ISSN: 0975-833X

Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 8, Issue, 11, pp.41307-41310, November, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

CASE STUDY

MTHFR GENE MUTATION IN THE GENESIS OF NEURAL TUBE DEFECT AND ASSOCIATED MULTIPLE CONGENITAL ANOMALIES

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ARTICLE INFO

Article History:
Received 16th August, 2016
Received in revised form
22nd September, 2016
Accepted 10th October, 2016
Published online 30th November, 2016

Key words:

MTHFR,
1p36.3,
Neural tube defects,
Folate,
Methylation,
Periconceptional period.

ABSTRACT

Introduction: The 5,10-methylenetetrahydrofolate reductase (MTHFR) gene is located on chromosome 1 at 1p36.3. MTHFR enzyme catalyzes the conversion of 5,10-methylene tetrahydrofolate into 5-methyltetrahydrofolate, which is the major circulating form of folate. Its deficiency results in insufficient methylation of crucial metabolites and direct toxicity of homocysteine, the two factors which have been suggested as possible mediators of teratogenesis.
Objective: To find out the cause for neural tube defect and multiple congenital anomalies in the case under scrutiny.
Materials & Methods: An anomalous female fetus of 37 weeks gestation, post demise, was procured from Department of Obstetrics & Gynaecology, Vydehi Institute of Medical Sciences & Research Centre. A written consent was taken from the parents. Mother had previous history of spontaneous abortion during 1st trimester. Blood samples of parents were taken for cytogenetic analysis, and to check for possible MTHFR gene mutations. The baby was then subjected to radiological investigations, CT & MRI, following which, it was dissected in the department of Anatomy after fixation in 10% formalin.
Observations & Results: MTHFR gene mutation was detected, and this accounts for all the findings observed in the various investigatory modalities.
Conclusion: To obtain high methylene tetrahydrofolate levels for an adequate homocysteine metabolism, individuals with a decreased MTHFR activity need a higher dietary intake of folate during the periconceptional period.

Citation: Dr. Athul Antony Simon, Dr. Shashirekha and Dr. Varsha Mokhasi, 2016. "Mthfr gene mutation in the genesis of neural tube defect and associated multiple congenital anomalies", *International Journal of Current Research*, 8, (11), 41307-41310.

INTRODUCTION

Congenital malformations constitute one of the leading causes of infant mortality in developing countries like India and posts major health issues in surviving children. Neural tube defects (NTDs) are a common group of central nervous system anomalies affecting 0.5–2 per 1000 pregnancies worldwide. (Greene *et al*., 2009) Various genetic and environmental factors interplay in the genesis of majority of these malformations. A strong genetic component is indicated by the high recurrence risk for siblings of affected individuals. (Detrait *et al*., 2005) Single nucleotide polymorphisms (SNPs) in folate metabolism genes like 5,10-methylenetetrahydrofolate reductase (MTHFR) gene and methionine synthase reductase (MTRR) gene are associated with complex congenital abnormalities and related to ectoderm, mesoderm and/or endoderm development. (Zhang *et al*., 2014) The MTHFR gene is located on chromosome 1, at 1p36.3. MTHFR enzyme catalyzes the conversion of 5,10-methylene tetrahydrofolate into 5-methyltetrahydrofolate, which is the major circulating form of folate that participates in single-carbon transfers involved in crucial metabolic pathways. Its deficiency results in both insufficient methylation of crucial metabolites and direct toxicity of the intermediate metabolite homocysteine. These two factors have been postulated as possible mediators of teratogenesis. (Lorenzo *et al*., 2000) The best-characterized MTHFR genetic polymorphism is a common missense mutation consisting of 677C→T transition, resulting in a thermolabile enzyme variant that has reduced catalytic activity. (Frosst *et al*., 1995) Another common genetic polymorphism of MTHFR is a missense mutation consisting of nucleotide 1298A→C transition, resulting in decreased MTHFR activity, which is more pronounced in homozygous than heterozygous state. (Van der Put *et al*., 1998)

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We would like to emphasize the importance of folate metabolism gene mutation that is prevalent in our society, by reporting a case of neural tube defect and multiple congenital anomalies resulting from MTHFR gene mutation encountered at our centre.

