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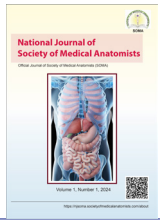

C677T Genetic Polymorphisms in Clinicodevelopmental Spectrum of Neural Tube Defects

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ABSTRACT

The present study was done in the Anatomy Department of JIPMER, Puducherry, in collaboration with departments of Neonatology, Obstetrics and Gynaecology, and Biochemistry. The aim of the study was to study the frequency and association of maternal C677T and A1298C Polymorphisms of the MTHFR gene in neural tube birth defects among cases and control groups in the South Indian population.

Study Procedure: Two groups were studied (cases and controls), with a sample size of 36 and 72, respectively. After obtaining written and informed consent from the participants of study and control groups, a brief antenatal history was taken as per the data proforma. 5ml of peripheral venous blood was collected from the participants of both study and control groups.

Methodology: DNA was isolated from the collected blood samples with Qiagen DNA Extraction Kits. Quantification of DNA was done using Nanodrop technique. The target DNA sequence was amplified, and polymorphism related to SNP C677T(rs18011133) of the maternal MTHFR gene was determined by Real-Time PCR technique by using gene-specific primers and probes. The frequency of mutant and wild-type SNPs of MTHFR gene was documented in both study and control groups. The Data were analyzed with GraphPadInstat software. Chi-square tests were used for the assessment of genotype frequency association between cases and controls. Fischer's exact test with the approximation of Woolf, was done to find out the association and the odds ratio of homozygous mutant variant in comparison with the other genotype.

Results: It was observed that the frequency of mutant maternal MTHFR gene, in particular C677T(rs18011133), was higher in cases compared to controls, and the association between the mutant C677T(rs18011133) polymorphism and the development of NTDs was statistically significant.

Introduction

Neural tube defects (NTDs), severe group of congenital anomalies affecting the central nervous system(Brain and spinal cord), affect over 300000 child births globally every year and constitute one of the most prevalent preventable congenital anomalies. The most commonly affected regions are the cranial portion in cases of anencephaly or the lower part of the vertebral column in cases of open spina bifida and myelomeningocele. In very severe forms, almost the entire neural tube fails to close, from the mesencephalon to the caudal spinal region, resulting in craniorachischisis. Neural Tube Defects (NTDs).In addition to the mortality rate, the morbidity burden caused to the individual and family members is drastically severe.[1-5] Geographically, the incidence of NTDs shows considerable variation, with a global average incidence rate of about 1:1000 live births.[6-10]

Methylenetetrahydrofolatereductase (MTHFR) is the rate-limiting enzyme in the methyl cycle of folic acid metabolism, encoded by the MTHFR gene. It catalyzes the conversion of 5,10 Methylenetetrahydrofolate to L-methylfolate (5-methyltetrahydrofolate). It acts as a co-substrate for the remethylation of homocysteine to methionine. In humans, the MTHFR gene is located on the short arm of chromosome 1 p36.3.[11-20] There are single nucleotide polymorphisms (SNPs) associated with this gene, which influences the activity of the enzyme. Two of the most commonly associated and investigated SNPs are C677T(rs1801133) and A1298C(rs1801131). [4,5,21-25]

Despite the decrease in the incidence of NTDs, after folic acid supplementation during the antenatal period, the causes of Neural tube defects are still poorly understood. The role of genetic polymorphisms of MTHFR gene as a risk factor for NTDs is not very well explored in South Indian population. Hence, this study attempted to determine the frequency of mutant MTHFR gene C677T(rs1801133) and A1298C(rs1801131) and to determine the association of genetic polymorphisms in maternal MTHFR gene with the development of Neural Tube defects. The present study was carried to study the frequency of maternal C677T polymorphisms of MTHFR gene in neural tube defects and to compare with that

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of controls and to study the association of maternal C677T polymorphisms of MTHFR gene with NTDs.

Material and Methods

The study design was case control study. Two groups(study group and control group) were chosen for the study. The study participants were mothers admitted or attending OPDs of Neonatology and OG departments of JIPMER during the period between January 2015 and December 2015. The sample size of study group was 36 and control group was 72.

Study group: Mothers with obstetric history of at least one stillborn/live baby with NTDs, in association with or without other congenital anomalies were included in study group. Mothers with obstetric history of stillborn/live babies with congenital anomalies other than neural tube defects, mothers exposed to teratogens/radiations during their antenatal period, mothers who have not taken folic acid supplementation (by history) during the antenatal period were excluded from the study group.

Control group: Mothers who delivered a clinically normal baby from the Department of Obstetrics and Gynaecology, JIPMER, were included in the control group. Mothers were matched for age, parity, and consanguinity. Mothers with bad obstetric history or history of stillborn delivery or history of any one child with congenital anomaly were excluded from the control group.

