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Original Research Article

Evaluation of Epidemiological and Genetic Risk Factors Associated with Idiopathic Congenital Talipes Equinovarus in the South Indian Population

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ABSTRACT

Background: The heterogeneity between studies in reported risk factors for Congenital Talipes Equinovarus (CTEV) may be due to many factors including definitions of CTEV, whether non-idiopathic cases are included, differences in study design, and chance as some series are relatively small. This study was aimed to evaluate epidemiological and genetic risk factors associated with Idiopathic Congenital Talipes Equinovarus (ICTEV) in a south Indian Population.

Methods: A prospective case parental control design - epidemiological data was collected in the form of factors associated with mother like age at index pregnancy, education, reproductive history, smoking history. Similarly for father we studied factors like age, education, alcohol intake and genetic risk factors mainly *MTHFR C677C>T* Gene polymorphism. Clinically severity graded by dimeglio scoring system and classified accordingly.

Results: Total 145 Case Parent triads were evaluated over a period of three years duration. Around 74 percent of ICTEV cases were males with positive family history. Positive association is found with first pregnancy, C – section, bilaterality, mother's education, father's alcohol intake during index pregnancy. There was negative association with increasing number of mutant T allele and severity of disease.

Conclusions: Our study is first study to show MTHFR C677C>T gene polymorphism and its protective role in ICTEV in an Indian population and also given an epidemiological picture of a large series of children in south India. There is a need of increasing awareness of folic acid use during index pregnancy and fortification of food with folic acid in national level programmes.

Keywords: ICTEV, genetic, folic acid, pregnancy

INTRODUCTION

Congenital Talipes Equinovarus (CTEV) often known as 'Club Foot' is a commonly studied developmental disorder of lower limb. Congenital Talipes Equinovarus is termed non idiopathic when it occurs in association with other features as part of a genetic syndrome, or it can occur in isolation in which case it may be termed as idiopathic. Non idiopathic CTEV arises in many neurological and neuromuscular disorders, e.g. spina bifida or spinal muscular atrophy, but idiopathic form is by far most common.

Birth prevalence of CTEV varies by race/ethnicity with low rates (about 0.6 per 1,000 live births) among Asians and high rates (more than 6 per 1000 live births) among Pacific Icelanders.[1,2] CTEV affected about twice as many males as females.[2-4] About half of infants with CTEV have B/L involvement, and

some studies have reported that the right leg is more commonly involved than left.[3,5] There is also variation by sex, rank of pregnancy, birth weight, type of delivery, gestational age, maternal and paternal age[3], and seasonal variation.[6]

The aetiology of condition has been little studied and is poorly understood. Neurological, muscular, bony, connective tissue and vascular mechanism have been proposed but only firm evidence is that mildest cases appear to be associated with intrauterine posture.[7] There is an evidence for genetic aetiology of idiopathic CTEV and is provided by the observation that concordance among monozygotic twins is greater than that of dizygotic twin.[8] Parent to child transmission of idiopathic CTEV has been noted in 20-50% of pedigrees of families with multiple affected members suggesting a potential genetic mechanism.[3,7] Effects of ethnicity on prevalence also suggest a genetic basic.[1] Although the exact genetic mechanism of CTEV has not yet been determined a multi factorial and possibly polygenic causation has been suggested.

Linda Sharp et al in her case-parent-triad study on CTEV in United Kingdom first time shown specific polymorphism associated with CTEV. Children carrying the Variant C677C>T allele of Methylenetetrahydrofolate reductase was associated with significantly reduced risk of isolated CTEV and risk decreases with increasing number of variant alleles. This association was not affected by whether the mother took supplemental folic acid in the preconception period.[9]

To the best of our knowledge no similar study has been done on Indian population regarding the epidemiology and genetic risk factors associated with Idiopathic CTEV, so the study was planned.

