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Prenatal ultrasound detection of talipes equinovarus in a non-selected population of 49 314 deliveries in Norway

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KEYWORDS: clubfoot; congenital anomalies; fetus; pes equinovarus; prenatal diagnosis; ultrasound

ABSTRACT

Objectives *To evaluate prenatal ultrasound detection of talipes equinovarus (TEV) in a large non-selected population and to study trends in detection rates over time, as well as the prevalence and outcome of isolated TEV and TEV with associated anomalies.*

Methods *All cases of pre- or postnatally diagnosed TEV between 1987 and 2004 within a non-selected population of 49 314 deliveries were investigated. The study period was divided into three 6-year periods to shed light on changes in detection rates and other aspects of the anomaly over time.*

Results *A total of 113 cases of TEV were registered during the 18-year period, of which 49% had isolated TEV and 51% had associated anomalies. During the three 6-year periods, there was a significant improvement ($P = 0.006$) in the overall detection of TEV from 43% to 67% and 77%, respectively. The detection rate for isolated TEV increased over time. Isolated bilateral TEV cases were detected more than twice as often as isolated unilateral TEV. The three largest groups of associated anomalies were syndromes/sequences (26%), chromosome aberrations (26%), and musculoskeletal disorders (24%). Pregnancies were terminated in 23% of the cases, all with severe additional anomalies. Treatment of TEV included surgery in 86% of the cases.*

Conclusion *The overall detection rate of TEV improved significantly over time. Prenatal detection was higher when TEV was bilateral and when other associated anomalies were present. Parents should be informed that, in suspected isolated TEV, associated anomalies might remain undetected prenatally.*

INTRODUCTION

Clubfoot, or congenital talipes equinovarus (TEV), is one of the most common congenital birth defects. TEV is characterized by a deformity of the fetal foot fixed in adduction, supination, and varus position. There is subluxation of the talo-calcaneo-navicular joint, with underdevelopment of the soft tissues on the medial side of the foot and frequently of the calf and peroneal muscles[1]. As a result, the foot is typically turned inwards giving the foot a club-like appearance. The diagnosis of TEV can be made as early as 13 weeks' gestation by transvaginal sonography[2,3] and at 16 weeks by transabdominal ultrasound[4,5]. Approximately one third of cases are reported to be isolated[6] when diagnosed in the neonatal period. However, TEV is frequently associated with other fetal anomalies and aneuploidy, thus a thorough examination of the whole fetus is important whenever the diagnosis of TEV is suspected in the prenatal ultrasound examination[7–9].

In Norway, the routine fetal ultrasound examination was introduced in 1986 and has been offered to all pregnant women between 17 and 20 weeks of gestation ever since[10]. Improvements in ultrasound technology and skills of examiners have led to an increased detection rate of malformations in general[11–16]. However, our knowledge regarding prenatal ultrasound of TEV is largely based on studies from tertiary referral centers with a selected population.

The objective of this study was to evaluate the detection of TEV in a large non-selected population and to study the prevalence and outcome of isolated TEV and cases with associated anomalies; an additional objective was to use our improved knowledge of TEV to provide information for better prenatal counseling for parents.

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PATIENTS AND METHODS

This prospective follow-up study covered the 18-year period from January 1987 to December 2004. The study included all cases of pre- or postnatally diagnosed TEV, registered with the nomenclature and coding system from the 9th and 10th revision of the International Classification of Disease (ICD-9, ICD-10). Other, less severe foot deformities such as talipes calcaneovalgus and metatarsus varus were not included. All cases of TEV were confirmed postnatally either through a physical examination by a pediatrician or at autopsy. The study comprised 49 314 deliveries, including miscarriages, terminations and intrauterine fetal deaths (IUFD), of fetuses beyond 16 weeks' gestation. The study population was a non-selected one residing in a geographically well-defined area consisting of the city of Trondheim and eight surrounding municipalities. Within this population approximately 97% of the pregnant women had a routine fetal examination at the National Center for Fetal Medicine (NCFM) at St Olavs University Hospital in Trondheim, and later delivered there. Cases of TEV referred to the NCFM as a tertiary referral center from outside our non-selected population were not included.