The case workup was aimed at:

- Finding out all the anomalies that exist in the fetus by thorough physical examination, radio-diagnostic imaging and systematic anatomical dissection.
- Establishing the cause for neural tube defect and multiple congenital anomalies in the case under scrutiny.

Case Report

We present a case of an anomalous female fetus born at 37weeks of gestation to a 20yr old second gravida. During her previous pregnancy she had history of spontaneous abortion during the 1st trimester. She had received regular Folic acid & Iron supplements during her antenatal period. There was no history of consanguinity or family history of any congenital malformations. In the current pregnancy, second trimester scan had showed a single live gestation with extensive thoraco-lumbosacral open spina bifida with meningomyelocele, Arnold-Chiari malformation, lumbosacral angular kyphotic deformity, and right talipes equinovarus.

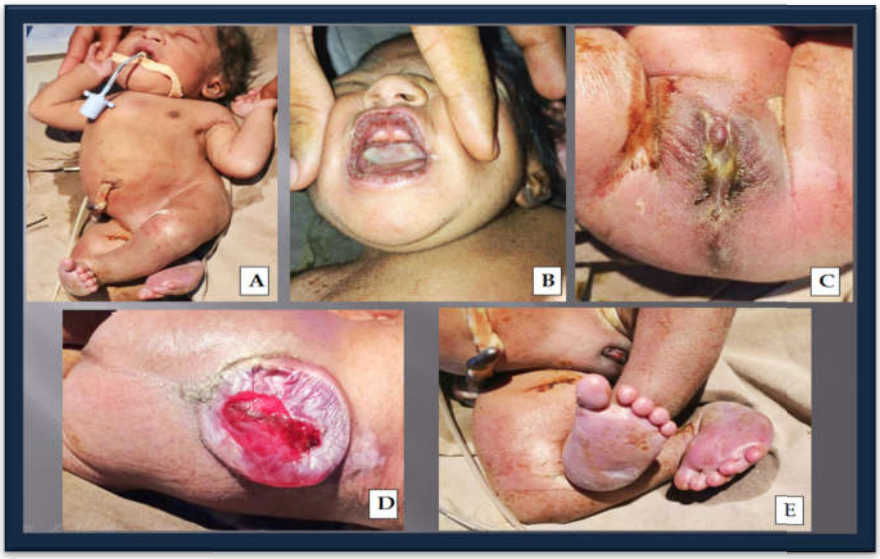

Figure 1. A- Intubated newborn at NICU; B- Low set ears, No cleft lip/ cleft palate; C- Perineum shows imperforate anus & meconium filled vagina (suggesting recto- vaginal fistula); D- A 7.5cm diameter meningomyelocele over the thoraco lumbar spine, Kyphoscoliosis, flattening of buttock; E- Right talipes equinovarus