MATERIALS AND METHODS

The recent study was done in the Department of Orthopaedics, SDM College of Medical Sciences & Hospital, Dharwad, Karnataka, India in collaboration with Department of Pharmacology from September 2020 to August 2023, after Institutional Ethics Committee approval**.** The study recruited all new CTEV patients and their parents presenting to OPD, orthopaedics department during the reference period. Patients were subjected to inclusion and exclusion criteria and were selected in the study sample. The study was designed as an epidemiological descriptive case series and case-parent triad linkage genetic study on South Indian population.

The patient with idiopathic CTEV and their parents who fulfil the pre-defined inclusion and exclusion criteria were enrolled for the study. Inclusion criteria was all fresh cases of idiopathic CTEV and their parents presenting to department of orthopaedics. Once patient agreed to participate in the study, the patient and the witness were asked to sign the written informed consent form. For all patients and their parents a detailed history about parameters under study was obtained. Patients were examined to confirm idiopathic CTEV and non idiopathic CTEV cases were excluded by clinical examination and appropriate medical test.

Blood sample were collected for genetic study from cases and both parents as a control. 5 ml venous blood was collected in polypropylene tubes containing 100 µL of 10% sodium EDTA (ethylene diamine tetra acetic acid) as anticoagulant. The date and time of blood collection was noted. The tube was marked with unique patient identification number. Sample was centrifuged at 2500 rpm (revolutions per minute) for 10 minutes at 4^{o}C. The supernatant plasma was stored in a separate tube, while the cellular sediment was stored in deep freezer at -80^{o}C till further processing for DNA extraction.

Genotyping for *MTHFR 677C>T* allele was carried out in following steps:

1. DNA extraction from cellular sediments by phenol-chloroform method.
2. Quality checking and quantification by biophotometer.
3. Allelic discrimination of *MTHFR 677C>T* polymorphism by Real-Time Polymerase Chain Reaction (RT-PCR).

For disease severity we used Classification given by Dimeglio et al. Classification divides CTEV in four grades but as the number of very severe cases was

small, for analysis we added severe and very severe cases together.

The above mentioned data was collected; continuous data was depicted as mean with standard deviation, categorical data as frequencies or percentages. Statistical analyses were performed using SPSS version 16.0 and GraphPad InStat version 3.06 software packages. To compare the categorical data Chi square test was used. To assess the relationship between variables parametric/non parametric correlational analysis was done. Regarding the factors associated with outcome, initially univariate analysis was done. All statistical analysis was carried out at 5% level of significance and $p<0.05$ was considered as significant.

For genetic part of study the Pearson chi square test was used to determine whether genotype frequencies in mothers, fathers, and children were in Hardy-Weinberg equilibrium. Log-linear methods were used to calculate relative risks associated with maternal and child alleles. These methods test for asymmetric distribution of the variant allele among affected offspring and their parents.

The genotypes of cases and parents were stratified into possible mating types, from which the relative risks for the child's and the mother's genotypes were computed by fitting a Poisson model. The initial analysis estimated separate relative risks for heterozygous (CT) and homozygous (TT) variant genotypes in both children and mothers, using homozygous wild-type (CC) as the reference category.

Trend tests were applied to assess whether there was a ''dose-response'' pattern in risk with increasing number of variant alleles. Because it is not clear what model of inheritance might be postulated a priori, this analysis was repeated by assuming both dominant (i.e., CT/TT vs. CC) and recessive (i.e., TT vs. CC/CT) transmission. The statistical models can be fitted with or without an assumption of Hardy-Weinberg equilibrium. The goodness of fit of both sets of models was compared; those without the assumption of Hardy-Weinberg equilibrium provided the better fit and were used in all analyses.

RESULTS

In current study the age of mothers at the birth of the index child was between 18 to 35 yrs, there were no mothers whose age was less than 18 or more than 35 years at the time of index pregnancy. Thirty six percent cases mothers had education more than SSLC (college education), 48% less than SSLC and 16% not studied at all.

