Abstract

Objective: To describe the long term outcomes of children at school age who were thought to have isolated idiopathic congenital talipes equino varus (ICTEV) at birth

Method: A retrospective review of all children attending a regional talipes clinic who had achieved school age.

Results: One hundred and sixty three children were followed up. ICTEV was more common in Maori and other Polynesian children and in males. Additional abnormalities were apparent in 30.1% overall, but higher in New Zealand Europeans (43%) than Maori (21%) or other Polynesians (22%). Of the abnormalities, 41% were associated with the central nervous system or with neurodevelopmental delay. Conventional G-band karyotyping, where performed, was not informative.

Conclusion: The rate of additional abnormalities was higher than previous reports. This has implications for prenatal counselling and postnatal follow up as a prenatal diagnosis of ICTEV may subsequently be found to have longer term implications in addition to orthopedic treatments of the clubfeet.

Introduction

Idiopathic congenital talipes equinovarus (ICTEV), or clubfoot, is a rigid foot deformity presenting at birth, and it is unassociated with other detectable abnormalities. It is one of the commonest congenital orthopedic problems, with a prevalence which varies with the population studied, but the condition occurs in around 1 per 1,000 live births in predominantly Caucasian populations[1]. Most talipes is thought to occur as an isolated and idiopathic congenital abnormality, hence the abbreviation ICTEV, but a small percentage are

associated with either a neuromuscular disorder or a generalized syndrome e.g. arthrogryposis, spina bifida or diastrophic dwarfism[1,2] . In the absence of other identifiable abnormalities on prenatal investigations, ICTEV is generally considered not only to be an isolated finding but also having a near normal functional outcome following correction of the foot deformity, usually with the Ponseti method which involves a series of casts followed by a tenotomy[3]and has been shown to have good short and long term functional results[4] .

In some ethnic groups, clubfoot is common and well known. For example, in New Zealand, Maori had a specific word for clubfoot; “waehape”, wae meaning foot and hape meaning crooked or broken. The high incidence of clubfoot in the New Zealand Maori has been confirmed in two previous studies which found a prevalence of 6-7 per 1000[5,6]. Similar birth prevalence has been reported in the other Polynesian (Hawaiian and Tongan) populations[7,8]. In contrast, the birth prevalence of clubfoot in the Caucasian and Chinese populations is 1-3 per 1000 and 0.57 per 1000 respectively [1,8]. There is no clear aetiology for ICTEV, though several hypotheses have been proposed namely genetic, developmental arrest, connective tissue or vascular abnormalities, and neurological, but the aetiology is generally thought to be multifactorial[9]. Congenital Talipes Equinovarus that is thought to be isolated and therefore idiopathic is frequently detected on prenatal ultrasound.

Recommendations for prenatal investigation range from detailed scanning to karyotyping[10,11]. Particularly in ethnic groups where ICTEV is common, it has been suggested

that it is generally associated with a normal outcome for the child following treatment for the orthopaedic deformity. Whilst some sources recommend karyotyping where "other" markers of aneuploidy may be present[11], it remains unclear what investigations and counselling are appropriate where no additional findings are detected on prenatal ultrasound scanning. Thus, it has been practice in the unit in this study to reassure parents that the outlook is excellent and postnatal orthopaedic assessment is all that is necessary, should no other defects be detected on the prenatal ultrasound.

Few studies have investigated the long term outcomes of children with ICTEV. The surgical outcomes in a series of 42 infants have been reported upon[12] and a series of 65 children compared prenatally diagnosed ICTEV with 1-2 year orthopaedic follow up[13]. Neither study commented on a range of other outcomes which may become manifest during childhood.

We sought to investigate the incidence of associated abnormalities and the developmental outcomes of children by the time they had reached school age in a large, mixed ethnicity New Zealand population with a prevalence of ICTEV of up to 6-7 per 1,000 live births[2] .We also reviewed the prenatal investigations and management of the index pregnancies, and considered the nature of prenatal counselling that could be offered after an ultrasound diagnosis of ICTEV had been made. Patients where other ultrasound abnormalities had been detected were excluded.

