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Prenatal diagnosis of skeletal malformations

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Objective

To describe phenotypic abnormalities of skeletal malformations detected by prenatal ultrasound and its correlation with genetic diagnosis.

Methods

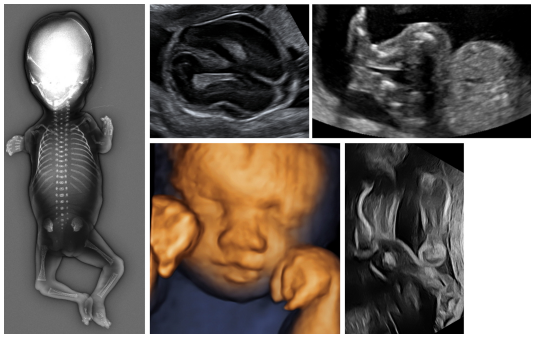
We retrospectively examined a series of 14 cases of fetal skeletal malformations diagnosed by prenatal ultrasound between 2017 and 2022. We analyzed the ultrasound findings and the genetic results.

Results

The genetic study confirmed the diagnosis of skeletal dysplasia in 13 of 14 (92.8%) cases obtaining 11 different disorders. The ultrasound phenotype malformations considered the key to reach the diagnosis were: bilateral upper limbs phocomelia with normal thumbs (thrombocytopenia-absent radius syndrome), severe micromelia with hypoplastic thorax and intrauterine fractures due to inadequate bone mineralization (2 cases of osteogenesis imperfecta), severe micromelia with hypoplastic thorax and bowing femur but normal mineralization (2 cases of thanatophoric dysplasia and one case of hypochondrogenesis), isolated micromelia (chondrodysplasia punctata), rhizomelia with angulated femur and normal mineralization (Stüve-Wiedemann syndrome), bilateral clubfoot (Potocki-Lupski syndrome and Wieacker-Wolf syndrome), limb fixed contractures with lack of mobility indicative of arthrogriposis (Costello Syndrome and arthrogryposis GLYT1 encephalopathy) and short femur at 3rd trimester of gestation (achondroplasia). Only one case with ultrasound findings of clubfoot, sandal gap and static fingers in flexion position remained without prenatal diagnosis (normal karyotype and microarray and clinical exome sequencing without findings) In 8 of 14 (57.1%) cases, after receiving the information about the presence of lethality signs in the ultrasound, the parents opted for termination of pregnancy. It was also performed a genetic study from parents blood samples in 12 of 14 cases, obtaining 4 cases with both parents carrying the abnormal genetic variant.

Conclusion

Despite the overlapping ultrasound signs of skeletal malformations, the accurate description of skeletal features and other phenotypic abnormalities, in cooperation with geneticists, allows to establish a diagnosis in the majority of cases of skeletal malformations.



CASE	PHENOTYPE	MINERALIZATION	BONE SHAPE	LETHALITY SIGNS	FINAL DIAGNOSIS	GESTATIONAL AGE AT DIAGNOSIS	GENE
1	Bilateral upper limbs phocomelia with normal thumbs	Normal	Normal	No	Thrombocytopenia-absent radius syndrome	17	RBM8A
2	Severe micromelia	Abnormal with fractures	Normal	Hypoplastic thorax	Osteogenesis imperfecta	21	IFT140
3		Abnormal with fractures	Normal	Hypoplastic thorax	Osteogenesis imperfecta	17	COL1A1
4		Normal	Bowing femur	Hypoplastic thorax	Thanatophoric dysplasia	20	FGFR3
5		Normal	Bowing femur	Hypoplastic thorax	Thanatophoric dysplasia	20	FGFR3
6		Normal	Bowing femur	Hypoplastic thorax	Hypochondrogenesis	15	COL2A1
7	Isolated micromelia	Normal	Normal	No	Chondrodysplasia punctata	20	EBP
8	Rhizomelia with angulated femur and normal mineralization	Normal	Angulated femur	No	Stüve-Wiedemann syndrome	20	LIFR
9	Bilateral clubfoot	Normal	Normal	No	Wieacker-Wolf syndrome	16	ZC4H2
10		Normal	Normal	No	Potocki-Lupski syndrome	20	PTLS
11	Short femur at 3rd trimester of gestation	Normal	Normal	No	Achondroplasia	28	FGFR3
12	Clubfoot, sandal gap and static fingers in flexion position	Normal	Normal	No	No diagnosis	20	No diagnosis
13	Fixed contractures and lack of mobility indicative of arthrogriposis	Normal	Normal	No	Costello Syndrome	20	HRAS
14		Normal	Normal	No	Arthrogryposis GLYT1 encephalopathy	20	SLC6A9