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ORIGINAL ARTICLE

Need for Fetal Autopsy and Genetic Diagnosis in Fetal Limb Anomalies

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Abstract Improved antenatal imaging has led to increased detection rates of fetal limb anomalies. While they are nonlethal, they could be the first indication of an underlying genetic disorder. In the event of termination, postmortem and genetic evaluation are rarely performed, missing the opportunity to diagnose genetic disorders. The aim of the present study was to examine the utility of fetal autopsy in antenatally detected limb anomalies and to determine the incidence of genetic disorders in the same cohort. This was a retrospective evaluation of 59 cases. Only fetuses terminated for limb anomalies, either in isolation or in association with other features, were included. Cases terminated for lethal skeletal dysplasia and arthrogryposis multiplex congenita were excluded. Cases where limb defects were diagnosed after termination were also not included. The antenatal ultrasound records were compared to postmortem findings to determine the concordance rates. Chromosomal studies along with fetal autopsy were performed in all cases. Mutation analysis was also carried out where possible. Complete concordance between antenatal and postnatal findings was observed in 61 % of the cases. In 23.7 % of the cases, additional major anomalies were observed, the commonest being orofacial clefts. A genetic association was present in 62.7 % of the cases, of which, 25.4 % had an abnormal karyotype. Bilateral limb involvement and presence of associated features were strong predictors of genetic syndromes.

Keywords Limb anomalies · Fetal autopsy · Chromosomal · Genetic · Ultrasound

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Introduction

Recent advances in imaging have led to improved detection rates of fetal limb anomalies [1]. While they are nonlethal and can be surgically corrected, they could be the first indication of an underlying genetic disorder [2]. Detailed evaluation is therefore, necessary to arrive at a diagnosis. This helps in guiding about prognosis, as well as in estimating the risk of recurrence. However, many couples opt for pregnancy termination even if the underlying anomaly is nonlethal due to the uncertainty in prognosis and the socio economic burden of a handicapped child [3]. While fetal postmortem evaluation is ideally recommended in all cases, it is often declined [4]. Further, genetic consultation is not always sought thus precluding attempts at precise diagnosis [5].

Expertise in genetics and fetal postmortem is available only at select centers in India and hence, remains out-of-reach of many patients. However, one cannot underscore the need for detailed evaluation in the background of fetal defects. Therefore, in the present study, the authors aimed to examine the utility of fetal autopsy in antenatally detected fetal limb anomalies. The incidence of genetic disorders in such a cohort was also analyzed.

Materials and Methods

This was a retrospective evaluation of fetal postmortem studies performed at the Center of Medical Genetics, Sir Ganga Ram Hospital, New Delhi which is a tertiary referral center. All cases which had undergone fetal postmortem examination from April 2003 through June 2014 were reviewed.

Inclusion criteria: All cases terminated after antenatal detection of fetal limb anomalies in isolation or along with other congenital malformations.

Exclusion criteria: Fetuses terminated for fetal skeletal dysplasia and arthrogryposis multiplex congenita were excluded. For positional defects like congenital talipes equinovarus (CTEV), those which could be attributed to result from confounding factors like open neural tube defect or oligohydramnios, were not included. Fetuses where limb anomalies were identified after termination of pregnancy only, were also excluded from the analysis.

The following protocol was followed for all autopsies: Pre-postmortem counseling, parental consent, a three generation pedigree, maternal illness, teratogens exposure, trauma, and a copy of ultrasound records. All fetuses were subjected to a detailed external and internal examination, anthropometric measurements, photographic recording of salient findings, radiographic examination, and chromosomal and histopathological analysis. DNA was extracted from placenta or fetal spleen and stored in all the cases with malformations. The fetal postmortem was performed by clinical geneticists with training in the performance of postmortems; microscopic examination was carried out in the affiliated histopathological department.

In order to analyze the utility of fetal postmortem examination, the authors first attempted to correlate the antenatal ultrasound and postmortem findings. The cases were categorized into four groups to understand the utility of postmortem, over and above a detailed genetic sonogram. These were:

Group A: Complete concordance between antenatal and postnatal findings. No additional information obtained via autopsy
Group B: Additional major anomalies detected.
Group C: Additional minor anomalies detected.
Group D: Anomalies detected on ultrasound, not confirmed at autopsy

The second phase of analysis was limited to understand the need of genetic testing in cases of fetal limb anomalies. For this purpose, the final conclusion arrived at, after the fetal post-mortem, was examined. Two types of results were included:

(1) Confirmed genetic syndrome, either through chromosomal or molecular studies
(2) Cases where the final diagnosis was stated as a particular genetic syndrome/sequence, although, confirmation by molecular studies was not available (due to economic constraints). For diagnosis of syndromes, established criteria were used. Cases with multiple malformations not pertaining to any well-defined established genetic syndrome, were excluded.

