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ORIGINAL RESEARCH ARTICLE

Prenatal diagnosis of isolated bilateral clubfoot: Is amniocentesis indicated?

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Abstract

Introduction: The aim of this study is to evaluate the benefit of cytogenetic testing by amniocentesis after an ultrasound diagnosis of isolated bilateral talipes equinovarus.

Material and methods: This multicenter observational retrospective study includes all prenatally diagnosed cases of isolated bilateral talipes equinovarus in five fetal medicine centers from 2012 through 2021. Ultrasound data, amniocentesis results, biochemical analyses of amniotic fluid and parental blood samples to test neuromuscular diseases, pregnancy outcomes, and postnatal outcomes were collected for each patient.

Results: In all, 214 fetuses with isolated bilateral talipes equinovarus were analyzed. A first-degree family history of talipes equinovarus existed in 9.8% (21/214) of our cohort. Amniocentesis was proposed to 86.0% (184/214) and performed in 70.1% (129/184) of cases. Of the 184 karyotypes performed, two (1.6%) were abnormal (one trisomy 21 and one triple X syndrome). Of the 103 microarrays performed, two (1.9%) revealed a pathogenic copy number variation (one with a de novo 18p deletion and one with a de novo 22q11.2 deletion) (DiGeorge syndrome). Neuromuscular diseases (spinal muscular amyotrophy, myasthenia gravis, and Steinert disease) were tested for in 56 fetuses (27.6%); all were negative. Overall, 97.6% (165/169) of fetuses were live-born, and the diagnosis of isolated bilateral talipes equinovarus was confirmed for 98.6% (139/141). Three medical terminations of pregnancy were performed (for the fetuses diagnosed with Down syndrome, DiGeorge syndrome, and the 18p deletion). Telephone calls (at a mean follow-up age of 4.5 years) were made to all parents to collect medium-term and long-term follow-up information, and 70 (33.0%) families were successfully contacted. Two reported a rare genetic disease diagnosed postnatally (one primary microcephaly and one infantile glycine encephalopathy). Parents did not

Abbreviations: aCGH, array comparative genomic hybridization; TE, talipes equinovarus.

report any noticeably abnormal psychomotor development among the other children during this data collection.

Conclusions: Despite the low rate of pathogenic chromosomal abnormalities diagnosed prenatally after this ultrasound diagnosis, the risk of chromosomal aberration exceeds the risks of amniocentesis. These data may be helpful in prenatal counseling situations.

KEYWORDS
amniocentesis, array comparative genomic hybridization, clubfoot, karyotypes, talipes equinovarus

1 | INTRODUCTION

Clubfoot or talipes equinovarus (TE) can be diagnosed by prenatal ultrasound. It occurs in 1–2 cases per 1000 births.[1,2] TE can be unilateral or bilateral, and isolated or associated with other fetal phenotypic anomalies (considered as complex). Around 75% of prenatal cases of TE are isolated and 25% are complex.[3] In these complex cases, multiple diseases must be ruled out, including chromosomal and genetic abnormalities, fetal immobility, and myelomeningocele. Amniocentesis is recommended in complex forms because of the high probability of chromosomal and genetic abnormalities.[4,5] In isolated forms, however, the very low frequency of chromosomal and genetic abnormalities raises questions about the need for amniocentesis.[4,6–9] Professional practices vary substantially for this indication. The largest cohorts are heterogeneous (unilateral and bilateral, isolated and associated TE) and contain limited numbers of patients. Furthermore, few recent data include molecular karyotype testing (array comparative genomic hybridization [aCGH]) in addition to conventional karyotype testing and rapid aneuploidy testing.[6,10,11]

The primary objective of the study was to evaluate the contribution of amniocentesis in testing for chromosomal abnormalities (with rapid aneuploidy testing, karyotyping, and aCGH) in isolated bilateral TE identified on ultrasound. The secondary objectives were to evaluate the impact of amniocentesis on prenatal management, the contribution of associated examinations such as fetal magnetic resonance imaging (MRI) and/or genetic prenatal biochemical testing for neuromuscular disease, and the children's postnatal outcomes.