Around half of mothers were primi gravida. 1/3 of mothers were gravid two and 1/6 of mothers were gravid three. At some time in her reproductive history, 14 % of cases mother had at least one abortion or still birth or intrauterine foetal death.

Forty percent of mother reported using nutritional supplements containing folic acid in the first three months (first trimester) of index pregnancy and 27% reported using after three month of confinement. Remaining 33% didn't take folic acid at all. Only around five percent of mothers had history of oligohydraminos during index pregnancy, most of these were detected during last trimester of pregnancy. Incidence of amniocentesis was very less with only 1.4% (n=2) of cases, mother had undergone amniocentesis late in first trimester. (Table 1)

The age of fathers was between 18 to 35 years for 85% of cases but for 15% of cases it was above 35 years. There were no fathers whose age was below 18 years at the time on index pregnancy. Thirty six percent of cases fathers had education more than SSLC (college education), 42% less than SSLC and 21% not studied at all. Around 30% of cases father reported smoking during the index pregnancy, no mother reported to smoke during index pregnancy. 35% cases fathers reported drinking alcohol during the index pregnancy, but no mother had same.

Around 74 percent of cases were males and remaining were females. The ratio of males to females was 3:1. Fifty one percent had bilateral ICTEV (69% of males; 41% of females). Of the unilateral cases, more had right foot involvement than left (2:1). Both females and males who were affected unilaterally were more than twice as likely to be affected on the right as the left, the difference was not

statistically significant. Twenty percent of cases were benign in severity while 52% cases were moderate in severity and 28% of cases were severe to very severe. Eighty nine percent of cases were mature and 11% were premature birth. In ninety five percent of cases birth weight was more than 2 kg, in only 5% of patient it was below 2 kg. The index pregnancy was the first for 45.5% of cases, second for 34.5% cases, third 16.6% cases and for 1.4% each for 4^{th} and 5^{th}. The index pregnancy was no more than sixth in ranking.

Eighty three percent of ICTEV deliveries were vaginal with cephalic presentation, 2% were vaginal with breech presentation and 16% were caesarean section deliveries. Around ninety six percent deliveries were singleton, only three percent (n=4) were twins deliveries. Seventy-three percent cases were born out of non consanguineous marriages; around 26% of cases were born out of consanguineous marriages out of which 19% by second degree consanguinity and 7% by third degree consanguinity.

A pedigree was available for all families. Only 4% of cases families reported a family history of CTEV; 3.5% percent of cases reported to have first degree family history in which 2 cases were having father affected with ICTEV, only one case having mother affected and two were with siblings affected. 0.6 %(n=1) case had a 2^{nd} degree cousin affected. There were no trios in which both a parent and a sibling were affected. No families had three or more cases of ICTEV in the family, the mode of inheritance were uncertain in all the pedigree. There was no association between sex of index child and mother or father involved or between sexes of siblings as well as cousins sex.

Male index cases were more likely to have a family history than female index cases; 4% of males (n = 6) and no female index case (n = 0) had a 1st–3rd degree family history. 3.5% percent of males (n = 5) and no female index case had a 1st degree family history, and 0.6% of males (n = 1) and no female index case had a 2nd degree cousin history. None of these differences reached statistical significance. Month of birth was highest (15.2%) for January and followed by February, July, December and June (10% to 11%). It was around 4% to 5% for remaining month of year.

While analysing severity of disease with rank of pregnancy, first pregnancy was associated with increasing severity of disease but there was no association with second or third and so on. There were no statically significant associations between severity and oligohydraminos or amniocentesis. (Table 1)

While correlating severity of disease with father associated variables there was statically significant association present between increasing severity of disease and alcohol intake but with smoking it was not statistically significant. Also there was suggestion of statically significant associations between increasing severity of disease and father's education more than SSLC but there was no statically significant association with father's age.

