Folate deficiency is not the only cause of neural tube defects: A Preliminary Study

Kulwant Singh1, S. K. Rai2, Preeti Kumari3, Rajniti Prasad4, Rashmi5, S.Shamal6, Royana Singh7

ABSTRACT

Neural tube defects (NTDs) are common non-infectious congenital malformations resulting from improper neural tube closure. It is well established that periconceptional supplementation of folic acid reduces the occurrence and recurrence of NTDs, which led to mandatory folate fortification by many countries. In India even after huge efforts by government regarding awareness and folic acid supplementation, prevalence rate of NTDs was found high. Therefore, this study focused on serum folic acid level among patients and their mothers in comparison to control counterparts. The finding of this study shows that population from eastern Uttar Pradesh and adjoining regions of Bihar are not folate deficient but still have high prevalence of NTDs. This study also hypothesizes that there may be the involvement of other factors responsible for high prevalence of NTDs apart from serum folic acid level. Where need to be studied

Keywords: Neural tube defects, birth defects, folate,

Introduction

Neural tube defects (NTDs) are developmental anomalies of the central nervous system resulting due to failure of neural tube closure around 28th days of gestational age1. The global prevalence of NTDs ranges between 1-10 per 1,000 births2. NTDs affected children are having mental and physical disabilities such as paraplegia, quadriplegia, bladder & bowel involvement3-5 and causes socioeconomic burden on family and society6. Despite surgical interventions and other health care services, life expectancy of three fourth NTD affected cases is about 10 days7. The most common forms of NTDs are anencephaly which is characterized by absence of cranial vault and spina bifida characterized by lack of closure below the head.

1. Associate Professor, Department of Neurosurgery, Institute of Medical Sciences, Banaras Hindu University
2. Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University
3. Department of Anatomy, Institute of Medical Sciences, Banaras Hindu University
4. Professor, Dept of Pediatric Medicine, Institute of Medical Sciences, Banaras Hindu University,
5. 6. & 8. Dept of Anatomy, Institute of Medical Sciences, Banaras Hindu University

Corresponding Author: Dr. Royana Singh, Cytogenetics Laboratory, Department of Anatomy, Institute of Medical Sciences, BHU, Varanasi-221005, Email : singhroyana@rediffmail.com; Tel.: (0542)6703451.
Folate deficiency is not the only cause of neural tube defects

These defects generally occur in almost equal frequencies at birth. However in our previous study we find anencephaly in very low frequency as compared to spina bifida.

NTDs are known to have polygenic and multifactorial origin, where both genetic and environmental factors reported to have major contributions. Among the environmental factors protective role of folate is well documented. Besides unknown preventive mechanism, periconceptional supplementation of folic acid reduces the incidence of NTDs up to 70%. After the major outbreak by aforesaid studies many part of western world, Australia and European countries have started mandatory folic acid fortification and later on reported decrease in incidences of NTDs cases.

**Figure-1:** Impaired folate status and various pathological conditions either acquired or congenital

Folate is water soluble vitamin, also known as vitamin B9. Lucy Wills in 1931 recommended the term “vitamin 11 for that as a twin of vitamin B12” and was first extracted from spinach leaves by Mitchell et al. Folate itself acts as cofactor for many enzymes, necessary for regeneration of methionine, which can be converted in S-adenosylmethionine (SAM) and leads to methylation of DNA and RNA. Despite of its importance and need for normal development, animals including human being can’t synthesize it de novo. Therefore, dietary supplementation of folate from natural and artificial sources is essential as maternal folate deficiency generates hyperhomocysteinemia and cellular accumulation of homocysteine elicits oxidative stress responses which may be cytotoxic, negatively regulates cellular methylation and impairs cell division and differentiation and may leads to embryopathy. Thus homocysteine formed due to any cellular activity must be neutralized to prevent cytotoxicity.

In eastern Uttar Pradesh and adjoining districts of Bihar, no study has been done so far regarding folate status in NTD affected children and their mothers but these areas from NTD patients are reporting in high proportion to their senile we are having high prevalence of NTDs. This study determines the folate status in children with NTD, their mother and control counterparts and...
to assess its role in NTD. The results led us to a stage from where we can conclude that folate deficient condition is not a prevailing factor among the NTDs affected children and their mothers.

**Material and Methods**

This study was approved by ethical committee of Banaras Hindu University, Varanasi and accomplished in Department of Anatomy with collaboration in Department of Pediatric Surgery, Department of Neurosurgery and Department of Pediatric Medicine in Institute of Medical Sciences, Banaras Hindu University, Varanasi.

