeletal anomalies                                                                                                                                                                                                 | Associated anomalies                                                                                                                                                                                                 |
|--------|----------------------|-------------------------|--------------|------------------|-------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Case 9* | 21                   | 24                      | F            |                  | 47,XX, +13        | Dysostosis                                                                                                                                                                                                                                                 | Bilateral agenesis of 11th and 12th ribs, bone defect of vertex, rocker-bottom foot                                                                                                                                                                       |
| Case 10 | 19                   | 21                      | F            |                  |                   | Hypoplastic fingers (right hand third and fourth fingers)                                                                                                                                                                                                        | Meningoencephalocele, single artery in umbilical cord                                                                                                                                                                                                       |
| Case 11 | 27                   | 22                      | M            |                  |                   | Dysostosis                                                                                                                                                                                                                                                 | Polydactyly (left hand and bilateral feet), Club foot, short neck                                                                                                                                                                                      |
| Case 12 | 25                   | 17                      | M            |                  |                   | Dysostosis                                                                                                                                                                                                                                                 | Polydactyly (bilateral hands and feet), rhizomelic extremities                                                                                                                  |
| Case 13 | 23                   | 19                      | M            |                  |                   | Dysostosis                                                                                                                                                                                                                                                 | Syndactyly (bilateral third and fourth fingers of the hands), rocker-bottom foot                                                                                                             |
| Case 14 | 29                   | 24                      | F            |                  |                   | Dysostosis                                                                                                                                                                                                                                                 | Bilateral radius aplasia and mesomelic upper extremities, oligodactyly (bilateral 1st finger)                                                                                               |

*Case 9 had a detailed skeletal anomaly of the 1st finger of bilateral feet.
| Case 15 | 30  | 20 | Dysostosis | agenesis of hands, Polydactyly (bilateral hands and feet) | Cardiac anomaly (Hypoplastic left heart, Ventricular septal defect) | Dysostosis | agenesis of 12th rib |
|---|---|---|---|---|---|---|---|
| Case 16 | 28 | 23 | Dysostosis | Short neck and bilateral dislocated phalanges of hands, Short right arm | Clubbing and palmar depression, low-set ears, Bridge, low-set ears | Dysostosis | agenesis of the hand |
| Case 17 | 37 | 17 | Dysostosis | Polydactyly (bilateral hands and feet), O-bain deformity of the hands | Clubbing and palmar depression, Low-set ears, Agenesis of the nose | Dysostosis | Polydactyly (bilateral hands and feet) |
| Case 18 | 30 | 17 | Dysostosis | Chromosomal analyze was normal | Dysostosis | Polycystic kidney disease, Neural tube defect (encephalocele), Deformed nasal bridge, Low-set ears |
| Case 19 | 20 | 17 | Dysostosis | Hemivertebrae, agenesis of 12th rib, Bilateral renal agenesis, Imperforate anus, Pulmonary hypoplasia, Agenesis of uterus and vagina, Frontal bossing, dolicocephaly |
| Case 20 | 32 | 24 | Dysostosis | Scoliosis, Syndactyly | Pulmonary hypoplasia, Pedal deformity |
| Case 21 | 22 | 21 | Dysostosis | | (Continued on next page) |
| Case | Maternal age (years) | Gestational age (weeks) | Fetal gender | Genetic analysis | Skeletal dysplasia | Detailed skeletal anomalies | Associated anomalies |
|------|---------------------|------------------------|--------------|------------------|-------------------|--------------------------|----------------------|
| Case 22 | 28 | 17 | M | Chromosomal analysis was normal | Dysostosis | Polydactyly (right foot), Syndactyly (second, third, fourth and fifth fingers of right hand; fourth and fifth fingers of left hand) | Immature kidneys and lung, cleft-lip and palate, nasal deformity, low-set ears |
| Case 23 | 32 | 20 | M | | Dysostosis | Costa bifida (right fourth rib) | Neural tube defect (meningomyelocele), fibrous bant of ileocecal valve, ureteropelvic dilatation of kidneys. |
| Case 24 | 37 | 15 | M | Chromosomal analysis was normal | Dysostosis | Bilateral agenesis of hands and feet, agenesis of left radius, tibia and fibula | Anal atresia, bilateral renal agenesis, bladder agenesis, cardiac anomaly (single cardiac outlet, agenesis of truncus pulmonalis, hypoplastic right heart), hypolobulated right lung, low-set ears |
| Case 25 | 18 | 39 | F | Chromosomal analysis was normal | Dysostosis | Syndactyly (second, third and fourth fingers of right hand; all fingers of left hand; third, | Agenesis of left kidney, localized cystic disease of right kidney, agenesis of right eye-lid |
| Case  | Age | Sex | Chromosomal analyze was normal | Dysostosis | Extraordinary Conditions |
|-------|-----|-----|---------------------------------|-----------|-------------------------|
| 26    | 24  | M   |                                 | Dysostosis | Hydrocephalia, hydroureronephrosis, low-set ears |
|       |     |     |                                 | Rhizomelic lower extremities, disorganization and retardation of physeal growth zone of femur (microscopic) | |
| 27    | 25  | M   |                                 | Dysostosis | Anal atresia, polycystic kidney disease, agenesis of external urethral ostium, distal located penis, low-set ears |
|       |     |     |                                 | Agenesis of right ulna and radius | |
| 28    | 23  | M   |                                 | Dysostosis | Polycystic kidney disease, depressed nasal bridge, low-set ears, micrognathia |
|       |     |     |                                 | Bilateral polydactyly | |
| 29    | 26  | F   |                                 | Dysostosis | Neural tube defect (meningocele) |
|       |     |     |                                 | Scoliosis, vertebral fusion defects, agenesis of 11th and 12th ribs | |
| 30    | 19  | F   |                                 | Dysostosis | Sacral agenesis |
| 31    | 22  | F   |                                 | Dysostosis | Sacrococcygeal teratoma |
|       |     |     |                                 | Olgodactyly (left hand), hypoplastic finger (right hand first finger) | |