The outcomes of all children in the regional talipes clinic followed up for at least 5 years to the start of school or later were examined. All the children were thought only to have isolated idiopathic talipes equinovarus, that is, ICTEV, after birth.

Method

This was a retrospective review of all children born with ICTEV over the eight-year period 1999-2006, enrolled in the Clubfoot Clinic at the Starship Children's Hospital, Auckland, New Zealand, and who were followed up for a minimum of 5 years. This is the only clinic for the management of ICTEV for children domiciled in the Auckland and Waitemata District Health Boards of New Zealand. Over a quarter of all births in New Zealand occur in this region.

At the first clinic visit between 2 and 6 weeks after birth in addition to a clinical examination, a clubfoot severity score (Pirani score)[14,15,16] was assigned to each clubfoot. The child's ethnicity and the presence of other abnormalities were recorded and categorized. Ethnicity was defined by the standard Ministry of Health New Zealand definitions, whereby ethnicity is self-determined, with parental determination of the child's ethnic group or groups. Where more than one ethnicity was recorded, it was prioritized using the NZ Ministry of Health protocol[17].

Children with unilateral and bilateral club feet were included. All children had now reached at least school age which was 5 years. The records of all pediatric assessments (not only orthopedic) for children who subsequently had other clinical diagnoses in addition to ICTEV were reviewed and the diagnoses categorized.

The birth records were obtained, and the child's National Health Index (NHI) was used to link to the maternal NHI and all the records of the maternal index pregnancy were reviewed. It was thus possible to trace the prenatal care and ultrasound scan findings and relate these with the subsequent outcomes of the children.

All karyotyping for the region in which the children had been born and now reside in was performed by one laboratory and the maternal and pediatric NHIs were checked against the laboratory records to determine whether chromosomal analyses had been performed. During the period of the study, micro array technology was not used in these children.

The inclusion criteria for the study were that the child remained alive at 5 years, no other abnormalities were detected on a pediatric assessment at birth and that at the time of formal Pirani scoring no other anomalies were apparent. To ensure that the children did have confirmed ICTEV, all had formal Pirani scores by the senior orthopedic staff in the clinic. All cases were required to have a Pirani score of a level that excluded positional or reducible talipes and have a minimum of 4 casts to correct the deformity.

Where appropriate, groups were compared using X^2 (Excel, Microsoft Office 2013 WA USA), statistical significance set at a p-value of less than 0.05.

Ethical approval was obtained from the New Zealand Northern Regional Ethics Committee, number 2008/AEC/015

Results

There were 163 children in the study. Almost all children had a Pirani score of at least 2.5 (97.5%) and all the cases were born with unilateral or bilateral clubfeet. The ratio of male to female was 2.7:1. Children belonging to Polynesian and New Zealand Maori ethnic groups comprised 59% of the cohort,(32% being New Zealand Maori and 27% Polynesian), with

New Zealand European/Caucasian making up 37%, and other groups (Chinese and Indian) 4%. Table 1 lists the demographic details of the cases of clubfoot in the study.

Table One

Overall 73% of cases were male, 27% were female and there were no significant differences between the ethnicities in the gender ratio between male and female. Except in Maori males, unilateral ICTEV was more common that bilateral, but this difference did not reach statistical significance. Review of the antenatal records of the mothers confirmed that other abnormalities had not been suspected on ultrasound scanning but 15 women (9%) underwent amniocentesis after CTEV had been detected. In no cases was the prenatal G-Band karyotype abnormal.

In 49 children (30.1%) associated abnormalities became apparent during the first 5 years of life, and 41% of these related to the central nervous system or neuro-development. When the presence of additional abnormalities was examined by ethnicity, it was found that there were 26 affected New Zealand European children (43%), 11 Maori (21%) and 8 Polynesian (22%). The differences between New Zealand European and the Maori and/or Polynesian groups were highly significant (X^2 =0.01304, p=0.0065). There were no significant differences in the presence of additional abnormalities by the gender of the child or whether the clubfoot was unilateral or bilateral. The other ethnic groups had too few cases for comment. A list of all the abnormalities is presented in Table 2. In all the cases listed, the condition had been severe enough to require additional pediatric assessment and treatment, and had caused the child morbidity.