While correlating child related variables with mother's folic acid intake; male sex, birth weight less than 2 kg and left sidedness were associated with increase in intake of folic acid during first 3 month of pregnancy. There were no statically significant association between folic acid intake during first 3 months of pregnancy and child gestational age, bilateral or right sided ICTEV and severity of disease. (Table 2)

While correlating severity of disease with child related variables there was suggestion of statically significant association between increasing severity of disease and incidence of bilateral ICTEV in cases but not with unilateral or right and left foot involved. There were positive association between prematurity and caesarean section and increasing severity of ICTEV. But there were no statically significant association between child sex, birth weight, rank of pregnancy, normal or breach delivery and consanguinity.

There were four twins and one triplets pregnancies amongst the cases (3.4% of all pregnancies), all of which were reported to be identical including triplet. One of the non index twins had ICTEV. There was suggestion of statically significant association present between twins and breach delivery. There was no

association present between twins and normal or caesarean delivery. Almost equal number of cases fathers taken alcohol or smoke during index pregnancy when index cases was male or female.

There was difference in mother's folic acid intake during index pregnancy when compared for male or female index child but the difference was not significant.

Table 1: Correlation of epidemiological and genetic variables of mother with severity of disease

Variables	Severity of disease			P value
	Mild/ Benign (n=29)	Moderate (n=76)	Severe and very severe (n=40)	
Age in years				
<18	-	-	-	1.000
18-35	29(100%)	76(100%)	40(100%)	
>35	-	-	-	
Education				
No	7(24.1%)	9(11.8%)	8(20%)	0.298
<SSLC	10(34.5%)	39(51.3%)	21(52.5%)	
>SSLC	12(41.4%)	29(38.2%)	11(27.5%)	
Abortion/Still Birth				
No	25(86.2%)	64(84.2%)	35(87.5%)	0.984
Yes	4(13.8%)	10(13.2%)	5(12.5%)	
Reproductive history(gravid)				
1	15(51.7%)	37(48.7%)	12(30%)	0.284
2	10(34.5%)	24(31.6%)	17(42.5%)	
3	2(6.9%)	14(18.4%)	11(27.5%)	
4	2(6.9%)	1(1.3%)	0(0%)	
5	0(0%)	0(0%)	0(0%)	
Antenatal history				
Oligohydraminos	0(0%)	5(6.6%)	2(5%)	0.371
Amniocentesis	0(0%)	2(2.6%)	0(0%)	0.709

Table 2: Correlation of folic acid intake with child variables like sex, birth weight, laterality, severity and gestational age.

Variables	Folic acid intake			P value
	Not taken (n=48)	After pregnancy before 3rd month (n=58)	After Pregnancy after 3 months (n=39)	
Gender of child				
Male	39(81.3%)	39(67.2%)	29(74.4%)	0.263
Female	9(18.8%)	19(32.8%)	10(25.6%)	
Birth weight(kg)				
<2 kg	2(4.2%)	4(6.9%)	1(2.6%)	0.706
>2 kg	46(95.8%)	54(93.1%)	38(97.4%)	
Laterality				
Right	17(35.4%)	20(34.5%)	11(28.2%)	0.745
Left	9(18.8%)	6(10.3%)	6(15.4%)	0.459
Bilateral	21(43.8%)	31(53.4%)	22(56.4%)	0.448
Severity				
Mild /Benign	6(12.5%)	12(20.7%)	11(28.2%)	0.188
Moderate	27(56.3%)	30(51.7%)	20(51.3%)	0.866
Severe and very severe	16(33.3%)	16(27.6%)	8(20.5%)	0.413
Gestational Age				
Premature	6(12.5%)	5(8.6%)	6(15.4%)	0.585
Mature	42(87.5%)	53(91.4%)	34(87.2%)	

Table 3: The genotype and allele frequencies for MTHFR 677C>T polymorphism.