Key message

This study confirms the need to offer amniocentesis for isolated bilateral talipes equinovarus and suggests that whole-exome or whole-genome sequencing may increase the diagnostic yield in fetuses with this condition.

2 | MATERIAL AND METHODS

2.1 | Population

This retrospective study took place at five referral centers for prenatal diagnosis associated with obstetrics departments in Paris level III university hospitals (Cochin/Port-Royal, Antoine Béclère, Armand Trousseau, Robert Debré, and Necker Enfants Malades). It included all cases of fetal bilateral and isolated TE diagnosed prenatally on ultrasound examination and confirmed by second-line ultrasound, from January 2012 through December 2021. We excluded unilateral cases, twin pregnancies, and cases with bilateral TE associated with any other fetal anomalies diagnosed by ultrasound examination at the time of the referral or during the prenatal follow up.

2.2 | Diagnosis

Talipes equinovarus cases were diagnosed during routine prenatal ultrasound examinations of women that were conducted either in the participating centers or in other regional hospitals/clinics before referral of the women to one of the five participating centers. As these centers are highly specialized in fetal medicine, after a confirmation of the bilateral isolated TE by referral practitioners, supplementary cardiac and central nervous ultrasound scans were not generally performed. TE was diagnosed on ultrasound when the plantar face of the fetal foot was observed in the same plane as both long bones of the lower leg (i.e. tibia and fibula) throughout the entire examination.[12]

2.3 | Prenatal investigations

All participating centers were equipped to perform prenatal screening for chromosomal abnormalities: rapid aneuploidy testing, karyotyping, and aCGH. They were also able to offer testing for neuromuscular diseases by two means: biochemical analyses of amniotic fluid (assays of acetylcholinesterase and α-fetoprotein) and/or various tests of parental blood samples (sequencing for Steinert disease or spinal muscular atrophy, and antibody testing for myasthenia gravis). Finally, a fetal brain MRI was possible and could be suggested in all centers between 31 and 33 weeks of pregnancy. Parents were

referred to an orthopedic surgeon for prenatal counseling and information about postnatal management.

2.4 | Postnatal care

All children underwent a clinical examination at birth to confirm the diagnosis and search for any other associated anomalies. They were also referred for a postnatal follow up with an orthopedic surgeon at a referral center (three pediatric orthopedic surgery centers at Armand Trousseau, Necker Enfants Malades, and Robert Debré hospitals). Management was discussed during this follow up: functional with physiotherapy and shoe orthosis, or surgical, either by tenotomy during the first months of life or by more substantial corrective surgery.

2.5 | Data collection

Prenatal and postnatal data were collected retrospectively from the medical records in each center. Long-term follow-up data were collected during the month of May 2022 by contacting parents by telephone and obtaining their consent before asking questions. The same three questions were asked of every parent to investigate postnatal follow up. what treatment/therapy did the children receive? Were they physically limited in their daily activities? Did they have any difficulties in learning/acquisition or more generally in school?

3 | RESULTS

3.1 | Population and characteristics

Over the study period, we reviewed files for 556 patients with fetuses diagnosed with or referred to the participating centers for TE. We excluded 159 patients with unilateral TE detected or suspected. Of the remaining 397 bilateral TE, 183 cases were excluded: 164 with other fetal ultrasound anomalies and 19 that were twin pregnancies. Our cohort therefore included a total of 214 patients with fetuses prenatally diagnosed by ultrasound with isolated TE (Figure 1).

Table 1 summarizes the patients' characteristics. Their median age was 31 years, with 57.9% nulliparous and 42.1% parous. Most patients were White (71.1%), with 24.2% of African origin. A history of isolated unilateral or bilateral TE was reported in 43 families, including 21 cases (9.8%) involving a parent and 5 cases (2.3%) with a recurrence in a sibling. The median gestational age at diagnosis was 23 weeks. The male:female ratio was 2.4:1.