Specially trained sonographer–midwives performed the routine fetal ultrasound examination between 16 + 1 and 22 + 5 weeks' gestation. At the ultrasound examination, the biparietal diameter, the mean abdominal diameter and the femur length were measured. The number of fetuses, the fetal anatomy including the extremities, and the location of the placenta were assessed. All pathology found at the second-trimester ultrasound examination was presented to specialists in fetal medicine at the center; these specialists also performed all ultrasound examinations for clinical indications, before and after the second-trimester routine ultrasound examination, including all necessary invasive procedures.

Data from the ultrasound examinations were prospectively stored in an electronic database. For each fetus with anomalies, video recordings, biochemical tests and karyotype were registered. After delivery or termination of pregnancy, further pre- and postnatal data from the pregnancy, birth and neonatal development and treatment including autopsy reports and photographs were recorded. All congenital anomalies or syndromes diagnosed even years later were reported back to the center to complete our database. All liveborn infants were followed up; the longest follow-up was over 18 years, the shortest about 2 years.

The study period was divided into three 6-year periods: the first period from 1987 to 1992, the second from 1993 to 1998 and the third from 1999 to 2004. For statistical analysis the SPSS 11 for Mac OS X (SPSS, Chicago, IL, USA) software package was used. The Chi-square test was used to test for significance of observed frequencies and the level of significance was set at 5%.

RESULTS

During the study period 113 fetuses or newborns in the total non-selected population were registered with TEV. Postnatal documentation was available for all 113 fetuses or newborns and the diagnosis was confirmed in all cases. There was one false positive case of isolated TEV: the 18-week scan was normal, but a new scan at 34 weeks, performed because of an abnormal symphysis-fundal height, revealed polyhydramnios and bilateral TEV. At birth the child had normal feet.

Isolated TEV was found in 55/113 (49%) and 58/113 (51%) had additional associated anomalies. Isolated TEV was bilateral in 55% (30/55) of the cases and unilateral in 45% (25/55). Fetuses with associated anomalies had bilateral TEV in 59% (34/58) and unilateral TEV in 41% (24/58) (Figure 1).

The prevalence of TEV with or without associated anomalies including abnormal chromosomes was 2.3 per 1000. For isolated TEV, the prevalence was 1.1 per 1000. There were 66/113 (58%) male and 47/113 (42%) female fetuses with the diagnosis of TEV, which gives a ratio of 1.4 : 1. In isolated TEV, the male to female ratio was 2 : 1. The median age of women giving birth to a child with TEV was 28 (range, 17–42) years, corresponding to the median age of our total pregnant population.

Of the 113 fetuses, 111 had had at least one prenatal ultrasound examination. Two women did not have a scan at NCFM, but moved to our area during the pregnancy and delivered at our hospital. TEV was diagnosed postnatally in these two cases.

TEV was detected by ultrasound at a median of 18 + 3 (range, 12 + 0 to 30 + 6) weeks' gestation. One case of TEV was detected before the second-trimester routine scan at 12 weeks. Five cases were detected after the routine scan between 24 and 31 weeks. Indications for additional scans in these five cases were: maternal hypertension, maternal diabetes mellitus, myoma uteri diagnosed in pregnancy, choroid plexus cysts diagnosed at the routine second-trimester scan and one scan for growth control.

TEV was detected prenatally in 69/113 (61%) of the cases for the total 18-year period, while 44/113 (39%) were diagnosed postnatally or at autopsy. In 10 of these postnatally detected cases of TEV, an associated anomaly had been diagnosed by ultrasound prenatally. For the three 6-year periods, there was a significant ($P = 0.006$) improvement in the overall detection rate of TEV from 43% (18/42) in the first period (1987–1992), to 67% (24/36) in the second period (1993–1998) and 77% (27/35) in the third period (1999–2004). An improvement in the detection rate was also found in the subgroup of isolated TEV without associated anomalies ($P = 0.001$) during the three time periods, from 23% to 55% and 81%, respectively. In the subgroup of TEV in association with other anomalies, the detection rate of TEV over the three time periods varied from 72% for the first period and 75% and 73% for the second and third periods, respectively, but the change was not significant.