Results

In the study period, 59 cases fulfilled the inclusion criteria. The gestational age ranged from 12 weeks to 30 weeks, with a mean of 17.5 weeks.

Maternal risk factors were present in four cases and included one each of uncontrolled maternal diabetes, maternal Wilson disease on penicillamine therapy, maternal valproate exposure, and presence of bicornuate uterus.

Four families had a *previous similar affected baby*, thus indicating, a high probability of a genetic etiology.

In 28 cases, the anomaly was limited to the lower limbs; upper limbs were affected in 14 cases while both limbs were involved in 17 fetuses. Limb defects were present along with other malformations in 44 cases, while in the remaining, the pregnancy had been terminated only due to the presence of limb malformations.

A complete concordance for all major and minor features was observed in 36 cases (61 %). Additional major anomalies were noted in 14 cases (23.7 %) as detailed in Table 1. Additional minor anomalies were observed in nine cases. These were microtia (n = 2), ear tags (n = 1), polydactyly (n = 4): preaxial polydactyly of thumb (n = 1), hallux duplication (n = 1), postaxial polydactyly of thumbs (n = 2), and absent thumbs (n = 2). There were no false positive findings.

A genetic etiology was identified in 37 (62.7 %) of the 59 cases (Fig. 1). Multiple anomalies were present in 33 (89.1 %) cases, while in 4 (10.8 %) cases pregnancies had been interrupted for bilateral limb anomalies. In 15 (45.5 %) of the 33 cases with multiple malformations, chromosomal abnormalities were identified. They included eight cases of trisomy 18, two with trisomy 13, two with triploidy, one with trisomy 21, and one with 22q11.2 deletion. Presence of conotruncal defect and cerebellar hypoplasia had prompted testing for 22q11.2 deletion. In yet another case where fetal sample was unavailable for culture, parental studies revealed a balanced translocation in the mother 46, XX, t (4; 18) (p16; q21). The findings of growth retardation, prominent occiput, bilateral mesomelia with hypoplastic thumbs, bilateral CTEV, hypoplastic left heart, left congenital diaphragmatic hernia (CDH), ventriculomegaly and ambiguous genitalia, in conjunction with the parental chromosomal findings, led the authors to conclude that the fetus probably was affected with trisomy 18.

Recognizable genetic syndromes/sequences were observed in 22 (59.4 %) of the 37 cases with a genetic etiology. Table 2 depicts details of this cohort. Of note, the fetal genetic evaluation did not reveal any additional findings in all cases which had been interrupted for unilateral limb anomaly. In 11 (n = 44) cases with multiple defects, no definitive conclusions regarding etiology were made.

Table 1 Comparison of antenatal and postnatal findings in discrepant cases—Group B