3.2 | Amniocentesis

Over the study period, the centers proposed 184 amniocenteses to these women (86.0%), and 129 were performed (70.1%). Karyotyping was performed in all cases of amniocentesis, and an aCGH in 103 (79.8%). Two karyotypes were abnormal (1.6%): one case of trisomy 21 and one case of triple X syndrome. Two aCGH results showed de novo pathogenic copy number variations (1.9%): one case with a 2-Mb deletion of the short arm of chromosome 18 and one case with a 22q11.2 deletion (DiGeorge syndrome) (Table 2).

3.3 | Other investigations

Exploration for neuromuscular diseases was performed for 56 fetuses (27.6%), with results showing no pathological findings. In addition, 77 (37.7%) fetal MRI were performed systematically as part of the investigations. In five cases (6.5%, 5/77), a cerebral variation not seen on ultrasound was diagnosed (one agenesis of the olfactory bulbs, two with minimal ventriculomegaly of 10 mm, one right dacryocystocele, and a discrete enlargement of the pericerebral spaces). Three of these cases had normal chromosomal tests on prenatal testing and two had not undergone amniocentesis (Table 2).

3.4 | Perinatal outcome

Immediate postnatal outcomes were available for 169 of the 214 cases. There were 165 live births (97.6%), three terminations of pregnancy (1.8%), and one stillbirth at 18 weeks (the fetopathological examination found no specific cause of death). Among the live births, the median gestational age at delivery was 39.3 weeks. The diagnosis of bilateral TE was confirmed in 98.6% of cases. The three terminations of pregnancy were performed at parental request for trisomy 21 (one case), the 22q11.2 deletion (one case), and the chromosome 18 deletion (one case) (Table 3). The newborn with triple X syndrome was asymptomatic at the evaluation.

3.5 | Postnatal follow up

For the long-term follow up, 72 patients (34.2%) responded to calls and provided information on their children's postnatal outcome. We attempted to contact parents of all 165 live births and sent several reminders (three). Only one woman affirmatively refused to participate in the study, 16 telephone numbers were no longer in service, and 76 women did not respond (the three mothers who underwent terminations of pregnancy and the mother with a stillbirth were not contacted). Median age at follow up was 4.5 years (0.8–10 years). Foot malposition was isolated in 91.7% (66/72). Two children were diagnosed with a severe monogenetic disease: one with infantile glycine encephalopathy (MIM #617301) with a mutation in the *SLC6A9* gene and another with primary microcephaly (MIM #619179) and a mutation in the *LMNB1* gene.

Four other children had diseases discovered in postnatal life. There were two cases of hematological or vascular diseases with