The blood sample of patient and their mother with age matched control groups were collected from Departments of Paediatric Surgery and Paediatric Medicine, Sir Sunderlal Hospital, BHU, Varanasi. Informed consent was obtained from parents. After confirmed diagnosis of NTDs by concerned authorities, 5 ml of blood from patient, their mothers and age matched control groups were collected in EDTA coated vials, centrifuged at 1500 rpm for 10 minutes, serum transferred into fresh sterile micro-centrifuge tubes and stored at -20°C till analysis. For estimation of folate in serum a kit based assay from Abbott (REF 1L71, ABBL268/R06) was used according to manufacturer’s instructions with deep concern. The data were presented as mean ± SD. The Student’s t-test was used to compare case and control groups for various examinations and statistical significance test was applied at 5 per cent level of significance.

**Results**

In the present study we have formed three groups on the basis of the age of mother, first age group belongs to 20 to 25 year old mothers with first child birth, second belongs 25 to 30 years old mothers with second child birth and third group have above 30 year old mother with order of defective pregnancy. We have correlated the level of folic acid and age of mother and found no significant correlation between age and serum folate status among mothers with defective child and control counterparts as well as in children with NTDs and age matched controls (Table 1).

**Table-1:** Summary of folate concentration in NTDs affected children their mothers and control counterparts.

<table>
<thead>
<tr>
<th>Groups</th>
<th>No.</th>
<th>Mean ± SD</th>
<th>‘t’ test</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>126</td>
<td>10.95 ± 4.31</td>
<td>1.76</td>
<td>P&lt;0.05 (NS)</td>
</tr>
<tr>
<td>Control</td>
<td>145</td>
<td>11.83 ± 3.91</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Children</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients</td>
<td>126</td>
<td>11.90 ± 5.48</td>
<td>1.75</td>
<td>P&lt;0.05 (NS)</td>
</tr>
<tr>
<td>Control</td>
<td>145</td>
<td>12.96 ± 4.47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In this study, we categorize the mothers of defective child in two groups to check any difference in serum folate status but we didn’t find any significant difference among the defective mothers (Table 2).

**Table-2:** Concentration of folic acid in mothers of different age groups having defective pregnancy.

<table>
<thead>
<tr>
<th>Age Groups</th>
<th>No.</th>
<th>Mean ± SD</th>
<th>‘t’ test</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 years</td>
<td>64</td>
<td>11.64 ± 4.28</td>
<td>1.78</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>&gt; 30 years</td>
<td>62</td>
<td>10.29 ± 4.20</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Discussion

In world, only few countries have made a compulsory rule of folic acid fortification, while others fortified it during the childbearing age. The earlier prediction regarding the benefits of folic acid supplementation takes on the result in significant reduction in neural-tube defects (NTD) within target population. Countries with compulsory supplementation achieved a substantial increase in folic acid intake and a significant reduction in the prevalence of NTD. However, the occurrence of NTD during the birth reduced about 5 cases per 10000 births including 7-8 cases of abortion per 10000 births\textsuperscript{32}. The reduction was independent from the quantity of folic acid distributed and clearly makes visible a ‘floor effect’ for folic acid-preventable NTD. Apart from beneficial effects of folate supplementation and prevalence of NTD, few other suspected harmful effects were also observed\textsuperscript{33}.

The assessment of potential role for genetic factors is restricted by gaps in knowledge of the enzymes, associated genes and their interaction with environmental factors\textsuperscript{34}. Apart from environmental, maternal health conditions and genetic factors, nutrition is also known for their contribution in NTDs. The relationship of depleted folate status in mothers is the one of the other causes of NTDs and best known, tested hypothesis till now by many scientists\textsuperscript{11, 12 & 35, 36}. However the exact mechanism behind the protective role of folate is still elusive. In Indian scenario after huge efforts of policy makers for folic acid supplementation the prevalence rate of NTDs are very high. Therefore, this study, we enrolled women having a defective pregnancy for estimation of serum folate level in cases of eastern Uttar Pradesh and adjoining areas of Bihar. The result of this study shows that population of aforesaid areas, whether control group women or women with defective pregnancy are not folate deficient. An intensive effort is required to design adequately powered studies to search the key factors responsible for high prevalence of NTDs in eastern Uttar Pradesh. This might have implications for public-health policies in respect of peri-conceptual folic acid intake, and call for a more individual supplementation practice and less for a general fortification of a basic food source. Therefore, the two basic conclusion could be in mind is that (1) the folic acid supplementation for increasing folate intake is not the only method to reduce the prevalence of NTD, and (2) Supplementation results in increase intake of folate for whole population and exhibiting huge non-targeted groups towards high status of folate might have unusual benefits or destructive effects in a number of individuals.

Acknowledgement: We are grateful to the parents who participated in this study.

References

Folate deficiency is not the only cause of neural tube defects


Folate deficiency is not the only cause of neural tube defects


----