*Case 8: Edwards Syndrome (Trisomy 18).
**Case 9: Patau Syndrome (Trisomy 13).
***F: Female.
****M: Male.
| Case | Maternal age (years) | Gestational age (weeks) | Fetal gender | Genetic analysis | Skeletal dysplasia | Detailed skeletal anomalies |
|------|---------------------|-------------------------|--------------|------------------|-------------------|--------------------------|
| 32   | 27                  | 22                      | M*           |                  | Achondroplasia     | Rhizomelic extremities,  |
|      |                     |                         |              |                  |                   | narrowed epiphysis,      |
|      |                     |                         |              |                  |                   | disordered chondrocytes  |
|      |                     |                         |              |                  |                   | in the growth zone of    |
|      |                     |                         |              |                  |                   | the femur (microscopic)  |
| 33   | 22                  | 25                      | M            | p.Arg248Cys/+     | Thanatophoric dysplasia| Bilateral rhizomelic    |
|      |                     |                         |              | mutation in FGFR3 |                   | extremities, bowed      |
|      |                     |                         |              | gene             |                   | femur, frontal bossing,  |
|      |                     |                         |              | 46,XX t(1,19)    |                   | narrowed thorax,         |
|      |                     |                         |              | (p11.1;p11),     |                   | distorted growth zone    |
|      |                     |                         |              | 13pss            |                   | of femur (microscopic)   |
| 34   | 33                  | 26                      | F**          | Chromosomal     | Thanatophoric     | Bilateral rhizomelic     |
|      |                     |                         |              | analyze was      | dysplasia          | extremities, bowed       |
|      |                     |                         |              | normal           |                   | femur, frontal bossing,  |
|      |                     |                         |              |                  |                   | narrowed thorax,         |
|      |                     |                         |              |                  |                   | pectus carinatum,        |
|      |                     |                         |              |                  |                   | distorted growth zone    |
|      |                     |                         |              |                  |                   | of femur (microscopic)   |
| 35   | 29                  | 16                      | M            | Thanatophoric    |                   | Bilateral rhizomelic     |
|      |                     |                         |              | dysplasia        |                   | extremities, bowed       |
|      |                     |                         |              |                  |                   | femur, narrowed thorax,   |
|      |                     |                         |              |                  |                   | shortened ribs, platyspondyly,  |
|      |                     |                         |              |                  |                   | small-squared iliac      |
|      |                     |                         |              |                  |                   | bones; distorted growth   |
|      |                     |                         |              |                  |                   | zone of femur (microscopic)|
| Case | Age | Gender | Diagnosis | Description |
|------|-----|--------|-----------|-------------|
| 36   | 26  | F      | Thanatophoric dysplasia | Bilateral rhizomelic extremities, bowed femur, frontal bossing, platyspondyly, small-squared iliac bones, distorted growth zone of femur (microscopic) |
| 37   | 30  | F      | Thanatophoric dysplasia | Bilateral rhizomelic extremities, bowed femur, short trunk, platyspondyly |
| 38   | 24  | M      | Osteogenesis imperfecta | Broad and short long bones with broad and beaded ribs, calvarial ossification defect (macroscopic), multiple fractures and healing long bones and ribs (radiology) |
| 39   | 24  | M      | Osteogenesis imperfecta | Broad and short long bones with broad and beaded ribs (macroscopic), multiple fractures and healing long bones and ribs (radiology) |
| 40   | 33  | M      | Chromosomal analyze was normal | Homozygous c.1878delA mutation in DYM gene |