Sr no.	Gestation and antenatal findings	Additional anomalies detected on autopsy	Diagnosis
1	22 week: clenched hands, cleft palate, SUA, oligoamnios, cerebellar hypoplasia	Cystic kidneys	Trisomy 18
2	20 week: bilateral clenched hands, IUGR	Micrognathia, mid-line cleft palate	Triploidy
3	20 week: clenched hands, U/L CTEV, IUGR small placenta oligoamnios, strawberry shaped skull, over-riding of aorta, TOF	Bilateral cleft lip and median cleft palate	Triploidy
4	15 week: lower limb only buds visualized, upper limbs normal, omphalocele, curvature in lower lumbar and sacral spine, pelvic bone not well visualized, SUA, short umbilical cord, NT −0.6 mm	Right foot attached to pelvis with ectrodactyly and presence of only great and fifth toe. Attached to the left pelvis is a limb bud, no definitive foot or any other limb structure seen, ambiguous genitalia. No bones of the lower limb seen	WNT7A mutations negative
5	18 week: left lower limb grossly malformed with foot seen to arise directly from pelvis. Only two toes visualized. Also attached to pelvis is a single bone ?femur, but no other structures are attached to it, SUA, occipital encephalocele, oligoamnios	Bilateral hypoplastic kidneys with cysts in right kidney	Multiple malformation syndrome
6	15 week: B/L rockerbottom feet with polydactyly with absent/fused long bones below knee (fibula present), hypoplastic mandible	Gastroschisis	?Acrofacial dysostoses
7	20 week: lower limbs anatomy not well defined, oligohydramnios, only single kidney visualized and shows multiple cysts, absent stomach bubble and bladder non visualized	Only stump-like projections in both lower limbs. Absent legs and feet, absent genitals	?Al Awadi/Raas–Rothschild syndrome
8	18 week: fused lower limb, sacrum not well visualized, omphalocoele, severe oligoamnios History of maternal diabetes, HbA1c performed in 14 weeks was 13 %	Renal agenesis, absent bladder, absent genitals	Caudal regression—uncontrolled maternal diabetes
9	19 week: only one lower limb visualized, absent liquor, lumbosacral spine not well visualized in lower end, cardiomegaly, pericardial effusion, VSD	Bilateral renal agenesis with absent ureters and bladder	Sirenomelia
10	22 week: B/L CTEV with sandal gap, hypoplastic nasal bone, overriding of aorta, hypoplastic cerebellum with absent vermis. Increased NT (4.1 mm) in first trimester, NFT—4.7 mm	Mid-line cleft palate	Distal arthrogryposis
11	20 week: B/L clenched hands, polyamnios, IUGR	Flexion contractures of elbows and knees	Fetal valproate syndrome maternal teratogens exposure: 1000 mg valproate per day till 18 weeks and switched over to tegretol 700 mg at 18 weeks of gestation
12	14 week: acrania with improper visualization of fetal nasal bone, heart and bilateral lower limbs	Amniotic band extending from posterior part of skull defect till left toe. Stump-like projection of right leg, no right foot	Amniotic band syndrome
13	22 week: U/L CTEV, cleft lip, only one great vessel originating from heart, diaphragmatic. Hernia, B/L polycystic kidneys, oligoamnios	Mid-line cleft palate	Fryns syndrome
14	21 week: club hands, left CDH, SUA, U/L cystic kidney	Left sided cleft lip extending to palate, facial tags extending from tragus to cheel along with the left sided cleft lip	Oculo-auriculo-vertebral spectrum

B/L bilateral, *CDH* congenital diaphragmatic hernia, *CTEV* congenital talipes equino varus, *IUGR* intrauterine growth restriction, *NFT* nuchal fold thickness, *NT* nuchal translucency, *SUA* single umbilical artery, *U/L* unilateral, *VSD* ventricular septal defect