The associated anomalies were often multiple and involved several organ systems (Tables 1 and 2). The

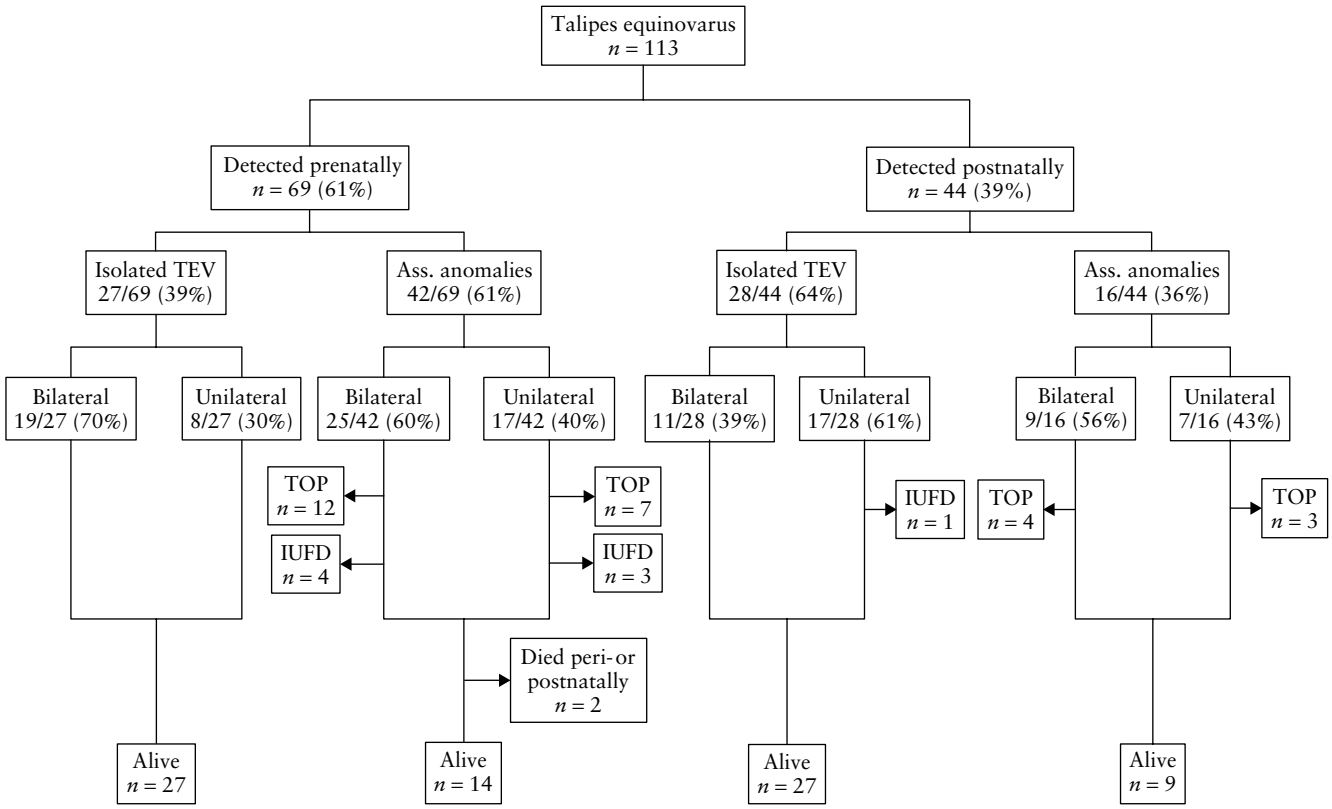

Figure 1 Clinical development of talipes equinovarus (TEV) diagnosed pre- or postnatally. Follow-up time ranged from 2 to 18 years. IUFD, intrauterine fetal death; TOP, termination of pregnancy.

group of musculoskeletal disorders included three cases of lethal multiple pterygium syndrome and five cases of arthrogryposis multiplex congenita. All but two cases of distal arthrogryposis multiplex with affected hands, fingers and feet only were terminated before 21 weeks. The terminated cases all had additional generalized hydrops or large cystic hygromas.