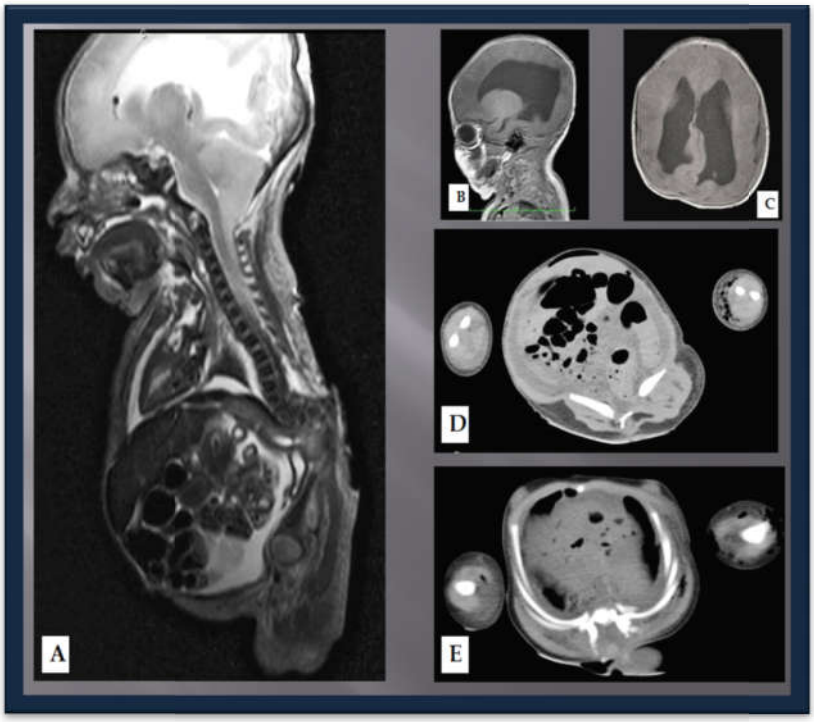

Figure 2. MRI & CT scan images; A - T2W MR sagittal section of fetus showing dilated lateral ventricle, compressed 4th ventricle, herniation of cerebellar tonsil, angular kyphotic deformity T6-L5 vertebral levels, thoraco lumbosacral spina bifida - meningomyelocele, tethered cord at T6 onwards. No pre-sacral mass detected. B & C - T1W MR sagittal and transverse sections of skull showing bilateral colpocephaly, underdeveloped/distorted corpus callosum. D - shows the sacral agenesis on left side - hemisacrum. Sacral anomaly Type 4 of Cama *et al* (1996). E – shows thoraco lumbosacral open spina bifida - meningomyelocele