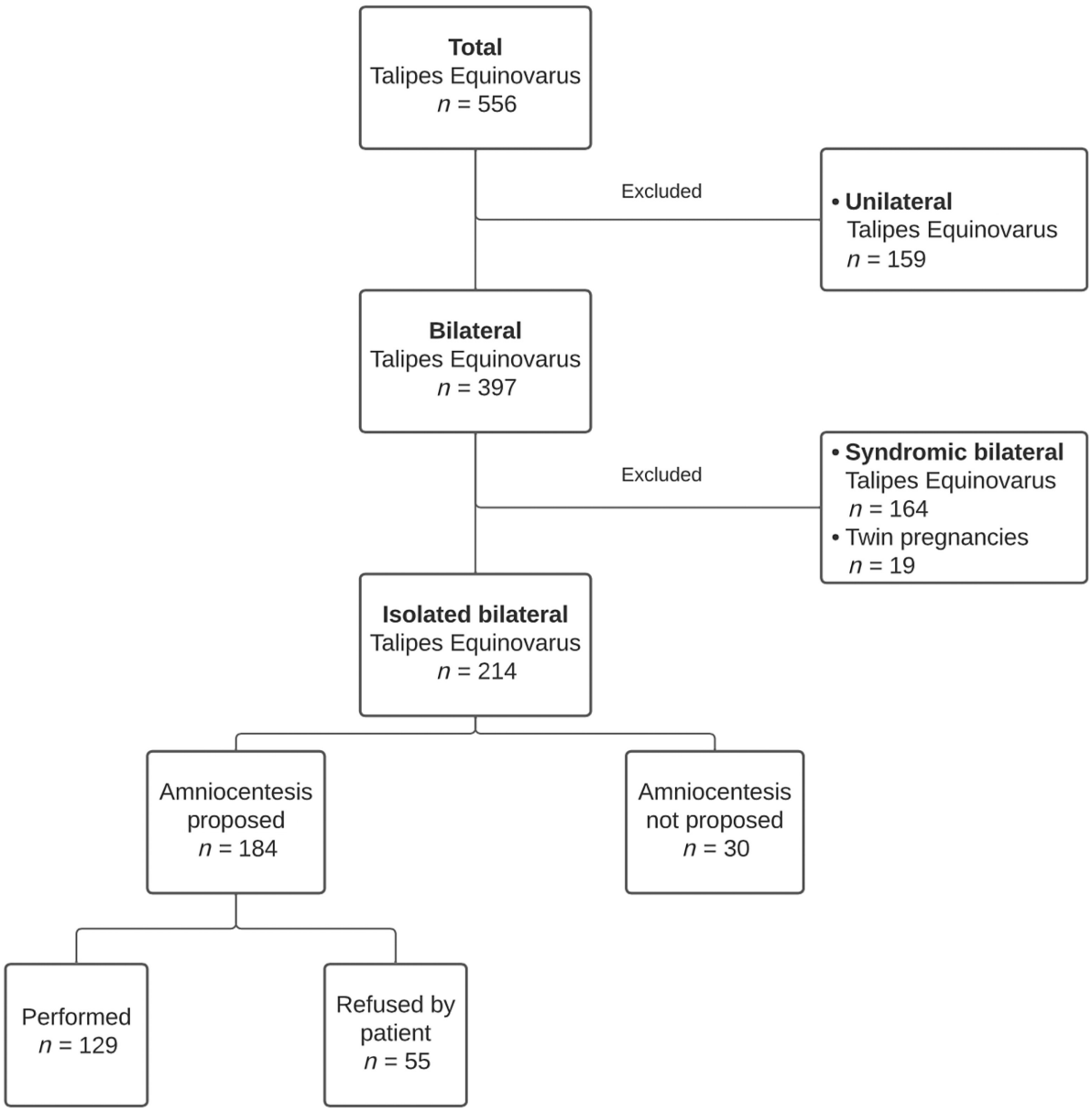

FIGURE 1 Flow chart.

no direct link to TE (one child developed an angioma on a thigh and another had von Willebrand disease). There was one case of Ehlers–Danlos syndrome (hypermobile form with no mutation identified after testing) discovered due to repeated substantial bruising, and one case of cardiac muscular septal defect that closed spontaneously.

Seventy-three children (87.5%) had functional treatment including tenotomy surgery (52.9%). Only nine children (12.9%) required more complicated surgery to correct the malposition (capsulotomies, retinaculum section, Achilles' tendon lengthening, or tendon transfer surgery). At the time of follow up (May 2022), 94.4% were walking independently, and 95.8% had psychomotor development appropriate to their age, according to the parents (Table 4).

4 | DISCUSSION

The main findings are that 86% of those diagnosed with bilateral isolated TE were offered cytogenetic testing by amniocentesis. Of these amniocenteses, 1.6% (2/129) detected karyotype abnormalities and 1.9% (2/103) found aCGH abnormalities.

Two abnormal karyotypes were reported: one trisomy 21 (47,XY +21) and one triple X syndrome (47,XXX). The association with TE is considered probably coincidental in these two conditions. First, TE is not reported to be associated with Down syndrome or Triple X syndrome in the Online Mendelian Heritance in Man (OMIM) database (MIM #190685). Second, even though studies report cases of trisomy 21[5,10,13–15] in their isolated TE cohorts, the incidence of Down syndrome and of TE being relatively

TABLE 1 Characteristics of the pregnancies with talipes equinovarus.