Table 1 Developmental disorders/syndromes among 58 fetuses with bilateral or unilateral talipes equinovarus (TEV) and associated anomalies

Disorder/syndrome	n *(%)*
Unilateral TEV	
Syndromes or sequences	10 (17.2)
Chromosomal aberrations (see Table 3)	6 (10.3)
Musculoskeletal	4 (6.9)
CNS including meningomyelocele	2 (3.4)
Genitourinary	0 (–)
Cardiovascular	1 (1.7)
Other	1 (1.7)
Bilateral TEV	
Syndromes or sequences	5 (8.6)
Chromosomal aberrations (see Table 3)	9 (15.5)
Musculoskeletal	10 (17.2)
CNS including meningomyelocele	5 (8.6)
Genitourinary	3 (5.2)
Cardiovascular	1 (1.7)
Other	1 (1.7)
Total	58

CNS, central nervous system.

Table 2 Deaths among the 58 fetuses with bilateral or unilateral talipes equinovarus and associated anomalies

Disorder/syndrome	*TOP*	*IUFD/perinatal death*
Syndromes or sequences	4	2
Chromosomal aberrations	9	4
Musculoskeletal	7	1
CNS including meningomyelocele	3	1
Genitourinary	3	0
Cardiovascular	0	0
Other	0	2
Total	26	10

CNS, central nervous system; IUFD, intrauterine fetal death; TOP, termination of pregnancy.

In 10/58 (17%) of the cases, the associated anomalies were not detected by ultrasound (Table 3). Case number 58 with associated anomalies moved to our area in late pregnancy, but did not have an ultrasound examination in our unit. A bilateral cryptorchism together with TEV was found postnatally.

Chromosomal aberrations

Fifty-six of 113 (50%) cases with TEV were karyotyped, 53 because of a variety of structural anomalies detected at the ultrasound examination. Two cases were karyotyped because of advanced maternal age; one fetus karyotyped in week 13 turned out to be a case of trisomy 18, the

Table 3 Associated anomalies undiagnosed prenatally among fetuses with talipes equinovarus (TEV)

Main diagnosis made postnatally	*TEV detected prenatally*	n
Charcot–Marie–Tooth disease	Yes	1
Torticollis	Yes	1
Trisomy 21	Yes	1
Anisomelia, Smith–Lemli–Opitz syndrome	Yes	1
Congenital hip dislocation	Yes	1
Kyphomelic dysplasia	No	1
Pulmonary stenosis	No	2
Congenital hip dislocation	No	1
Rectal atresia, unilateral foot amputation at the ankle	No	1
Total		10

other was karyotyped at week 15, and at the routine scan 4 weeks later bilateral TEV was diagnosed. The third case was karyotyped in week 15 because of the woman's obstetric history; the chromosomes were normal. In this case, bilateral TEV was diagnosed after the routine scan in week 27.

Fifteen of 113 (13%) cases with TEV had chromosome aberrations and 13 of these 15 had additional structural anomalies apart from the TEV that led to karyotyping. The two other fetuses with chromosome aberrations presented with no abnormality other than TEV, detected by ultrasound. One fetus was karyoptyped and had 47,XYY. The pregnancy was continued. The other fetus was not karyotyped and a child with trisomy 21 was delivered. All chromosome aberrations are listed in Table 4. The two fetuses with chromosome aberrations, with no structural anomalies other than TEV, correspond to 1.8% of the total TEV population or 3.6% of the assumed isolated TEV population.

Family history

For 9/55 (16%) of the cases with isolated TEV there was a positive family history of TEV: four fathers, one mother, two siblings, one uncle and one first cousin. For 10/58 (17%) of the cases with TEV and additional associated anomalies there was a positive family history of TEV: two fathers, one sister, three first cousins, one uncle and three fourth-degree relatives.

Amniotic fluid volume

Two cases presented with anhydramnios. In both cases a severe urinary tract anomaly was diagnosed, and TEV was diagnosed postnatally at autopsy. Oligohydramnios was registered in six cases. All had associated anomalies. TEV was undiagnosed prenatally in four of these cases, which had severe structural anomalies leading to IUFD in two cases and two terminations of pregnancy. In the other two cases unilateral TEV was diagnosed prenatally and both were born alive and survived with severe disabilities. One fetus was observed with polyhydramnios, mild hydrothorax, diaphragmatic hernia, echogenic kidneys, unilateral TEV and syndromic profile features; this fetus had Simpson–Golabi–Behmel syndrome, but this was not diagnosed until approximately 6 years after birth. None of the isolated cases with TEV had an abnormal amniotic fluid volume.