C677C>T polymorphism	Number of subjects (n=45)	%
MOTHER		
CC	38	84.4
CT	6	13.3
TT	1	2.2
FATHER		
CC	41	91.1
CT	4	8.9
TT	0	0.0
CHILD		
CC	41	91.1
CT	4	8.9
TT	0	0.0

Table 4: Observed and expected frequency of C677C>T polymorphism in father, mother and child

C677C>T			Observed frequency (n=45)		Expected frequency (n=45)	
FATHER	**MOTHER**	**CHILD**	**No**	**%**	**No**	**%**
CC	CC	CC	33	73.3	33.5	74.4
CC	CC	CT	3	6.7	3.5	7.7
CC	CT	CC	2	4.4	2.5	5.6
CT	CC	CC	5	11.1	5.5	12.2
CT	CT	CC	1	2.2	0.5	1.1
TT	CT	CT	1	2.2	0.5	1.1

Table 5: Correlation of MTHFR C677C>T genotype between Child and mother

Variables	MOTHER C677C>T			P value
	CC (n=38)	CT (n=6)	TT (n=1)	
CHILD				
CC	35(92.1%)	6(100.0%)	0	0.094+
CT	3(7.9%)	0	1(100.0%)	
TT	0	0	0	

Table 6: Log-Linear model analysis of C677C>T polymorphism

Effect (C677C>T)	Polymorphism	Estimate	SE	P value	95%CI
father*mother*child	CC	-0.092	0.394	0.815	-0.86-0.68
	CT	0.071	0.447	0.874	-0.81-0.95
father*mother	CC	0.74	0.394	0.060+	-0.03-1.51
	CT	-0.07	0.447	0.875	-0.95-0.81
father*child	CC	0.445	0.394	0.259	-0.33-1.22
	CT	0.352	0.447	0.431	-0.52-1.23
Mother*child	CC	0.254	0.314	0.419	-0.39-0.67
Father	CC	0.91	0.394	0.021*	0.14-1.66
	CT	-0.15	0.447	0.728	-1.03-0.72
Mother	CC	0.395	0.314	0.209	-0.22-1.01
Child	CC	0.522	0.314	0.097+	-0.09-1.14

Table 7: Correlation of C677C>T polymorphism with strata of disease severity

Variables	Severity of disease			P value
	Mild/Benign (n=9)	Moderate (n=21)	Severe and vey severe (n=15)	
MOTHER				
CC	9(100%)	17(81%)	12(80%)	0.659
CT	0(0%)	3(14.3%)	3(20%)	
TT	0(0%)	1(4.8%)	0(0%)	
FATHER				
CC	9(100%)	18(85.7%)	14(93.3%)	0.662
CT	0(0%)	3(14.3%)	1(6.7%)	
TT	0(0%)	0(0%)	0(0%)	
CHILD				
CC	8(88.9%)	19(90.5%)	14(93.3%)	1.000
CT	1(11.1%)	2(9.5%)	1(6.7%)	
TT	0(0%)	0(0%)	0(0%)	

Allele and genotype frequencies of study participants

Frequencies of wild and mutant genotypes (observed and expected) given in Table 4 shows observed frequency are almost equal which shows that genotype frequencies are in Hardy-Weinberg equilibrium.

There were positive trend towards reduced risk of ICTEV for children, with heterozygotes (CT) compared with CC individuals. There was no strong association between maternal genotype and risk of ICTEV in the offspring. Compared with offspring of CC mothers, offspring of CT mothers had a slight, non significant, decreased risk of ICTEV. (Table 5)

The Table 6 shows the results of the log-linear analysis of maternal and child genotypes. Polymorphism of C677C>T log-linear models with effect like child (CC), Father (CC) and Father/Mother interaction (CC) is statistically significant and as T allele decrease there is increased risk of ICTEV. When the analysis was repeated by assuming either dominant or recessive models no association was found. We were not able to analyse the effects of genotype stratified by maternal folic acid use in either time period due to small sample of child parent triad with one or two copies of T allele. In current study no mother reported consuming alcoholic at some point during the index pregnancy. So we were not able to analyse interaction between maternal alcohol consumption and child's genotype.