The participants of the study (mothers) were explained in detail about the study procedure and outcome. Written and informed consent was obtained from the willing mothers of both study and control groups before the initiation of the study. A brief antenatal history and relevant details for the present study were taken and entered in data collection proforma. 5 ml of peripheral venous blood was collected from the participants of both study and control groups. A 5 mL of peripheral venous blood was collected in 15 mL vacutainers(preloaded with 100 microlitre EDTA) by venepuncture following strict aseptic conditions. Collected blood samples were centrifuged at 3000 rpm and plasma was separated. The red cell mass with buffy coat was labelled and stored at minus 800C in the deep freezer for doing DNA extraction and subsequent procedures later. The separated plasma was also labeled and stored.

Before processing, the samples were thawed by transferring from the deep freezer to the refrigerator (-80 degrees to 40C) and then kept at room temperature for 20 minutes.

DNA extraction from the samples was done using Qiagen DNA extraction kits following standardised spin protocol. The DNA extraction kit consists of Qiagen protease in lyophilised form, solvent for protease, Wash Buffers(AW1 and AW2), Elution Buffer(AE) and Lysis Buffer(AL).

The first step was preparation of Qiagen protease and was done by dissolving the lyophilised powder of the enzyme protease in the solvent provided along with the kit. Then the wash Buffers (Buffer AW1 and Buffer AW2) were prepared by adding 100% ethanol. The Elution Buffer(AE) provided with the kit was preheated to 560C by keeping inside incubator, before the following steps.

For each sample, a separate 1.5 mL microcentrifuge tube was taken and 40 microlitre Qiagen protease was pipetted into the bottom of it. 200 microlitre of the sample, preferably buffy coat and then 200 microlitre Buffer AL (Lysis buffer) were added to it. The contents were mixed well by pulse vortexing for 30 seconds. The mixed contents were incubated at 560C for 5 minutes. The pulse vortexing and incubation were repeated as necessary. To remove the droplets from the lid, pulse centrifugation, followed by a short spin was done. 200 microlitre of 100% ethanol was then added to the mixture. Subsequent mixing was done by pulse vortexing for 15 seconds followed by a short spin.

The total contents were transferred to Q1 Amp Mini spin column and pulse centrifugation was done. 500 microlitre of wash buffer AW1 was added to the mini column without wetting the rim. Centrifugation was done at 14000rpm for 1 minute and 2 mL collection tube containing the filtrate was discarded. 500 microlitre wash buffer AW2 was then added to column without wetting the rim. Centrifugation was done at 14000 rpm for 3 minutes. centrifugation was repeated at 14000rpm for 1 minute after discarding the filtrate. Then Q1Amp Mini spin column was placed in a clean 1.5 mL microcentrifuge tube. 100 microlitre preheated Elution Buffer(AE) was added to it. Incubation was done at 15 to 25 degree Celsius for 5 minutes. Centrifugation was done at 8000 rpm for 1 minute. Finally the eluted filtrate containing the extracted DNA was transferred to -800C for storage.

The concentration (absorption in A260) and purity (A260/ A280) of the extracted DNA was estimated by nanodrop and data was exported in .xls format.

Genotyping of the MTHFR gene rs1801133 (C677T) and rs1801131(A1298C) polymorphisms was carried out using HELINI Human SNP Real-time PCR kit, and the reactions were carried out in BioRad CFX Thermocycler.

PCR reactions for both the SNPs of the cases and the controls were carried out separately in a 96-well plate separately using 25 µl final volume reaction mixture consisting 8 µl of SNP Probe PCR master mix (8 microlitre), 2 µl of working stock of TaqMan genotyping assay(Taq enzyme mix), 5-10 microlitre purified DNA sample and 5 µl of primer-probe mix. Nuclease-free water was used as a negative control. Before placing in the thermocycler the PCR vials were centrifuged for a brief period. The amplification protocol for the thermocycler was as follows: for Taq enzyme activation, 2 min at 50°C followed by 15 min at 95°C. Then, 40 cycles of PCR reaction with denaturation for 20 seconds at 95°C, annealing at 60°C for 20 seconds, and extension for 20 seconds at 72°C.with FAM for C allele and HEX for T allele for rs1801133(C677T). Scatter plots assay was done to record the final fluorescence values from amplification of each allele.

The frequency of homozygous wild, mutant and heterozygous variants for both the SNPs was calculated. The difference in the frequency of homozygous and heterozygous variants between the cases and the control group were statistically analysed using Fischer Exact test of the Graph Pad Software. The odds ratio was calculated to find out the association between the variants of SNP in the maternal gene and congenital neural tube birth defects. The results were tabulated and analyzed.