Outcome of cases with talipes equinovarus

Twenty-six of 113 cases (23%) were terminated because of serious or lethal associated malformations (Table 2). Among these cases, 19/26 fetuses had TEV diagnosed prenatally and seven had TEV diagnosed postnatally. No termination of pregnancy was performed for isolated TEV.

Eight fetuses died *in utero*. In six of these fetuses, severe malformations were diagnosed prenatally, but the mothers chose to continue the pregnancy; two fetuses had a limb–body-wall complex, two had a trisomy 18, one fetus had hydrocephaly and a heart anomaly and the last fetus with multiple severe anomalies unspecific for a particular syndrome/sequence was part of a twin pregnancy with an unaffected co-twin. Another fetus with no prenatally detected anomalies revealed kyphomelic dysplasia with TEV at autopsy, at 27 weeks' gestation. The last IUFD, at 20 weeks' gestation, could not be explained; the only abnormal finding at autopsy was TEV, but no chromosome analysis was performed. Two fetuses with a prenatal diagnosis of trisomy 13 and 18 respectively, with multiple associated anomalies died

Table 4 Chromosomal aberrations among 113 fetuses/newborns with talipes equinovarus (TEV)

Chromosomal aberration	n *(%)*	*Detected prenatally*	*Reason for detection*
Trisomy 18	10 (9)	Yes	9 cases with structural anomalies, karyotyped 1 case detected week 13, karyotyped because of maternal age
Trisomy 13	1 (0.9)	Yes	Structural anomalies, karyotyped
Deletion chromosome 13	1 (0.9)	Yes	Structural anomalies, karyotyped
Triploidy 69,XXX	1 (0.9)	Yes	Structural anomalies, karyotyped
Triploidy 47,XYY	1 (0.9)	Yes	TEV detected at ultrasound examination, karyotyped
Trisomy 21	1 (0.9)	No	TEV detected at ultrasound examination, karyotyped postnatally
Total	15 (13)		

perinatally. The pregnancies were continued until delivery at weeks 32 and 39.

Sixty-six of 77 (86%) liveborn infants required surgical treatment. Serial plaster-cast treatment was performed in 96% of the cases with a median time of treatment between 2 and 3 months. There was a good clinical result of the deformity in cases that had no additional neurological or musculoskeletal disorders. Of the 55 isolated TEV cases, eight (15%) required no surgery, only serial plaster-cast treatment, 31 (57%) required one operation and 16 (30%) required two or more surgical procedures in addition to plaster-cast treatment.

DISCUSSION

The present study was performed in a large, well-defined, non-selected population, served by one ultrasound unit only, located at the hospital where all women from the region gave birth. In addition, one pediatrician or pathologist followed up all pathological findings in the newborns. Follow-up at our center is complete for every delivered infant with a congenital anomaly. Even diagnosed conditions or syndromes years later are reported back to complete our database. Thus, the bias associated with tertiary referral commonly found in publications could be avoided. Our results are therefore representative of a non-selected population and suitable for use as a reference when counseling parents.

The distribution of isolated TEV in males to females (2 : 1) was similar to that in published reports[17]. The 55% frequency of bilateral isolated TEV in our study also corresponded with that found in previous studies with a range from 44 to 59%[18–20]. Prevalences of all TEV of 2.3 per 1000 in our non-selected Norwegian population and 1.1 per 1000 for isolated TEV are in agreement with those of published studies with an estimated birth prevalence of 1 per 1000 live births[21–23].

Our findings were comparable with those of other studies, which found no association between TEV and amniotic fluid levels[6,23–25]. None of the isolated cases had oligohydramnios; only the two fetuses with severe genitourinary anomalies had anhydramnios.

The incidence of cases of isolated TEV with a positive family history in our study was lower than that in the published literature. Lochmiller *et al.*[23] found a family history in 24.4%, and Miedzybrodzka[26] in 30% of cases. In contrast, we found that only 16% of the fetuses with isolated TEV had a positive family history, while 17% of the fetuses with associated anomalies had a positive family history. One possible explanation for the higher rates of a positive TEV family history in the previously published studies may be selection bias.