Population characteristics	*N* = 214
Maternal age, years, median (IQR)	31 (27–34)
Parity, *n* (%)	
Nulliparous	124 (57.9%)
Parous	90 (42.1%)
Origins, % (*n*/*N*)	
White	71.1% (106/149)
African	24.2% (36/149)
Asian	2.7% (4/149)
Other	2.0% (3/149)
Consanguinity[a]	8 (3.7%)
Pre-pregnancy body mass index, kg/m^2, median (IQR)	23.7 (21–26.3)
History of TE, *n* (%)	
Parents	21 (9.8%)
Previous pregnancy	5 (2.3%)
Family (>first degree)	24 (11.2%)
Gestational age at diagnosis (weeks), median (IQR)	23 (22–24.1)
Male:female ratio	2.4:1

Abbreviations: IQR, interquartile range; TE, talipes equinovarus.

[a]If the patient and co-parent were 2nd or 3rd degree relatives.

TABLE 2 Amniocentesis, neuromuscular, and fetal brain MRI results.

Amniocentesis	Proposed, % (*n*/*M*)	86.0% (184/214)
	Performed, % (*n*/*M*)	60.3% (129/214)
	Refused, % (*n*/*M*)	25.7% (55/214)
Gestational age at amniocentesis, weeks, median (IQR)	24.0 (22.6–26.3)	
Abnormal results	Karyotype abnormalities, % (*n*/*M*)	1.6% (2/129)
	aCGH abnormalities, % (*n*/*M*)	1.9% (2/103)
Neuromuscular explorations[a]	Performed % (*n*/*M*)	27.6% (56/203)
	Anomalies % (*n*/*M*)	0% (0/56)
Fetal cerebral MRI	Gestational age (weeks), median (IQR)	32.4 (32–33.3)
	Performed, % (*n*/*M*)	37.7% (77/204)
	Variation, % (*n*/*M*)	6.5% (5/77)

Abbreviations: aCGH, array comparative genomic hybridization; IQR, interquartile range; MRI, magnetic resonance imaging; TE, talipes equinovarus.

[a]Biochemical analyses of amniotic fluid (assays of acetylcholinesterase and α-fetoprotein) and/or various tests of parental blood samples (sequencing for Steinert disease or spinal muscular atrophy, and antibody testing for myasthenia gravis).

high, there is a strong likelihood of fortuitous association. The overall 1.6% rate of abnormal karyotypes is consistent with the results of others. The meta-analysis by Di Mascio et al.[10] reported a karyotype abnormality rate of 3.6% (95% confidence interval 1.7%–6.2%) in a population of isolated (unilateral and bilateral) TE (25 studies, 1567 fetuses), including one case of trisomy 21, one trisomy 18, four sex chromosome abnormalities, and one chromosome inversion. In a population of isolated bilateral TE, Viaris de le Segno et al. reported a 3.1% (1/32) rate of abnormal karyotypes: one sex chromosome anomaly 47,XXY.[5] In both studies, TE was part of the phenotypic spectrum only for trisomy 18, although very rarely when isolated prenatally. Several studies found no karyotype abnormalities at all in the population of newborns with isolated TE.[4,6–9] Other studies have found higher karyotype abnormality rates, while Sucu and Demir,[13] Sharma et al.,[16] and Shipp and Benacerraf[15] reported rates of respectively 11% (2/19), 6% (1/17), and 11.8% (4/34). Sucu and Demir[13] reported one case of trisomy 21 and one of 47,XXY, whereas Shipp and Benacerraf[15] found one case of trisomy 21, one trisomy 18, one 47,XXY, and finally one triple X syndrome. In the latter study, only two cases had bilateral TE and when examined in detail, there was only one truly ultrasound-isolated case (the triple X syndrome). This summary of the available data focusing on isolated bilateral TE identified by ultrasound shows likely coincidental associations and one case of trisomy 18, a condition very rarely missed prenatally.[17]