Data was analyzed with Graphpad Instat software. Genotype frequencies and its association with the cases and controls were assessed with 3×3 contingency table chi-square tests and p-value and odds ratio calculated. Fischer's exact test with the approximation of Woolf was done with 2×2 contingency tables, and the specific potential risk factors of each genotype, compared to the others, were assessed along with the p-values and odds ratios.

Results

Out of the 36 subjects in the case group and 72 subjects in the control group, the mean age of subjects in the case group was 23.27 years with standard deviation of 2.02 and among controls was 24.5 years with standard deviation of 2.49.

The sample size of the study group (cases) was 36 (mothers who had delivered a live or stillborn baby with NTD). Out of 36 cases, 22 cases were mothers who had given birth to babies with meningomyelocele (20 lumbo-sacral meningoceles, 1 thoracic and 1 cervical), 6 cases were mothers who had delivered babies with anencephaly, 4 cases were mothers who had delivered babies with encephaloceles, and 4 cases were mothers who had delivered babies with spina bifida.

Out of 36 cases, 8 cases were CC genotype (22.2%), 22 cases were CT genotype (61.1%) and 6 cases were TT genotype(16.7%). Out of 72 controls, 18 were CC genotype(25%), 52 were CT genotype(17.2%) and 2 controls were TT genotype(2.8%). Association of genotype frequencies among cases and controls was assessed with the help of 3×3 contingency table chi-square test and p-value obtained was 0.0341; genotype association might be clinically significant (p value<0.05). Fischer exact test was done with 2×2 table (CT+TT Vs CC genotypes) and p value obtained was 0.8153 with Odds ratio 1.167 (95% CI:0.4512-3.016). Fisher exact test was done with 2×2 table (TT Vs CC+CT) genotypes and p-value obtained was 0.0159 with OR 7.000 (95%CI:1.335-36.701), i.e., TT genotype turned out as a clinically and statistically significant potential risk factor for NTDs.

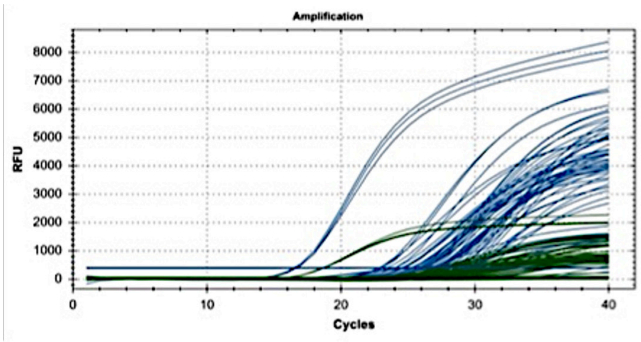

Figure 1: Amplification graph – Real time PCR

Table 1: Age distribution among cases and controls (*P value<0.05)

Groups	Mean ± SD (in years)	P value
Cases (n = 36)	23.27 ± 2.02	0.05*
Controls (n = 72)	24.5 ± 2.49	

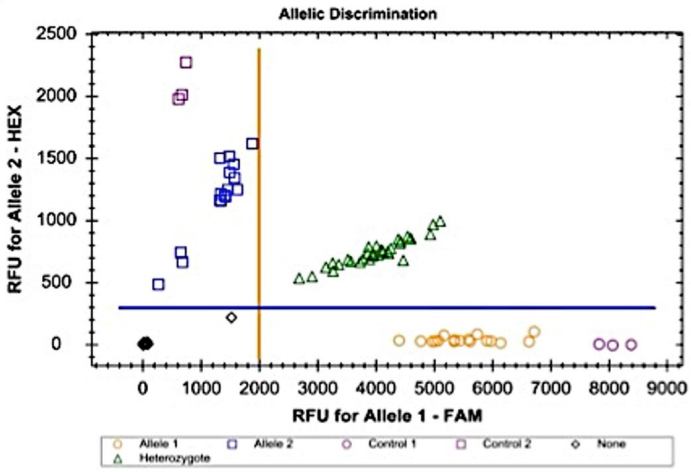

Figure 2: Scatter plot analysis

Discussion

Regarding the genotype frequency of C677T (rs18011133) polymorphism, 8(22.2%) cases showed CC genotype; 22 (61.1%) cases were of CT genotype and 6(16.7%) cases showed TT genotype (homozygous mutant allele), i.e., 28 cases (77.8%) turned out as C>T polymorphs (CT+TT), whereas in the control population, 18 showed CC genotype (25%), 52 (72.2%)controls were of CT genotype and 2 (2.8%) were of TT genotype, i.e., 54 controls (75%) were polymorphs with CT+TT genotype.