Table 2 lists the associated abnormalities subsequently found in the children.

Discussion

In this study of long term follow up of presumed ICTEV, we have found a high rate of additional important abnormalities which were not suspected either prenatally or at birth. Few other studies appear to have reported this. The results of this large follow up study confirm the higher incidence of TEV in Maori and Pacific compared with other ethnic groups in New Zealand. The higher rate of TEV in males is also noted. Whilst significantly many more additional abnormalities were found in the New Zealand European group, 21% of the Maori and Polynesian children also had other problems apart from the talipes.

These findings do emphasize not only the need to perform a careful search for other structural and functional abnormalities in the fetus, but raise an issue of the nature of counselling parents with regard to the long term outcome for such children as has been commented upon[10]. Most data relate to short term outcomes. In those studies, the frequency of undetected associated malformations ranges widely, possibly due to small sample sizes but one study which included 311,480 infants over a 30 year period found 142 children who had “isolated TEV”. Six children (4.2%) had other problems including hip dislocation, post axial polydactyly and hypospadias, but there was no long term follow up[18]. The few series of longer term follow up appear to have both small numbers and lower rates of adverse outcomes than we have found. A study of 87 fetuses, of whom 68 had complete records, found 3 of 61 live births (4.4%) had seizures or developmental delay but follow up

was limited to the perinatal period[19]. Other studies have focussed on the surgical orthopaedic outcomes with little mention of other morbidities[20] and a review of 28 cases of ICTEV in a series of 42 cases of CTEV had complete follow up for one year during which there did not appear to be additional abnormalities in the ICTEV group[12] .

The literature on whether amniocentesis is indicated in isolated congenital talipes equinovarus is equivocal. Benacerraf et al[21] discussed 5 patients out of whom, 4 had associated ultrasound findings and suggested that as clubfoot deformities may be associated with unbalanced chromosomal rearrangements, amniocentesis should be offered. Malone FD et al[22], retrospectively reviewed 51 cases over a 5 year period and concluded that in isolated unilateral or bilateral clubfoot following a tertiary ultrasound scan there is no indication for invasive testing. Lauson[13] also found no increased risk of aneuploidy among patients with isolated congenital talipes equinovarus. However, that review noted that the literature suggested a risk of sex chromosome aneuploidy associated with talipes to be 1.6-3.5%[12,19,23]. A study of over 49,000 deliveries over an 18 year period in Norway found a prevalence of abnormal karyotype of 1.1/1,000 in isolated TEV[23] . A study of 174 cases of whom 83 were isolated found only 1 abnormal karyotype in the 17 amniocenteses performed, though in the complex group 17 of 57 amniocenteses were abnormal[24] .

Amniocentesis had been offered in 41% of our patients out of whom 27% declined and of those who had testing (13%) all had a normal G-Band karyotype. It would seem therefore that in the absence of another ultrasound abnormalities, that G-band karyotyping in cases of unilateral or bilateral TEV is unlikely to detect a chromosomal abnormality.

It is apparent from our studies and others which include short and longer term follow up, that ICTEV may be associated with abnormalities not apparent prenatally or at birth. Lauson et al[13] showed a 10% risk of abnormalities noted in the postnatal period including neurological problems. In our study, by school age it was over 20% in Maori-Polynesian and over 30% in New Zealand Europeans. The epidemiological case control study over a period of 18 years from Norway[23] showed that 17% (10/58) cases of antenatally diagnosed unilateral or bilateral ICTEV were subsequently found to have additional abnormalities. In that study, there was a significant improvement in overall ultrasound detection of TEV (and associated anomalies) from 43% in 1987 to 77% in 2004. Our study would have been comparable with the latter period of the Norwegian study. All our cases were scanned in a tertiary unit by senior experienced sonographers.