(Continued on next page)
Table 3. Clinical features of Turkish isolated skeletal dysplasia (*Continued*).

| Maternal age (years) | Gestational age (weeks) | Fetal gender | Genetic analysis | Skeletal dysplasia | Detailed skeletal anomalies |
|----------------------|-------------------------|--------------|------------------|-------------------|----------------------------|
| Case 41              | 33                      | 31           | M                | Chromosomal analyze was normal | Dysostosis | Mildly shortened extremities and mild irregularity in iliac crests (radiology). |
| Case 42              | 33                      | 21           | M                | Chromosomal analyze was normal | Dysostosis | Amelia (Bilateral upper extremity) |
| Case 43              | 26                      | 18           | F                | Dysostosis         | Dysostosis | Amelia (agenesis of right hand) |
| Case 44              | 29                      | 22           | F                | Dysostosis         | Dysostosis | Bilateral clinodactyly, shortened right tibia |
| Case 45              | 35                      | 14           | M                | Dysostosis         | Dysostosis | Agenesis of left radius |
| Case 46              | 25                      | 18           | M                | Dysostosis         | Dysostosis | Intrauterine aplasia of distal ulna and radius of left arm |
| Case 47              | 32                      | 16           | F                | Chromosomal analyze was normal | Dysostosis | Syndactyly (third and fourth finger of left hand) |
| Case 48              | 28                      | 34           | M                | Dysostosis         | Dysostosis | Bilateral phalangeal agenesis of hands |
| Case   | Age | Gender | Chromosomal Analysis         | Syndrome                                    |
|--------|-----|--------|------------------------------|---------------------------------------------|
| 49     | 30  | M      | Chromosomal analyze was normal | Dysostosis Bilateral agenesis of ulna, radius and lower extremities. |
| 50     | 23  | M      | Chromosomal analyze was normal | Dysostosis Bilateral shortened arms (hyoplastic ulna, radius, humerus) |
| 51     | 41  | M      | Chromosomal analyze was normal | Dysostosis Shortened lower extremities      |
| 52     | 35  | M      | Chromosomal analyze was normal | Dysostosis Syndactyly (left hand and right foot) |
| 53     | 27  | M      | Chromosomal analyze was normal | Dysostosis Shortened right lower extremity  |
| 54     | 33  | M      | Chromosomal analyze was normal | Dysostosis Hypoplastic right femur          |

*F: Female. **M: Male.
went genetic analysis and we did not find any mutation on 7 and 10 exons of \textit{FGFR3} gene. Fetal autopsy confirmed the prenatal diagnosis.