While comparing child's genotype with severity of disease there was positive trend between child genotype CT/TT and decreasing severity of disease but was not statically significant. There was no such trend between mother or father's genotype and severity of disease in children. (Table 7)

DISCUSSION

Most of recent studies have shown increasing incidence of CTEV.[1,2,6] The pertinent question is then: Why do we have an increase in the incidence of CTEV? Since the aetiology of CTEV is still unknown, explanations for the increased incidence are necessarily speculative. There are two main possible hypotheses: either change in the genetic material of the population or change in the environment.

In current study three percent of cases were twin births. The rate of twinning in our cases was significantly lower than Cardy et al[10] study and was higher than the Scottish rate for 1996–2000 of 1.4%. Uterine restriction is the earliest known hypothesis proposed to account for CTEV, with references dating back to Hippocrates in the 5th century BC. We also found a positive association between risk of ICTEV and the rank of the index pregnancy (first and second pregnancies associated with more with occurrence of CTEV); if it is assumed that the primary gravid uterus is more restrictive than a multi gravid uterus, uterine restriction is a major factor in our series. Increased intrauterine compression was originally implicated as a risk factor [5,7,9] but recent evidence does not appear to favour this hypothesis.[11,12]

Early amniocentesis (in the thirteenth week of gestation) has been demonstrated to increase the risk of talipes equinovarus compared to chorionic villus sampling performed at the same gestational time.[9] Hoffa suggested deformity arises from oligohydramnios sequence, i.e. believing that reduced amniotic fluid volume is itself a cause. Current study consisted of population of cases whose fathers were having predominantly agriculture as their occupation, very less cases fathers were having occupation like fishing or working in hotel. Almost all cases mothers were housewife. So we didn't consider occupation as a study variable in current study.

As the distribution of cases are not uniform among different months of year and increase doesn't coincide with fall and summer season, geographic area and our study population is consisting predominantly of low socioeconomic group and area under study is rural population and not densely populated so our study finding doesn't support pollutant or enterovirus infection as a etiological agent of CTEV.

Maternal smoking has been implicated as a risk factor for CTEV. In Cardy et al[10] study more cases than control mothers smoked during pregnancy (34% vs. 27%), although the difference was not statistically significant. Cardy et al[10] also observed a stronger effect of maternal smoking in girls than boys; but in current study there were no mother who smoked during pregnancy as it is very uncommon to Indian population except some tribes. In our study there was association between severity and paternal smoking. If family history is considered a marker of genetic involvement, this relationship may indicate an interaction between smoking and an as yet unknown gene or genes, although it is unclear why the relationship should be with paternal rather than maternal smoking. One quarter of cases were born out of consanguineous marriage out of which majority were marriage between uncle and niece. Around three fourth of children born out of non consanguineous marriage and 1/4th by consanguineous marriage predominantly second degree as in our study population and geographical area under study there is custom of marriage between niece and maternal uncle.

Most recent studies have shown that more cases of ICTEV are delivered by the breech and caesarean deliveries as compared to controls; nevertheless, the vast majority of cases have a normal vaginal delivery with cephalic presentation (are born head first).[2,10] In current study Eighty three percent of ICTEV deliveries were vaginal with cephalic presentation, 2% were vaginal with breech presentation and 16% were caesarean. There were positive association between caesarean section and increasing severity of CTEV.

The association with folic acid supplement use may be a chance finding, or may suggest that the initiation of ICTEV is earlier than previously thought. That folic acid may play a role in the development of CTEV is also indicated by a small decrease in the birth prevalence of ICTEV in Texas, United States, after the introduction of folic acid fortification of grains, although the decrease was not statistically significant [13]

As in current study a significant number of mothers have not taken folic acid supplementation during index pregnancy and severity of disease increases with decrease in folic acid intake, it indicates a possible role of folic acid in causation of CTEV, but to confirm our finding it should be compared with normal population intake of folic acid in our geographical area of study.