Our study also focused on aCGH results. This technique is currently widely used as a first-tier method for chromosomal analysis of amniotic fluid samples. In our cohort, 103 fetuses had aCGH (with karyotyping); that is, 26 cases did not undergo aCGH analysis, mostly before 2014 and so before aCGH entered routine use in France. Two cases (1.9%) had pathological aCGH results: one 22q11.2 deletion responsible for DiGeorge syndrome and one 2-Mb 18p deletion, both de novo copy number variations. One article reports that TE is associated with DiGeorge syndrome, estimating the TE prevalence in this disease ranges from 1.1% to 13.3% (without specifying if the condition was diagnosed prenatally or if it was isolated or complex).[18] No 18p deletion has previously been reported in the literature, to the best of our knowledge. Only a few previous studies have evaluated the contribution of aCGH to the search for an etiology of bilateral TE. Neither the meta-analysis by Di Mascio et al.[10] nor the retrospective study by Fantasia et al.[6] found any aCGH abnormalities, but they performed very few aCGH tests (two and five cases, respectively). A study in 2020 by Singer et al.[11] among 5750 pregnant patients (and 269 fetuses with ultrasound-identified isolated TE, unilateral or bilateral) showed more aCGH abnormalities in those with isolated TE than in those without ultrasound abnormalities: 3.9% vs 1.41% (relative risk 2.7, 95% confidence interval 1.4–5). Based on the rate of abnormalities detected prenatally and leading to a change in pregnancy management (terminations of pregnancy) in our study, we estimate that 43 amniocenteses are needed to reveal one significant chromosomal abnormality.

TABLE 3 Fetal and perinatal outcomes.

Outcomes	Live-born	Live born, % (*n*/*M*)	97.6% (165/169)
		Gestational age at birth, weeks, median (IQR)	39.3 (38.2–40.3)
		Weight at birth, g, median (IQR)	3210 (2893–3620)
		Confirmation of bilateral TE, % (*n*/*M*)	98.6% (139/141)[a]
		Neonatalogy/Intensive care unit, % (*n*/*M*)	11.1% (15/135)
		Neonatal death, % (*n*/*M*)	0% (0/142)
	Termination of pregnancy, % (*n*/*M*)		1.8% (3/169)
	Stillbirth, % (*n*/*M*)		0.6% (1/169)

Abbreviations: IQR, interquartile range; TE, talipes equinovarus.

[a]Two cases of fetus with normal position of the limbs at birth.

TABLE 4 Postnatal follow up.

Postnatal follow-up	Age at follow-up call in years, median [Min–Max]		4.5 [0.8–10]
	Isolated TE in postnatal form at the time of call, % (*n*/*N*)		91.7% (66/72)[a]
	Treatment	Functional, % (*n*/*N*)	33.3% (24/72)
		Tenotomy, % (*n*/*N*)	54.2% (39/72)
		More major surgery, % (*n*/*N*)	12.5% (9/72)
	Walk without handicap, % (*n*/*N*)		94.4% (68/72)
	Neurocognitive development appropriate for age,[b] % (*n*/*N*)		95.8% (69/72)

Abbreviation: TE, talipes equinovarus.

[a]Six cases of non-isolated TE: one case of Ehlers–Danlos disease, one of von Willebrand disease, one with a cardiac muscular septal defect, one with thigh hemangioma, one infantile glycine encephalopathy (mutation of the *SLC6A9* gene), and one primary microcephaly (mutation of the *LMNB1* gene).

[b]Neurocognitive development was parent-reported.

Prenatal neuromuscular investigations for TE are neither systematic nor consensual. Each center follows its own local protocol. Some measure acetylcholinesterase in the amniotic fluid to screen for spina bifida; others analyze parents for heritable neuromuscular diseases such as spinal muscular atrophy, Steinert disease, or myasthenia. No study has yet investigated the relevance and association of these prenatal conditions with TE. Neither spina bifida nor any other neuromuscular disease was found in our cohort during the prenatal period (note that the genetic research used parental blood samples, none of which showed any relevant gene mutation, no molecular genetic testing for neuromuscular disorders in the fetus was performed).

Two studies have investigated the role of fetal cerebral MRI examination. Nemec et al.[19] did not find that it provided any additional information, in particular, at the cerebral level in the group with isolated TE. Gat et al.[20] reported one case of moderate ventriculomegaly diagnosed by MRI (not identified by ultrasound) in a cohort of 14 cases of isolated TE (7.5%). These cohorts lack the power to be conclusive. The abnormalities diagnosed in our study show the value of MRI in reclassifying isolated forms into complex forms, with a less reassuring prognosis and possibly pathological genetic findings in a very few patients. However, MRI abnormalities were not associated with adverse postnatal outcome.