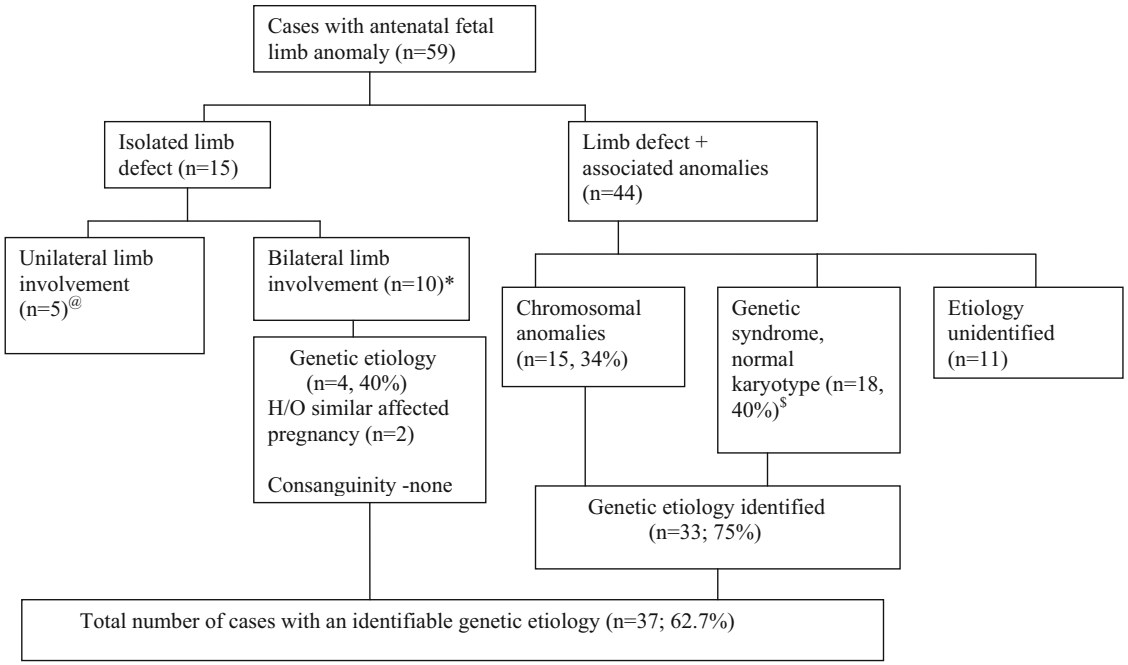

Fig. 1 Description and etiology of the cases included in the study. [@]Isolated bent femur (n = 2), focal femoral hypoplasia (n = 1), unilateral transverse limb defect (n = 1), unilateral CTEV (n = 1). *Bilateral CTEV (n = 6, maternal penicillamine intake in one), Cenani–Lenz syndactyly (n = 1, recurrent anomaly), LRP2 associated polydactyly (n = 1, recurrent anomaly), split hand foot malformation (n = 1), Klippel–Trenaunay–Weber syndrome (n = 1)—details in Table 2; cases 19–22. [$]Details provided in Table 2 (cases 1–18). Maternal risk factors (n = 2, maternal diabetes, maternal valproate exposure. Consanguinity (n = 1, Meckel–Gruber syndrome). Previous similar affected pregnancy (n = 2, Carpenter syndrome, Meckel–Gruber syndrome)

Discussion

The aim of fetal postmortem evaluation is to try and understand why a particular adverse fetal outcome occurred. Additionally, it also serves as a quality control check for antenatal ultrasounds. While conventional fetal autopsy is the gold standard, its uptake seems to be declining [24]. In India, limited availability of postmortem facilities, as well as the cost involved, are the other constraints. Further, with the development of better ultrasonographic and noninvasive autopsy techniques, there is a need to re-examine the utility of conventional autopsy [25]. The authors attempted to do the same through this study and specifically chose the cohort of limb anomalies for this, as majority of them are well detected on ultrasound [1]. Complete concordance was detected in 61 % cases. Concordance rates for fetal malformations varying from 49 to 90 % have been reported earlier [26, 27]. Since the inclusion criteria were limited to cases where antenatal limb anomalies had been identified, there were no false negative cases.

While there were no false positives, a better delineation of the limb defect was possible only after termination in three cases (refer Table 1). The antenatal ultrasound had stated that the lower limbs were malformed/anatomy not well delineated in case 7 of Group B. The accompanying oligoamnios could have precluded visualization. In the second case (case 11 of Group B), the pregnancy had been interrupted for bilateral clenched hands, while the autopsy revealed arthrogryposis with dysmorphism attributable to maternal teratogenicity. In the third case (case 12 of Group B), the amniotic band stretched from the posterior skull and to left leg, and hence, the visualization of other structures was not possible. In this case removal of the band revealed an amputation of the right lower limb below the knee with only a pointed stump-like projection. Interestingly, a bicornuate uterus was noted in the same instance and could also be a contributing factor [28].

In five (35.7 %) of 23 discrepant cases, cleft palate was noted to be the major discrepant finding. An accompanying cleft lip was present in two cases, being bilateral in one fetus. All the ultrasounds in these cases were 2D, which has a sensitivity of 75 % in detection of orofacial clefts [29]. Oligoamnios emerged as the major contributing factor for discrepancy and was present in seven (50 %).

The next purpose was to calculate the incidence of genetic syndromes in fetuses terminated for fetal limb anomalies. Traditionally, the fetal postmortem includes fetal anthropometry, external and internal macroscopic as well as microscopic examination, and evaluation of the fetal placenta. Chromosomal analysis is recommended in cases with multiple malformations and genetic referral is