Although MTHFR has been investigated in several congenital malformations including a single study in ICTEV by Linda Sharp et al[14], to our knowledge this is the first study of genetic variation in folate metabolism in idiopathic CTEV in an Indian population. For children, carrying the variant 677T allele was associated with a significantly reduced risk of idiopathic CTEV.

Main strength of current study is the case-parental-control design and a prospective study, which is efficient and has greater power than the case unrelated control approach for investigating associations between polymorphic genes and disease. Moreover, it avoids the possibility of population stratification (i.e., that case-control differences are due to selection of controls whose genetic background differs systematically from that of cases). Confounding occurs if the child's genotype is measured when the mother's genotype was actually the relevant one. To avoid this problem, we used the log-linear approach developed by Wilcox et al. and Weinberg et al. , which permits investigation of the independent effects of both maternal and child genotypes.

It is well established that alcohol interferes with folate absorption and utilization, and this knowledge provided the rationale for investigating interactions between maternal alcohol consumption and maternal and child genotype. Although in current study we didn't have mother with alcohol intake during index pregnancy, but study by Linda sharp had shown a borderline significant interaction between maternal alcohol consumption and maternal genotype, interestingly, this interaction was in the same direction as the maternal genotype–folic acid association (i.e., the risk reduction associated with the T allele was observed among only those mothers who reported drinking alcohol).

Alternatively, their result may reflect an interrelation between alcohol, folate, and folate-metabolizing genes. They showed that when they repeated analysis of maternal genotype–folic acid by stratifying on maternal alcohol consumption, the genotype–folic acid association was observed for only that group who reported drinking alcohol.

Our observation of a reduced risk of clubfoot in children with the variant T allele is similar to previous study by Linda sharp[14] and study finding is important particularly in view of the fact that the T allele is associated with reduced enzyme activity.

The decreased risk of ICTEV with the ‘‘low-activity’’ T allele suggests that this Pathway could be relevant in clubfoot development, such that the presence of the MTHFR T allele in the fetus provides increased levels of circulating methylenetetrahydrofolate, thus maintaining (or raising) DNA repair capacity and protecting against ICTEV.

Participation bias may also play a role, possibly with multi-case families or those with more severely affected children more likely to take part. Studies of family history of CTEV are likely to vary in the degree of evidence considered sufficient for a 'diagnosis' of CTEV in relatives. The aetiology of CTEV is undoubtedly complex and it is probable that both environmental and genetic factors are involved. The genetic influence itself is likely to be complex and may involve multiple genes or genetic pathways, themselves interacting with environmental factors.

Our findings suggest that folate status could be relevant in ICTEV aetiology. The importance of replication of findings of genetic association studies has been emphasized in recent years, and we recognize that together with previous study in UK require further confirmation. Folate metabolism is complex, and several other nutrients and polymorphic genes are involved. In addition, despite numerous hypotheses, the pathogenesis of club foot is very poorly understood. Further aetiologic and mechanistic research is warranted to elucidate the role of the folate pathway in this common developmental disorder.

Our findings emphasize the importance of birth defects surveillance programs and their usefulness in investigating potential risk factors. Given a national representative sample, multiregional studies are needed to provide greater statistical power to investigate risk factors and provide the opportunity to identify variation between different surveillance areas.

Limitations

Limitations of this study include the relatively small number of affected parent-child pairs. This could have resulted in a loss of significance in certain groups in the study. For example, there did not appear to be a significant difference between affected mothers and fathers with regard to their rate of transmission of clubfoot to daughters, although the data trended toward higher rates of transmission by the mothers. The inability to detect a significant difference may have been due to the paucity of affected female-child pairs secondary to both the lower prevalence of clubfoot in females and the reduced fecundity of affected females with clubfoot. Future studies including larger numbers of patients are necessary to further investigate this phenomenon, as it may have implications with regard to understanding of both the social and the genetic aspects of ICTEV deformity.