Our confirmation rate for isolated bilateral TE at birth is consistent with the literature.[8,9,13,15,21] The French study[5] preceding ours confirmed 100% of diagnoses at birth.

In the postnatal follow up, there were six cases for which the TE could arguably still be considered to be isolated. The child who developed an angioma on a thigh and the other with von Willebrand disease had diseases unrelated to TE. The hypermobile Ehlers-Danlos disease detected in one patient was most likely unrelated to isolated TE. This condition is not detectable prenatally, except in cases of known parental transmission. Another child had a minimal muscular septal cardiac defect (unrelated to TE) that resolved spontaneously. Finally, two children developed severe pathologies: one infantile glycine encephalopathy (mutation in the *SLC6A9* gene) and the other a primary microcephaly (mutation in the *LMNB1* gene). TE is a symptom of the phenotype in patients with mutations of the *SLC6A9* gene, but has not been described for mutations of the *LMNB1* gene. More importantly, neither can be identified by karyotyping or by aCGH analysis. Prenatal whole-exome sequencing might have detected these abnormalities.

This study presents data to support the usefulness of amniocentesis to test chromosomal abnormalities, especially aCGH, for counseling and decision making in clinical practice in cases of bilateral isolated TE detected during prenatal follow up. Amniocentesis should be offered to these couples for rapid aneuploidy testing, karyotyping, and aCGH.

The results of our study and, in particular, the discovery of two postnatal monogenetic disorders possibly related to fetal TE suggest that an evaluation of prenatal molecular genetic testing, such as whole-exome sequencing, to determine if it increases the diagnostic yield in fetuses with bilateral isolated TE, would be interesting. We have found no published data describing the performance of such sequencing after an ultrasound diagnosis of TE. It is possible that we have underestimated the rate of genetic abnormalities detected postnatally due to the lack of data for nonresponding patients.

To the best of our knowledge, this study presents the largest cohort of fetuses diagnosed prenatally with isolated bilateral tracheo-esophageal anomalies. It encompasses data collected from five referral centers specializing in prenatal diagnosis over a span of a decade. One of the notable strengths of our research lies in the elucidation provided by these aCGH results. They underscore the advantages of using amniocentesis as a valuable tool in investigating the etiology of this malformation. It is worth noting that the existing literature on this subject is limited, with only three previous studies reporting aCGH results in cases of isolated TE: Fantasia et al.[6] reported on five patients, Di Mascio et al.[10] included two patients in their meta-analysis, and Singer et al. examined 229 cases.

A limitation to our study is the fairly large number of children for whom we lack follow-up information. Another limitation is the nonobjective measurement of psychomotor delay in the follow-up questions to parents about their children. We have assumed that these children's psychomotor development was normal when parents' answers did not indicate any delay.

5 | CONCLUSION

The rate of pathogenic chromosomal abnormalities diagnosed prenatally after ultrasound diagnosis of isolated bilateral fetal TE was low and some of them concerned incidental associations. Some clinically relevant chromosomal abnormalities were detected prenatally. These data may help to improve both the information given to couples and decision making about performing amniocentesis for this indication especially as the risk of these abnormalities exceeds that of amniocentesis. The postnatal diagnosis of some monogenetic disorders possibly related to fetal TE suggests that prenatal whole-exome sequencing for this indication merits evaluation.

AUTHOR CONTRIBUTIONS

Study conception and design: EL, OA, VT, YA. Acquisition of data: EL, YA. Analysis and interpretation of data: EL, YA, OA, VT. Drafting of manuscript: EL, YA. Critical revision of manuscript: EL, OA, PJ, AJV, AB, LS, MJ, J-MJ, FD, TC, JR, EP, FG, VT, and YA.

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

ETHICS STATEMENT

These data were collected with the approval of the local institutional review board (CEROG 2022-OBS-0504, granted on June 16, 2022). Furthermore, patient consent was waived because we used retrospective data collected during routine care.

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