The genetics and inheritance of ICTEV is complex with a range of factors being implicated including impacts of ethnicity[25,26]. The findings of the potential association of a deletion in the chromosomal region 2q31-33, containing candidate genes which are regulators of apoptosis in white and Hispanic subjects, provides a basis to consider such genes in the etiology of talipes[27]. This would be pertinent as data from Chapman et al suggested in New Zealand Maori that the best genetic model was a single dominant gene with 33% penetrance and a predicted gene frequency of 0.9%[7] . To date, molecular studies in Maori or Polynesian populations have not been undertaken to further elucidate this.

The strengths of this study are that the data are from one large regional clinic with consistent senior staffing and standardised management over a long period of time. All children born with talipes from a large catchment area are seen in the one clinic. Being based in the largest children's hospital in the country ensures ready access to a full range of

pediatric assessment as needed for each subject in the study. Thus full ascertainment of additional problems is readily achievable and the clinical details readily accessible for review.

Limitations of this review are that it is not a case controlled study, however, it does describe the natural history of children with ICTEV who survive to school age and beyond. As this is a regional service covering a large geographical area, few children are lost to follow up. Children who may have died before the age of 5 years have not been included, but if they died of complications of additional abnormalities our data would represent an underestimation of risk unless they died of accidents, trauma or infection. Categorisation of ethnicity is self-declared and whilst this cannot be verified, the concordance between the self-declared maternal and child ethnicity would suggest internal consistency and is the statutory process required to be used in New Zealand[15].

Our study is important because it demonstrates that in apparently ICTEV, there is an increased chance of additional abnormalities or morbidities for the child by school age. These problems are not likely to be elucidated by conventional karyotyping. Some of the additional abnormalities may be associated with talipes whilst others may be independent. For example, cerebral palsy is a neurological problem which is not usually manifest at birth and hence the diagnosis of ICTEV becomes incorrect as time passes. Osgood Schlatter's disease maybe associated with the etiology of ICTEV or maybe a consequence of the abnormal gait in talipes. Although the risk of additional problems is higher in Europeans, talipes, though commoner in Maori and other Polynesians, is not necessarily benign. Parental counselling should include these issues. Prenatal orthopaedic counselling may also be difficult as determining the severity and need for postnatal treatment is imprecise. A

small study of 14 cases detected prenatally showed that no cases were completely normal at birth, thus there were no true false-positives but a third of cases required no active treatment[10] .

Conclusions.

Long term follow up of children with apparently isolated CTEV at birth is needed as there is a high incidence of additional abnormalities.

Parental counselling needs to include information about the possibility that other abnormalities may become manifest over time. Currently, given the uncertain nature of the genetics of ICTEV, conventional karyotyping or gene studies are not likely to be contributory to prognosis or management of this condition.

Consideration needs to be given to having all children with presumed ICTEV examined by a paediatrician in addition to the orthopedic assessments performed as part of planning corrective treatment for the foot deformity.

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References:

1. Werler MM, Yazdy MM, Mitchell AA et al.. Descriptive Epidemiology of Idiopathic Clubfoot. Am J Med Genet A. 2013 ; 161: 1569–1578

2. Wynne Davies R, Littlejohn A, Gormley J. Aetiology and interrelationship of some common skeletal deformities. J Med Genet 1982;19:321-28

3. Ponseti IV. Treatment of congenital club foot. J Bone Joint Surg Am. 1992; 74:448–454

4. Pavone V, Testa G, Costarella L, Pavone P, Sessa G. Congenital idiopathic talipes equinovarus: an evaluation in infants treated by the Ponseti method. Eur Rev Med Pharmacol Sci. 2013; 17:2675-2679.