CONCLUSIONS

In current study, genetics as well as uterine restriction appears to play a role in causation of disease. Current study doesn't support role of pollutant and infective aetiology in causation of disease.

As the folic acid supplementation during index pregnancy is very small and as folic acid has role in causation of disease as evident by protective role of MTHFR 677T polymorphism in our study there is need for increasing awareness of folic acid use during index pregnancy and of fortification of food with folic acid in national level programmes.

To conclude our study is first study to show MTHFR gene polymorphism and its protective role in ICTEV in an Indian population and also given an epidemiological picture of a large series of children in south India.

REFERENCES

1. Cartlidge I. Observations on the epidemiology of club foot in Polynesian and Caucasian populations. J. Med. Genet. 1984 Aug;21(4):290–2.
2. Boo NY, Ong LC. Congenital talipes in Malaysian neonates: incidence, pattern and associated factors. Singapore Med J. 1990 Dec;31(6): 539–42.
3. Gurnett CA, Boehm S, Connolly A, Reimschisel T, Dobbs MB. Impact of Congenital Talipes Equinovarus etiology on treatment outcomes. Dev Med Child Neurol. 2008 Jul;50(7):498–502.
4. Chesney D, Miedzbroska Z, Barker S, Deans J, Haites N, Maffulli N. Facial features in children with idiopathic congenital talipes equinovarus. Acta Orthop Belg. 2009 Feb;75(1):57–63.
5. Culverwell AD, Tapping CR. Congenital Talipes Equinovarus in Papua New Guinea: a difficult yet potentially manageable situation. Int Orthop. 2009 Apr;33(2):521–6.
6. Danielsson LG. Incidence of congenital clubfoot in Sweden. 128 cases in 138,000 infants 1946-1990 in Malmö. Acta Orthop Scand. 1992 Aug;63(4):424–6.
7. Wynne-Davies R. A review of genetics in orthopaedics. Acta Orthop Scand. 1975 Jun;46(3):338–49.
8. Byron-Scott R, Sharpe P, Hasler C, Cundy P, Hirte C, Chan A, et al. A South Australian population-based study of congenital talipes equinovarus. Paediatr Perinat Epidemiol. 2005 May;19(3):227–37.
9. Farrell SA, Summers AM, Dallaire L, Singer J, Johnson JA, Wilson RD. Club foot, an adverse outcome of early amniocentesis: disruption or deformation? CEMAT. Canadian Early and Mid-Trimester Amniocentesis Trial. J. Med. Genet. 1999 Nov;36(11):843–6.
10. Cardy AH, Torrance N, Clark D, Miedzybrodzka Z, Sharp L. Amniocentesis in the second trimester and Congenital Talipes Equinovarus in the offspring: a population-based record linkage study in Scotland. Prenat. Diagn. 2009 Jun;29(6):613–9.

11. Carey M, Mylvaganam A, Rouse I, Bower C. Risk factors for isolated talipes equinovarus in Western Australia, 1980-1994. Paediatr Perinat Epidemiol. 2005 May;19(3):238–45.

12. Preface to "A treatise on the nature of club-foot and analogous distortions; including their treatment both with and without surgical operation. Illustrated by a series of cases and numerous practical instructions". By W. J. Little, 1839. Clin. Orthop. Relat. Res. 1988 Aug;(233):3–6.

13. Moorthi RN, Hashmi SS, Langois P, Canfield M, Waller DK, Hecht JT. Idiopathic talipes equinovarus (ITEV) (clubfeet) in Texas. Am. J. Med. Genet. A. 2005 Feb 1;132(4):376–80.

14. Sharp L, Miedzybrodzka Z, Cardy AH, Inglis J, Madrigal L, Barker S, et al. The C677C>T polymorphism in the methylenetetrahydrofolate reductase gene (MTHFR), maternal use of folic acid supplements, and risk of isolated clubfoot: A case-parent-triad analysis. Am. J. Epidemiol. 2006 Nov 1;164(9):852–61.

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