The data from the study showed that there is an increase in the frequency of the mutant allele C677T (rs18011133), particularly homozygous mutant (TT) in the cases in comparison with the control group (16.7% versus 2.8%), which was statistically significant ('p' value 0.0423).

The association between the T allele and the NTDs was significant in the present study with a p-value 0.0341. When the CT+TT genotype was compared with the frequency of CC (dominant model comparison), the odd ratio was 1.167, which implies that there is a risk of NTDs with T allele, but the association in our present study was not statistically significant (p value – 0.8153). But when TT genotype was compared with CC + CT genotype

Table 2: Subtypes of NTDs among cases

Types of NTD	Meningomyeloceles			Anencepha-lies	Encephalo-celes	Spina Bifida	
	Cervical	Thoracic	Lumbo-sacral			Open	Close
No of cases	1	1	20	6	4	3	1

Table 3: Comparison of association of genotypes for rs1801133 between cases and controls (*P value<0.05 and it is significant)

Genotype	Cases (n = 36)	Controls (n = 72)	P value
CC	8 (22.22%)	18 (25%)	0.0341*
CT	22 (61.1%)	52 (72.2%)	

Table 4: Comparison of TT versus CC genotypes(rs1801133) among cases and controls (*P value<0.05)

Genotype	Cases (n = 36)	Controls (n = 72)	P value	OR
TT	6 (16.7%)	2 (2.8%)	0.0423*	6.750 (95%CI - 0.4512 to 3.016)
CC	8 (22.22%)	18 (25%)		

Table 5: Comparison of CT+TT versus CC genotypes(rs1801133) among cases and controls (*P value<0.05)

Genotype	Cases (n = 36)	Controls (n = 72)	P value	OR
CT + TT	28 (77.78%)	54 (75%)	0.8153*	1.167 (95%CI - 0.4512 to 3.016)
CC	8 (22.22%)	18 (25%)		

Table 6: Comparison of TT versus CC+CT genotypes(rs1801133) among cases and controls (*P value<0.05)

Genotype	Cases (n = 36)	Controls (n = 72)	P value	OR
TT	6 (16.7%)	2 (2.8%)	0.0159*	7.000 (95%CI –1.335 to 36.701)
CC + CT	30 (83.3%)	70 (97.2%)		

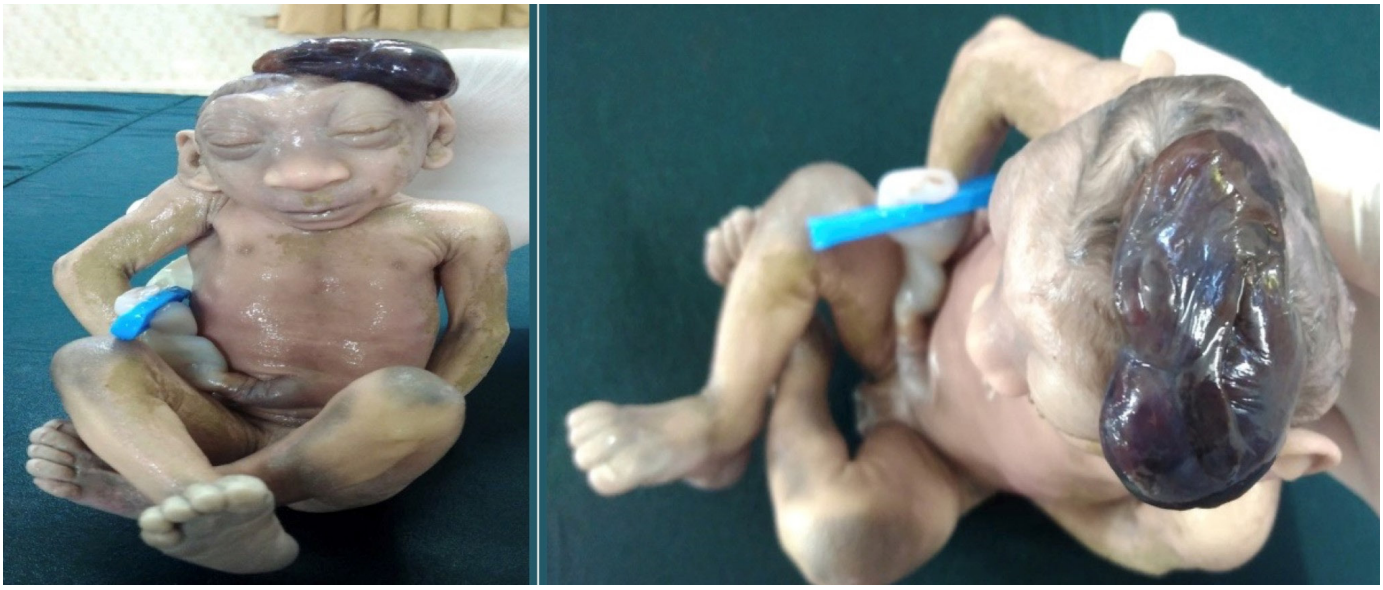

Figure 3: Stillborn with anencephaly / exencephaly (anterior and superior view)