5. Beals RK. Club foot in the Maori: a genetic study of 50 kindreds. NZ Med J 1978;88:144-6.

6 Cartlidge IJ. Club foot in the Polynesian: an epidemiological survey NZMedJ 1983;96:515-7

7. Chapman C, Stott NS, Port RV, Nicol RO. Genetics of club foot in Maori and Pacific people. J Med Genet 2000;37:680–683

8. Chung CS, Nemechek RW, Larsen IJ, ChingGH. Genetic and epidemiological studies of clubfoot in Hawaii. General and medical considerations. Hum Hered 1969:19:321-42

9. Barker S, Chesney D, Miedzybrodzka Z, Maffulli N. Genetics and Epidemiology of Idiopathic Congenital Talipes Equinovarus. J Pediatr Orthopedics. 2003;23:265-272

10. Tillett, R L. Fisk, N M. Murphy, K. Hunt, D M. Clinical outcome of congenital talipes equinovarus diagnosed antenatally by ultrasound. J Bone Joint Surgery 2000;82:876-80,

11. Griffin DR, Chitty LS. Fetal Skeletal Abnormalities in High Risk Pregnancy Management Options 4th ed eds James DK, Steer PJ, Weiner CP, Gonik B, Crowther CA, Robson SC. Elsevier Saunders, StLouis MO. ISBN 978-1-4160-5908-0 pp363-364

12. Canto MJ, Cano S, Palau J, Ojeda F. Prenatal diagnosis of clubfoot in low-risk population: associated anomalies and long-term outcome. Prenat Diagn 2008;28:343-346

13. Lauson S, Alvarez C, Patel MS, Langlois S. 2010. Outcome of prenatally diagnosed isolated clubfoot. Ultrasound Obstet Gynecol 35: 708–714

14. Flynn JM, Donohue MPT, Mackenzie WG. An Independent Assessment of Two Clubfoot-Classification Systems. J Pediat.Orthopaedics. 1998;18:323-

15. Dyer PJ, Davis N. The role of the Pirani scoring system in the management of club foot by the Ponseti method. J Bone Joint Surg Br. 2006;88:1082-4

16 David BH, Olayinka O A, Oluwadare E, Ayodele OE, Joseph O M, Olujide A. Predictive value of Pirani scoring system for tenotomy in the management of idiopathic clubfoot. J Orthop Surg (Hong Kong). 2017; 25:536-545.

17. http://www.stats.govt.nz/surveys_and_methods/methods/classifications-and-standards/classification-related-stats-standards/ethnicity.aspx

18. Toufaily MH, Westgate M-N, Holmes LB. Congenital talipes equinovarus: frequency of associated malformations not identified by prenatal ultrasound. Prenat Diag. 2015;35: 254-257

19. Shipp TD, Benacerraf BR. The significance of prenatally identified isolated clubfoot: is amniocentesis indicated? Am J Obstet Gynecol. 1998 ;178:600-602.

20. Sobel E, Giorgini RJ, Michel R, Cohen SI. The natural history and longitudinal study of the surgically corrected clubfoot. J Foot Ankle Surg. 2000;39:305-320.

21. Benacerraf BR, Frigoletto FD. Prenatal Ultrasound diagnosis of Clubfoot. Radiol. 1985;155:211-213.

22. Malone FD, Marino T, Bianchi DWet al. Isolated clubfoot diagnosed prenatally: is karyotyping indicated? Obstet Gynecol. 2000;95(3):437-40.

23. Offerdal K, Jebens N, Blaas HGK, Eik-Nes SH. Prenatal ultrasound detection of talipes equinovarus in a non-selected population of 49 314 deliveries in Norway. Ultrasound Obstet Gynecol 2007; 30: 838–844.

24. Sharma R, Stone S, Alzouebi A. et al. Perinatal outcome of prenatally diagnosed congenital talipes equinovarus. Prenat Diagn 2011; 31: 142–145.

25. Wang JH, Palmer RM, Chung CS. The role of major gene in clubfoot. Am J Hum Genet 1988;42:772-776.

304 26. Yang HY, Chung CS, Nemechek RW. A genetic analysis of clubfoot in Hawaii. Genet
305 Epidemiol 1987;4:299-306.

306 27. Heck AL, Bray MS, Scott A.et al Variation in CASP10 Gene Is Associated With
307 Idiopathic Talipes Equinovarus. J Pediatr Orthop 2005;25:598–602.