On the other hand, hypochondroplasia is characterized by a similar but milder phenotype compared to ACH, which includes the main features of micromelia, short stature and lumbar lordosis as well as \textit{FGFR3} gene defect \cite{25}. This is due to the wide spectrum between ACH and TD. In our series, we did not have any hypochondroplasia cases. However, we should keep in mind that DMCS (OMIM 223800), an autosomal recessive spondylo-epimetaphyseal dysplasia, is also characterized by short trunk dwarfism, microcephaly, a coarse facial appearance and mental retardation. Radiographic findings of our cases showed multiple abnormalities including vertebral platyspondyly, lacy iliac wings, laterally displaced irregularly ossified femoral heads and a hypoplastic odontoid. Since all these findings usually manifest themselves at 2 or 3 years after birth, it is almost impossible to diagnose DMCS prenatally without genetic analyses \cite{26}. However, one of our cases had a sibling diagnosed with DMCS; diagnosed by genetic analysis and is still being followed-up at the Department of Pediatrics in our Institution.

On the other hand, OI (OMIM 166210) is a heterogeneous heritable disorder and involves connective tissues. It is characterized by bone fragility, decreased bone mass, other connective tissue manifestations such as blue sclera, hyperlaxity of skin and ligaments and hearing loss \cite{27,28}. It is well known that OI type II is lethal and results in intrauterine death or perinatal death \cite{29}. All of our cases were also type II (case 5, 38 and 39), and presented with multiple fractures and intrauterine death.

The Jarcho-Levin syndrome (spondylocostal dysostosis; OMIM 277300) is a kind of dysostosis effecting spine and ribs. It is characterized by short-neck, short-trunk, normal-sized limbs and multiple vertebral and rib defects \cite{30}. This syndrome was first described by Jarcho and Levin, in 1938 \cite{31}. One of our cases had segmentation anomalies of vertebral bones (hemivertebrae, absent vertebrae, fused vertebrae, block/ wedge vertebrae, sickle shaped vertebrae), costal defects (posterior fusion of the ribs and absent, irregular and bifid ribs) and pulmonary hypoplasia.

Moreover, in our series, 72.1% of the cases belonged to the dysostosis group. Since this group sometimes is clinically severe, a detailed and complete pathology report with a true diagnosis is important for further new classifications of dysostosis. Thus, prenatal and pathological examination plays an important role in determining the cause of the mortality and morbidity of the fetus.

In summary, identification of dysplasias antenatally is important in the management of pregnancy and in genetic counseling. Many disorders in this group involve disproportionate short stature of prenatal onset and structural abnormalities that may lead to intrauterine death or fatal perinatal complication. Our retrospective archive search showed that SD is usually detected clinically after 20 gestational weeks. This gestational age could be considered as late to plan termination of pregnancy because of the psychological and clinical complications. It is important to perform genetic analyses for SDs, which can provide benefits for early diagnosis and management.

\textbf{Authors’ Contributions}

Havva Serap Toru carried out clinical analysis of the patients and drafted the manuscript; Havva Serap Toru conceived, designed and performed the experiments and analysis of the pathologic data; Havva Serap Toru, Gulden Tasova Yilmaz, and Fatma Şeyda Karaveli collected and reviewed the pathologic data; Banu Guzel Nur, Cem Yasar Sanhal, İnanç Mendilcioğlu, and Ercan Mihci carried out clinical analysis of the patients and reviewed the manuscript; Ozgul M. Alper and Elanur Yılmaz per-
formed the experiments and analysis of the genetic data; Ozgul M. Alper reviewed the final form of drafted manuscript.

Declaration of Interest
All authors have read and approved the manuscript and declare no competing financial interests. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article. This study was supported by Akdeniz University, Scientific Research Project Management Unit.

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