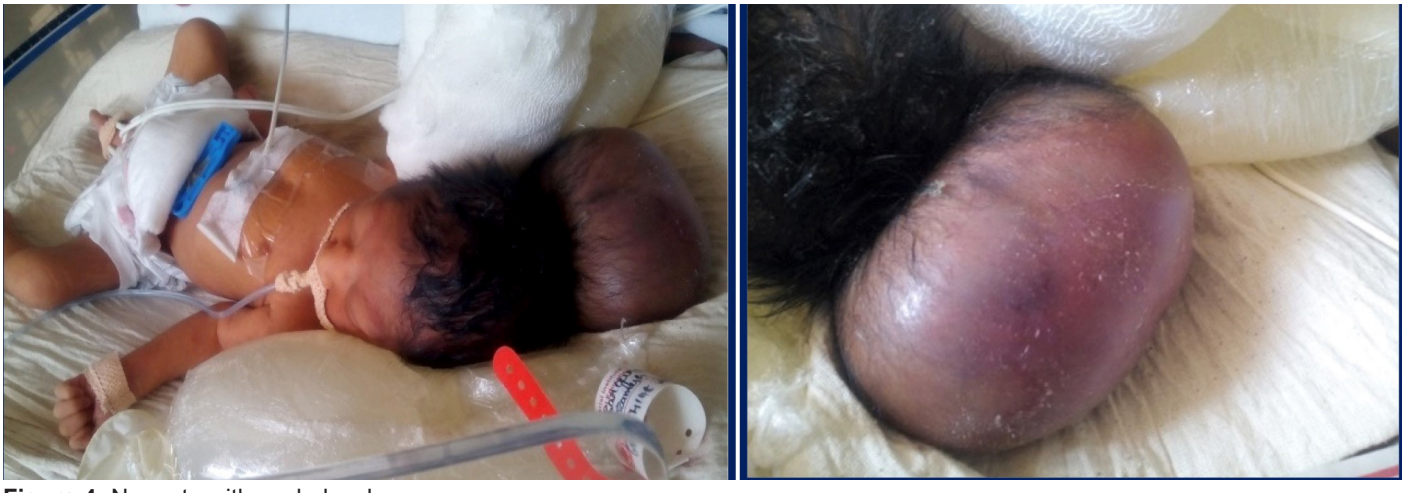

Figure 4: Neonate with cephalocele

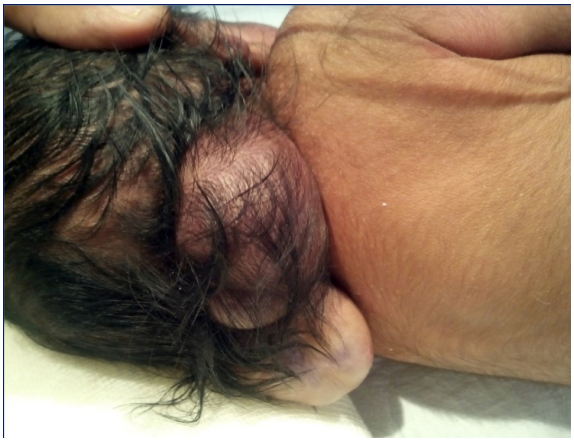

Figure 5: Neonate with occipitocele

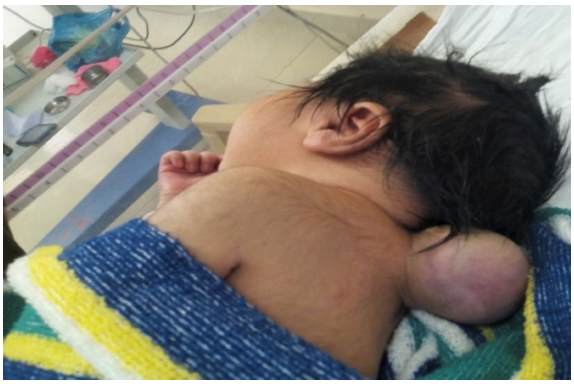

Figure 6: Neonate with thoracic meningomyelocele

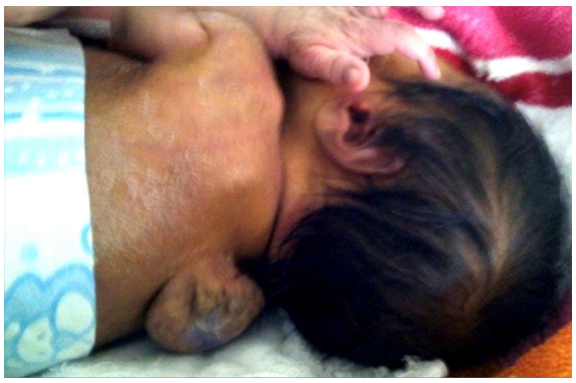

Figure 7: Neonate with ulcerated thoracic meningomyelocele

(recessive model comparison), it was found that there is a significant association, with a 'p' value of 0.0159, OR of 7.000 with 95% CI (1.335 to 36.701).

In comparison to the meta-analysis done in the Chinese population by Lifeng, Lin et al in 2012 (2429 cases and 3570 controls), our results were similar to the meta-analysis data and has established the association of C677T polymorphism and the neural tube birth defects.[26] But the odds ratio in our study was very high, may due to limitation of inadequate sample size (less number of NTD cases within the particular period). Both the TT genotype frequency and the recessive model frequency showed a significant association with the NTDs in the present study. Similar findings were established by the study done in Chinese population of Shanxi province by Zhang et al, which revealed genetic variants of rs1801133 (MTHFR C677T) was associated with the risk of ectoderm and endoderm-derived neural tube malformations.[27]

Qin Zhang, BaolingBai, Xiaozhen Liu et al and Yang Yu, Fang Wang, YihuaBao et al. in their respective studies have analyzed and stated vice versa i.e the genotype CC or the allele C in rs1801133 (MTHFR C677T) had a protective role for the development of NTDs, especially for the anencephaly.[22]

Though most of the studies done in various population of Chinese, Norway, UK (CL Relton, C S Wilding, M S Pearce) have established the association of rs1801133 (MTHFR C677T) polymorphism with the development of NTD, the study done by Atsuo Kondo, Hiromi Fukuda et al (2013) in the Japanese new born (230 spina bifida cases and 9034 controls) had established that there is no association between the rs1801133 (MTHFR C677T) polymorphism and the spinal bifida cases.[26-30]