Table 2 Description of cases with an identifiable genetic syndrome

Sr no.	Clinical features	Diagnosis
1	Facial dysmorphism—hypotelorism, micrognathia, long smooth philtrum and thin upper lips, bilateral short femur, unilateral renal agenesis, absent bladder, hypoplastic uterus	Femoral hypoplasia unusual facies syndrome [6]
2	Omphalocele, single bone in lower limb, no foot, absent internal and external genitalia, bilateral renal agenesis, sacral agenesis. History of maternal diabetes with HbA1c performed in 14 weeks was 13 %	Caudal regression syndrome due to maternal diabetes [7, 8]
3	Absent left lower limb, placenta attached to the lower fetal abdomen. On separation a large abdominal defect seen with visualization of intestines and stomach. Very short umbilical cord. No external genitalia seen. Imperforate anus. Internal examination: testis	Limb body wall complex [9]
4	Right upper limb reduction defect, left CDH, IUGR, dysmorphism: synorphys, prominent philtrum	Cornelia-de-Lange syndrome [10]
5	Single lower limb (fused bones), SUA, bilateral renal agenesis, sacral agenesis, imperforate anus, no identifiable external or internal genitalia (n = 4)	Sirenomelia [11]
6	Clenched hands, B/L CTEV, DWM, high narrow palate, ambiguous genitalia	Distal arthrogryposis [12]
7	Omphalocele, bladder exostrophy, lumbar meningomyelocele, imperforate anus, malrotation of gut, B/L club foot	OEIS [13]
8	Facial dysmorphism (hypertelorism, depressed nasal bridge, long smooth philtrum, thin upper lip, B/L clenched hands, flexion deformity of wrists, elbows and knees, syndactyly of toes and fingers and oligodactyly of foot, broad great toes	Fetal valproate syndrome Maternal teratogens exposure : 1000 mg valproate per day till 18 weeks and switched over to Tegretol 700 mg at 18 weeks of gestation
9	Anencephaly with a band of scar tissue extending from skull to left foot. The right foot was encased within this stretch of scar tissue. On removal, the right leg was found to end in a pointed stump-like projection below the knee. No foot present	Amniotic band syndrome [14]
10	Left cleft lip, Median cleft palate, bilateral postaxial polydactyly in upper limbs, hypoplastic nails, truncus arteriosus with VSD, left CDH bilateral polycystic kidneys	Fryns syndrome [15]
11	Dysmorphic coarse facies, ambiguous genitalia, nail hypoplasia, hypoplastic terminal phalanges of all fingers and toes, left CDH, B/L CTEV	Fryns syndrome
12	Left CDH, club hands, unilateral cleft lip, cleft palate, multiple tags present in left side of face extending from the tragus to the outer part of lip	Oculo-auriculo-vertebral syndrome [16]
13	Left radial and ulnar hypoplasia with absent thumbs, esophageal atresia with two blind ends, collapsed stomach, horseshoe kidneys, hemivertebra in the upper thoracic region	VATER [17]
14	Frontal bossing, craniosynostosis, proptosis, mitten hands and feet	Apert syndrome
15	Clover leaf skull, ambiguous genitalia, Rt. toe duplication, postaxial polydactyly of bilateral hands. Previous similar affected pregnancy	Carpenter syndrome [18] RAB23: c.1093T>G (hom);p.Stop238E
16	Occipital encephalocele, hexadactyly of all four limbs, bowing of bilateral tibia and radius and ulna, bilateral enlarged cystic kidneys. Consanguineous couple (first cousins). Previous affected pregnancy terminated.	Meckel–Gruber syndrome [19]
17	Low set ears, depressed nasal bridge, unilateral cleft lip, right hand: 2–3 finger amputated, left hand—1–2 finger cutaneous syndactyly with scar tissue hanging forms the second finger, constriction band in left hand and bilateral absent hallux	Amniotic band syndrome
18	Clenched fists with overlapping fingers, ulnar deviation of the hand, B/L rockerbottom foot, median cleft palate, low set ears, left hydroureter, only 11 pairs of ribs	Distal arthrogryposis ?type 3 [22]
19	Reddish brown discoloration of the skin on the entire left side of the body, with hypertrophy of the left thorax and lower limb. The index finger of the right hand was long and deviated medially. In the feet there was hypertrophy of the feet with bilateral long second toes and sandal gap. Histopathology revealed a cavernous hemangioma	Vascular malformation type IV—Kleippel–Trenaunay–Weber syndrome [20]