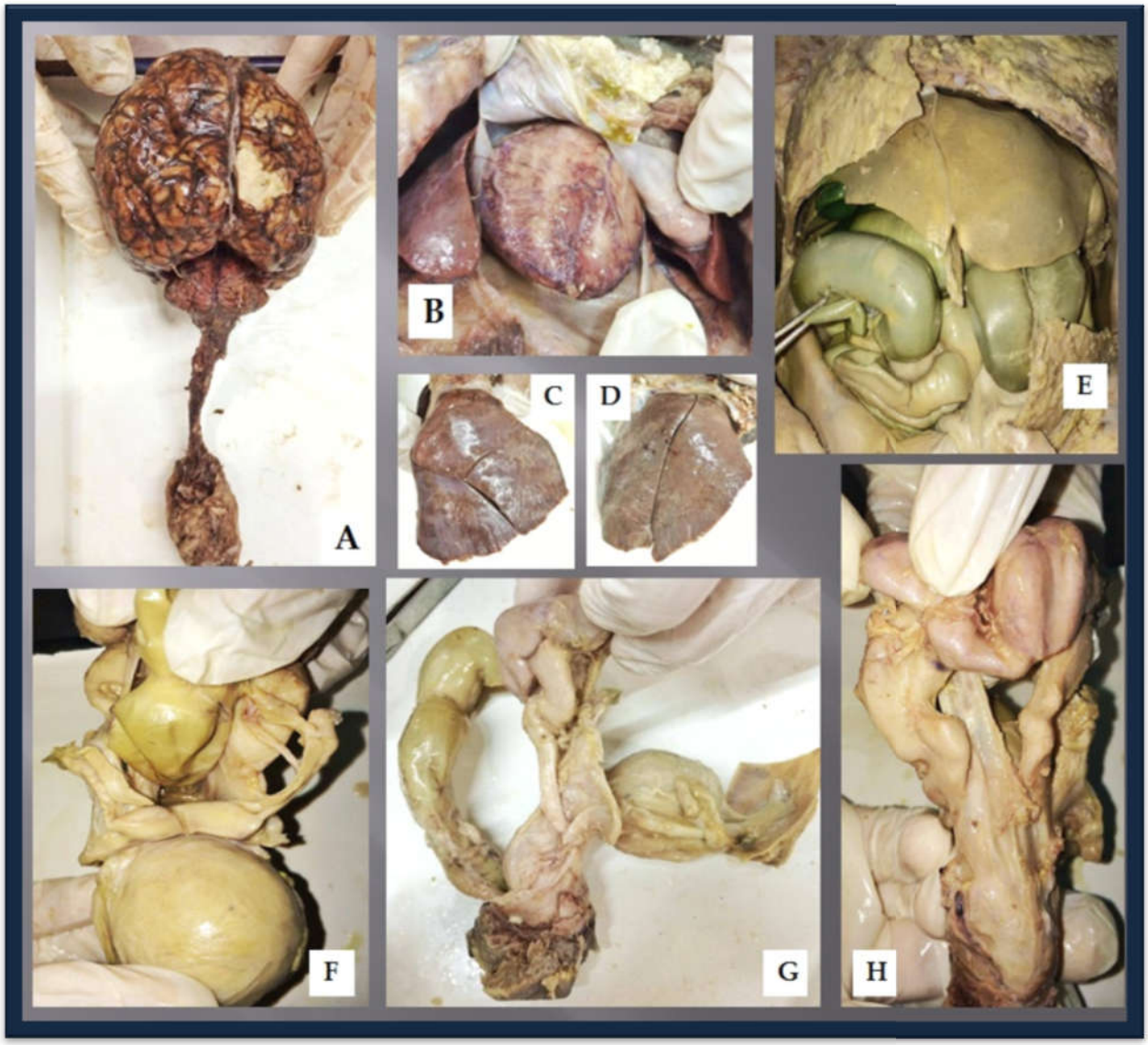

Figure 3. Dissection findings; A - Tonsillar herniation noted & Arnold-Chiari malformation confirmed. There was tethering of spinal cord at lower thoracic levels, meningomyelocele was dissected open and clumping of the lower cord elements with a malformed sacrum (hemisacrum) observed. B, C, D - Thoracic viscera - lungs, heart and other mediastinal structures were well developed without any defects. E - No malrotation of gut. Well developed liver and spleen. F - Bicornuate uterus noted. G - Recto-vaginal fistula appreciated. Distension of urinary bladder with meconium. H - Horseshoe kidney with bilateral hydroureteronephrosis

The baby was born by normal vaginal delivery but did not cry at birth. Heart rate was nil at birth and resuscitation was started. Meconium aspiration was noted and the child was intubated following which endotracheal suctioning and positive pressure ventilation was given. APGAR score at 5 minutes was 3/10, with a heart rate of 40/min; both improved after adrenaline administration. However, there was no spontaneous respiratory effort. The baby was shifted to NICU for further management. On physical examination, it was noted that the child had central cyanosis, kyphoscoliosis of thoracolumbar spine, low set ears, imperforate anus, flattening of the buttock, meconium at the vagina suggestive of rectovaginal fistula, talipes equinovarus deformity of right foot and a 7.5cm diameter spina bifida cystica in the thoracolumbar region. The heart rate continued to be low (about 80/min), and the baby was limp with reduced muscle tone. The baby succumbed to death on the second day due to respiratory failure and meconium aspiration. After getting written consent, blood samples of parents were obtained in sodium heparinized and EDTA vacutainers for cytogenetic analysis and to check for possible MTHFR gene mutations respectively. The baby was then subjected to CT & MRI, following which; it was dissected at the department of Anatomy after fixation in 10% formalin.