The association of rs1801133 (MTHFR C677T) and the development of NTDs seems to be indirect. The possible mechanisms for the association could be due to decrease in the activity of the enzyme coded by the MTHFR gene due to the mutant variety, and has resulted in increased homocysteine levels, damage to the DNA or defective maturation of cells resulting in early cells death or improper differentiation which would have resulted in the improper initiation or formation or closure of neural folds/tubes leading the NTDs.[21-28]

The results of the present study cannot be taken or extrapolated as such since there are some limitations in the present study. A very small sample size in the cases is a major limiting factor but it could not be overcome due to the paucity in the number of mothers who have given birth the babies or stillborn with NTDs in one and a half period at JIPMER. This limitation, to some extent, compensated in the study design by doubling the number of controls to increase the power of the study.

Secondly, since the role of folic acid in the development of NTDs was well established in the literature, in the exclusion criteria, the present study have ruled out mothers who have not taken folic acid during the antenatal period since this could be a confounder to the present study, but it was largely depended upon the history taken from the mothers, in which there was a possibility of recall bias or the details may not have been given correctly by the mothers. A study with a larger sample size or a meta-analysis incorporating various other studies of different subsets of South Indian population will yield much more definitive data, which will be useful to screen antenatal mothers for mutant MTHFR genes so that the vulnerability of these mothers for the development of babies with NTDs can be predicted so that an appropriate intervention could be done at the earliest.