Table 2 continued

Sr no.	Clinical features	Diagnosis
20	Right hand: five digits with absence of the third finger and fusion of the little finger to an extra digit present postaxially. Left hand revealed four digits with complete fusion of 2nd and 3rd fingers and presence of a lump of tissue attached to the third finger. Bilateral syndactyly of the second and third toes were present. Multiple absent phalanges on radiography—oligosyndactyly with absent phalanges	Cenani–Lenz syndactyly [21] LRP4: c.4330T>C; p.W1444R and c.4561dupA; p.T1521Nfs*5
21	B/L postaxial polydactyly type B of upper limbs	LRP2 mutations: c.4995G>C (p.D1499H) and c.3434C>T (p.S1145L)
22	Bilateral severely shortened femurs, bilateral tibiofibular aplasia with bilateral ectrodactyly in both feet- only great toe and little finger visualized with a deep crease extending into the plantar surface of the foot. Due to long bone shortening and absence both feet seem to originate very close to the pelvis	Split hand foot malformation with long bone deficiency [23]

CDH congenital diaphragmatic hernia, *CTEV* congenital talipes equinovarus, *DWM* Dandy–Walker malformation, *IUGR* intrauterine growth retardation, *OEIS* omphalocele, exostrophy bladder, imperforate anus and spinal defects, *SUA* single umbilical artery, *VATER* vertebral anomalies, anal defects, tracheo-esophageal, renal and radial, *VSD* ventricular septal defect

limited to certain cases as deemed necessary by the fetal pathologist.

A well-defined genetic syndrome was present in 62.7 % cases with presence of a chromosomal anomaly in 25.4 % (Fig. 1). This is along the lines of what has been reported previously [30, 31]. Pajkrt et al. documented a genetic syndrome in 59.4 % of 66 cases, while Paladini et al. observed it in 76 % of their cases. Preferential referral of cases known to be associated with an unfavorable outcome like bilateral involvement or presence of multiple defects could be a contributing factor for the larger number of genetic syndromes. The present cohort comprised only five cases with unilateral limb defects. No syndrome was associated with this group and the risk of recurrence is low in this category, as observed earlier [30, 31].

While multiple syndromes, both chromosomal and nonchromosomal, were identified in the cohort, two cases deserve a special mention. The first is that of fetal Cenani–Lenz syndactyly syndrome (case 20 in Table 2). This was the second affected pregnancy of a nonconsanguineous couple. The first conception had been interrupted at 18 weeks for bilateral oligosyndactyly and unilateral renal agenesis. No fetal evaluation had been undertaken. In their second conception, a chorionic villous sampling had been performed at 12 weeks for a raised nuchal translucency and was normal. A genetic sonogram at 19 weeks revealed recurrence of oligosyndactyly for which the pregnancy was terminated. The postmortem examination revealed complex oligosyndactyly, with absent phalanges, which along with a history of unilateral renal agenesis led to the diagnosis. This may be the first case of Cenani–Lenz syndactyly syndrome to be reported in a fetus. It also adds to the growing list of etiologies associated with increased nuchal translucency.

The second case involves recurrent postaxial polydactyly (case 21 in Table 2). This nonconsanguineous couple had requested fetal evaluation for recurrent postaxial polydactyly. Fetal postmortem in their previous conception had confirmed isolated postaxial polydactyly type B and subsequent microarray had been normal. Considering recurrence, exome sequencing was undertaken and trio study revealed compound heterozygous mutations in LRP2 gene with the parents being carriers. Mutations in LRP2/megalin which is a low-density lipoprotein receptor, have been previously implicated in Donnai–Barrow syndrome and Stickler syndrome [32, 33]. However, there are no reports of LRP2 involvement in limb development. Bioinformatic analysis was performed which revealed the p.D1499H to be highly conserved and predicted it to be pathogenic. As the mutation p.S1145L was present in three affected fetuses along with mutation p.D1499H, it was considered to be pathogenic though it is a weakly conserved residue.

The present study has provided evidence of the necessity of genetic considerations in fetal limb anomalies. However, it is not without limitations. The first and foremost being its retrospective nature. The high genetic association in this study could be biased as terminations are most commonly done in cases which have severe limb malformation or have multiple malformations. Secondly, cost constraints precluded molecular testing in many cases. Thirdly, culture failures prevented extensive studies in some instances. Amongst the eleven cases without a definitive conclusion, features suggestive of Fanconi anemia were present in two, but failure of culture on fetal sample prevented chromosomal breakage studies. This could have been averted by sample collection during the antenatal period.

In spite of the above drawbacks, the present study has provided strong evidence of the need to consider not only fetal autopsy, but also genetic disorders in all cases with limb anomalies, especially when these are bilateral or associated with other malformations.

Conflict of interest None.

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