There was an improvement in the detection of isolated TEV during the 18-year study period, from 23% in 1987–1992, to 55% in 1993–1998 and 81% in 1999–2004. A similar increase over time was reported by Keret *et al.*[27], who found that the detection rate was 42% on average in 1987–1999, but increased to 66% and 70% in 1998 and 1999, respectively. Far lower detection rates (of 20–25%) in the time period from 1989 to 1996 are also reported in the literature[28,29]. One obvious explanation for the improved detection rates over the years is the improvement in ultrasound equipment. However continued education of ultrasound examiners may also lead to better detection rates[30].

Our data showed that 51% of all fetuses with TEV had associated anomalies; this is similar to the 48.6% found in a large unselected study by Bakalis *et al.*[31]. Associated anomalies have been reported to occur in around 67%[7,32], 69%[33] and 80%[9] of cases of TEV. These studies were conducted in tertiary referral centers, and the high rates may reflect referral bias. Nevertheless, the diagnosis of TEV may indicate the presence of other anomalies and should lead to a further detailed anatomical survey of the fetus.

As Figure 1 indicates, cases of isolated bilateral TEV were detected more than twice as often as isolated unilateral TEV, which leads to the assumption that some ultrasound examinations investigated only one extremity carefully. But the improved detection rate for isolated talipes equinovarus over time shows that there has been a higher awareness of TEV in recent years. The training of midwives–sonographers to make sure that both feet are examined will most likely increase detection rates in the future. In cases with associated anomalies, the detection rates for unilateral and bilateral TEV were similar, perhaps indicating that the examination was performed more carefully in these cases. Similarly, the detection rate of cardiac malformations increased in cases with associated anomalies[34].

Not all associated anomalies in our study were detected prenatally when TEV was diagnosed. A number of the associated anomalies are difficult to detect by ultrasound.

In our study, aneuploidy was present in 13% of the cases. There has been a discussion concerning whether karyotyping is indicated when isolated TEV is suspected prenatally. No indication has been seen by some authors[35,36] whereas others suggest that this is an indication for karyotyping[5,29,37]. Our results support the notion that karyotyping should be offered to all suspected cases of isolated TEV, since not all fetuses with chromosomal aberrations have detectable structural anomalies. 9% (10/113) of all fetuses with TEV had trisomy 18; this shows the strong association between these chromosomal aberrations and TEV[38], but all of these fetuses had structural anomalies easily detected with ultrasound. Other studies showed that in fetuses with sonographically diagnosed TEV, aneuploidy rates varied from 5.9%[37] to 22.2%[5]. However the high rate in these studies might represent a selection bias[25]. Rijhsinghani *et al.*[29] found a similar rate of chromosome aberrations (14.3%) as we did in our study. In their study, however, all cases had additional anomalies, which might indicate a selection bias.

We found that 14% (8/58) of all TEV with associated anomalies had arthrogryposis multiplex congenita or multiple pterygium syndrome. TEV is the most common type of deformity in arthrogryposis multiplex congenita[39].

In our unselected population, only one case out of nine with arthrogryposis did not have TEV.

In our study, there was no request for termination of pregnancy in fetuses with suspected isolated TEV. When these cases are counseled it is nevertheless of importance to be aware of long-term neurodevelopmental or musculoskeletal problems associated with TEV that may remain undetected at the routine ultrasound examination. This will most likely remain a difficulty in the years to come.

The total number of infants with TEV requiring surgery was 86%. In cases of isolated TEV 85% needed surgery. More cases of isolated TEV required surgery than would be expected from the literature[33,40,41]. One study reported surgical treatment in only 26% of cases. The series comprised 34 infants with isolated talipes from a cohort of 68 patients undergoing prenatal ultrasound examination[37]. The lower rates reported for surgical intervention in this study could reflect a stricter diagnosis at our center, a selection bias at other centers, or a true variation in treatment approach.

CONCLUSIONS

In conclusion, this investigation of a large non-selected population identified 113 cases of TEV; 49% were isolated and 51% had associated anomalies. Over the three 6-year periods of the study, there was a significant improvement ($P = 0.006$) in the overall detection of TEV from 43% to 77%. This is most likely caused by improvements in ultrasound technology as well as the continuous teaching and training of ultrasound personnel. Our study showed that in a small number of cases of suspected isolated TEV, associated chromosomal aberrations or severe syndromes were not diagnosed until after delivery. Thus, we suggest that karyotyping should always be offered when isolated TEV is found. Parents should be provided with information about possible underlying syndromes and neurodevelopmental conditions.

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