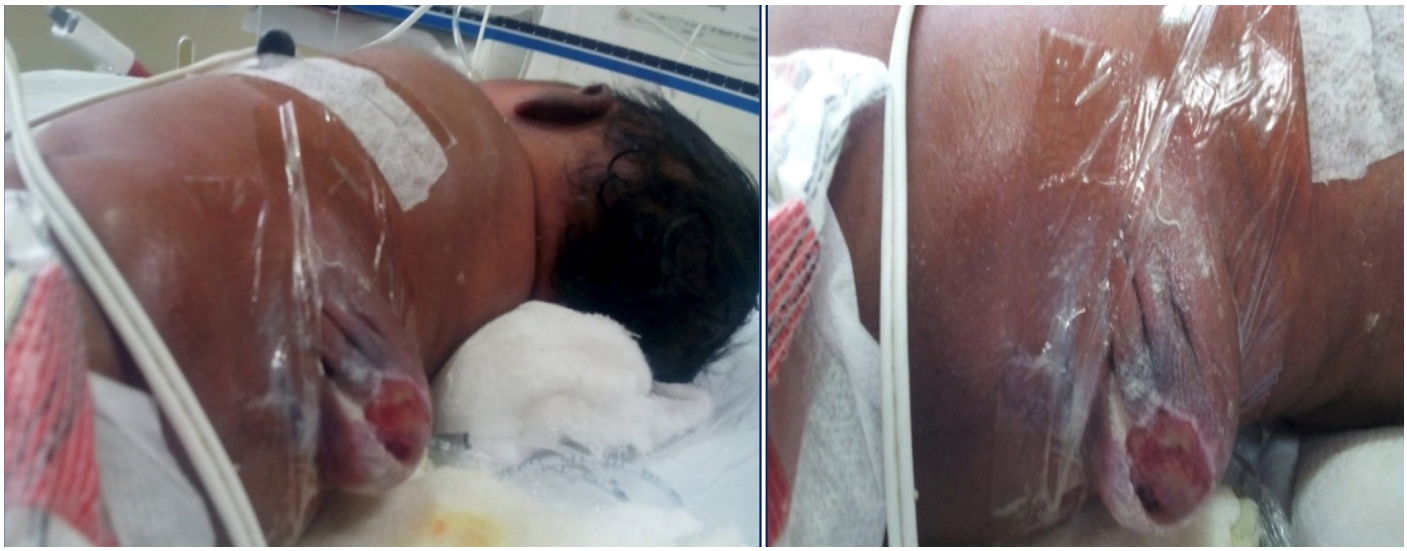

Figure 8: Infant with ulcerated lumbar meningomyelocele

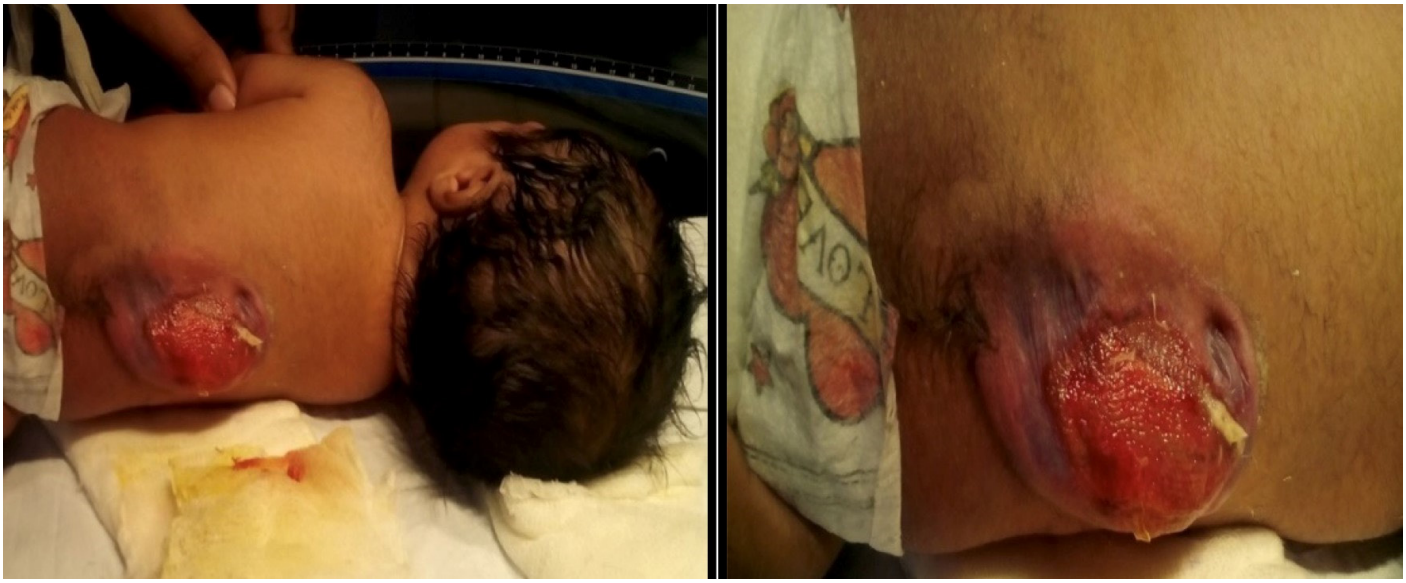

Figure 9: Infant with deeply ulcerated lumbar myelocele

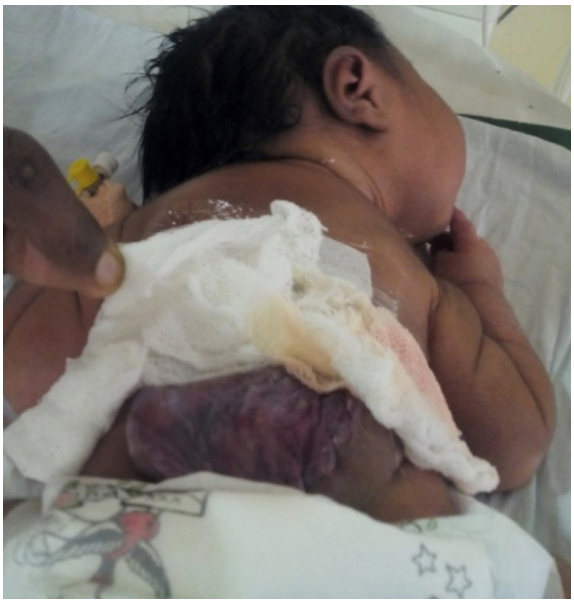

Figure 10: Infant with massive lumbosacral meningocele

Conclusion

There is a significantly increased frequency of the mutant genotypes of the SNP of maternal MTHFR gene (C677T) in cases compared to the controls. There is a significant association between maternal MTHFR SNP mutant genotypes of C677T(rs1801133)with Neural tube defects (NTDs). TT genotype of SNPrs1801133(C677T) in maternal MTHFR gene (mutant variant) may be a potential risk factor for Neural tube defects.