Observations

The blood samples of the parents were subjected to karyotyping and gene mutation studies:

- Karyotype of both the parents was normal.
- Genotypes of MTHFR gene were isolated and determined.
- Genotype of mother was identified to have CT and AC, suggesting a compound heterozygous status at 677 and 1298, respectively, of the MTHFR gene.
- Genotype of father was identified to have CC and CC genotypes, suggesting homozygous wild status at 677 and homozygous mutant status at 1298, respectively, of the MTHFR gene

DISCUSSION

Among folate-related genes, MTHFR has been the principal focus of attention, following reports that the 677CT polymorphism is associated with increased risk of NTDs (Van der put *et al*., 1995; Shields *et al*., 1999). Hence the MTHFR genotype of the parents of the anomalous fetus with NTD were analysed. According to Weisberg (1998) and Laxmi V. Yaliwal (2012), people who are compound heterozygous for the A1298C and C677T alleles tend to have a biochemical profile similar to that seen among C677T homozygotes, with increased serum homocysteine levels and decreased serum folate levels. (Weisberg *et al*., 1998; Yaliwal and Desai, 2012) These two factors have been implicated in the teratogenesis causing NTD and other associated anomalies. In our study, the mother was identified to have C677T and A1298C compound heterozygous status of the MTHFR gene. This explains the neural tube defect and multiple other anomalies detected in the fetus. McLone's unifying theory tells us that failed neurulation creates a dorsal myeloschisis, causing excessive ventricular CSF drainage through the defect. The ventricular system, unable to distend normally does not exert required inductive effect of pressure and volume on surrounding mesenchyme and endochondral bone formation. This results in a small posterior fossa causing the developing cerebellum and brain stem to herniate through the incisura and foramen magnum. (Vivek Joseph and Michael G Fehlings, 2011) Apart from the Arnold-Chiari malformation, the tonsillar herniation had compressed the 4th ventricle resulting in bilateral colpocephaly in our case. Notochord is the secondary organiser that induces development of brain and spinal cord from the overlying neuroectodermal plate. Neural tube in turn acts as the teritary organiser that differentiates the mesoderm and initiate somite formation from paraxial mesoderm. (Datta, 2010) Insult has occurred to these organisers due to altered folate metabolism which possibly hampered adequate methylation of various substrates involved in crucial metabolic pathways of the fetus. This helps explain the various defects observed in the fetus like kyphoscoliotic spine, hemisacrum, bicornuate uterus, horseshoe kidney, hydroureteronephrosis, imperforate anus and recto-vaginal fistula. Efforts to club our case under a syndrome turned futile. The syndrome most similar to the fetal condition was "Currarino Syndrome (CS)" an autosomal dominant condition having a triad of anorectal anomaly, hemisacrum and a presacral mass. CS is a type of caudal regression syndrome associated with HLXB9 gene mutation. (Currarino *et al*., 1981) However this fetus had other anomalies which made the diagnosis of CS inappropriate. Up to 70% of human NTD can be prevented by folate supplementation during the periconceptional period (Czeizel and Dudas, 1992). Several studies show that folate intake high enough to prevent NTD cannot be achieved by a diet of folate-rich nutrition. Only intake of folate supplements or fortified foods such as flour and cereals can achieve the recommended daily values (Van der put *et al*., 1997).

Conclusion

The key culprit for NTDs is MTHFR gene mutation which often goes unnoticed. Under conditions of low folate intake or high folate requirements, such as pregnancy, this mutation manifests phenotypically and is of utmost clinical importance. To obtain high methylene tetrahydrofolate levels for an adequate homocysteine metabolism, individuals with a decreased MTHFR activity need a higher dietary intake of folate during the periconceptional period.

Acknowledgement

I wish to extend my sincere gratitude to Dr. Preetha Thilak, Genetics department, St.John's Medical College, Bangalore, for karyotyping and gene mutation studies. I am thankful to all the staff of departments of Anatomy, Obstetrics & Gynaecology, Pediatrics & Radio-diagnosis at Vydehi Institute of Medical Sciences & Research Centre, Bangalore.

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