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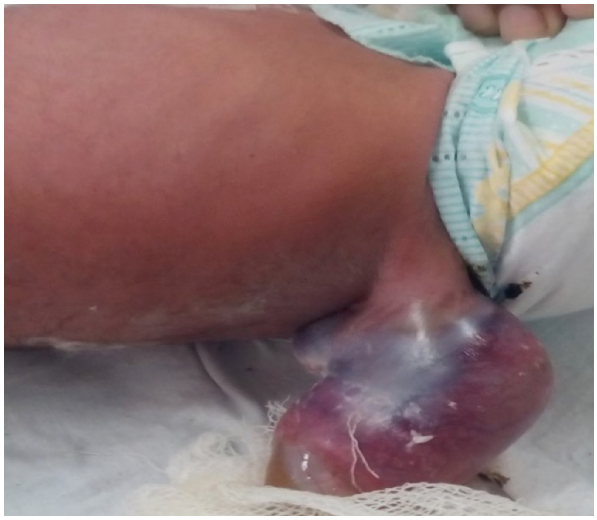

Figure 11: Infant with massive lumbosacral meningomyelocele

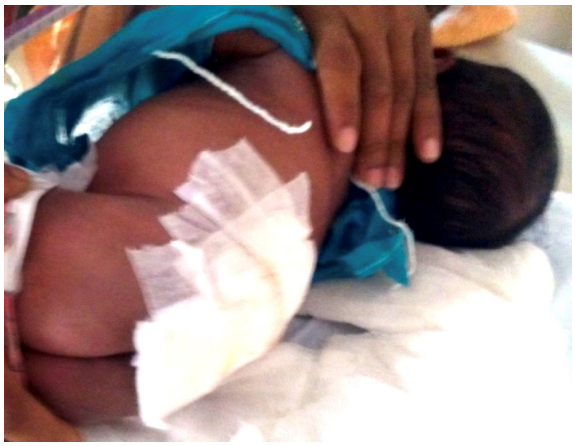

Figure 12: Infant – post-surgery – lumbosacral meningomyelocele

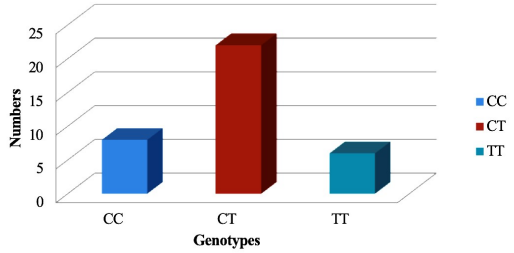

Figure 13: Genotype frequency in Cases (n = 36) for SNP rs1801133(C677T)

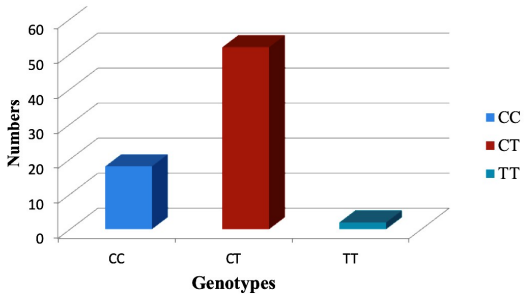

Figure 14: Genotype frequency in controls (n = 72) for SNP rs1801133(C677T)

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