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Case Report
Level of Folic Acid and Vitamin B12 in Mothers and Children with Neural Tube Defect

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Abstract

Background and Objective: Neural Tube Defect (NTD) is the leading cause of death in infants younger than one year. Incidence of congenital anomalies has approximately 1 in 1000 live births in the United States. Less dietary folic acid and vitamin B12 in the mother during the critical period of pregnancy reported to play a role in the occurrence of neural tube defects. The aim of this study was compared the level of folic acid and vitamin B12 in both mother and her child with and without NTD. **Methodology:** This study was cross-sectional design and will be examined levels of folic acid in six mothers and children with and without neural tube defect in Saiful Anwar Hospital during September, 2009 until September, 2013. **Results:** This study showed no significant differences of folic acid and vitamin B12 level between NTD and control group in mothers ($p>0.05$). The study also showed no significant differences of folic acid and vitamin B12 level between NTD group and control group in children ($p>0.05$). **Conclusion:** The level of folic acid and vitamin B12 in the mother having neural tube defect child as much as the mother with haven't neural tube defect child. Additionally, the result of the children above a year with neural tube defect and without neural tube defect has same folic acid and vitamin B12 level.

Key words: Neural tube defect, folic acid, vitamin B12, transforming growth factor β, insulin like growth factor 1

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Neural Tube Defect (NTD) is the terminology that used to encompass all clinical variation for not closing neural tube[1]. This malformation can results disorder on brain and spinal cord[2], affecting 0.5-2 per 1000 established pregnancies[3] , with the sex ratio (males: females) was[4] 0.73 and severe NTD have a 15-fold increased risk of death during the first year of life[5]. Neural tube is formed in the third and fourth weeks of fetal age[6]. The spinal cord forms early in embryonic stems from the region that is the flat area, which will then be rotated to form the neural tube when the fetus is 28 days old. If the neural tube does not close completely, then formed NTD. Neural tube defects are created when most women do not realize that she was pregnant[7].

The main flaw is the failure of neural folds fused in the midline. Then form the neural tube, called neuroectoderm. The next defect is a deviation in the formation of the mesoderm, which, in turn, forming the structure of bones and muscles that cover the underlying neural structures[1]. The central nervous system occurs in the third week of embryonic, shaped like a shoe-shaped plate ectoderm thickening, called the neural plate. The plates were located in the dorsal region, in the middle and front blastoporus. The lateral edges of these plates immediately rise to form two neural fold[8].

In further development, neural folds increasing, each approaching the halfway line and eventually united, thus forming the neural tube (neural tube). Unification began on the neck, take place towards the cephalic and caudal with an irregular pattern. At the end of the caudal and cranial fetus, the unification somewhat delayed, so neuroporus anterior and posterior to temporarily connect with a neural tube cavity amniotic cavity. Neuroporus anterior closure occurred on the 25th day of embryonic life, while the posterior neuroporus closed approximately two days later[1,8,9]. Failure closing the posterior neuroporus cause spina bifida, while failure of neural tube closure of the anterior portion causes anencephaly, eksensefalus, encephalocele or meningocele[9,10].

The cells of the neural plate and induction neuroectoderm prepare them to introduce what is called a neurulation process. Induction of cells is a complex process, involving the stimulation of a group of cells of the surrounding tissue. This process occurs repeatedly during organogenesis. Signals from the various processes and genes that regulate these events are still not clearly known. Various signaling molecules believed to be members of the superfamily of Transforming Growth Factor-β (TGF-β) including activin and Fibroblast Growth Factor (FGF)[1].

Neural tube defect is the leading cause of death in infants less than one year of age. The incidence of congenital anomalies has approximately 1 in 1000 live births in the United States. This defect is the second highest birth deformities after congenital heart defects[6]. The incidence of meningocele is 1-2 in 1000 live birth in South East Asia and the frequency of this clinical variation is eight until nine percent in Malang and Surabaya[11].The etiologies of NTD are nutrition, teratogen and genetic[12].

Some chromosomal and single-gene disorders have been associated with NTD. Spina bifida occurs more often in autosomal trisomy. Studies in animals show that there are 100 mutant genes that affect neurulation and almost all of them have homologs in humans[13]. The experimental studies on NTD provide some evidence that the number of physical agents (example X-ray radiation, hyperthermia, stress), drugs (example thalidomide, folic antagonists androgenic hormone, anti-epileptics such as valproate and carbamazepine and hypervitaminosis A), alcohol abuse, substance chemistry (example organic mercury, lead), maternal infections (such as rubella, cytomegalovirus, toxoplasma gondii, syphilis), metabolic conditions mom (example phenylketonuria, diabetes mellitus, cretinism endemic), capable of causing congenital malformations of the structure of the central nervous system[14,15].

Folic acid deficiency during conception until the end of the third month of pregnancy is believed to play a most important factor in NTD. Has observed that Transforming Growth Factor-β (TGF-β1) and Insulin-like Growth Factor-1 (IGF-1) play an important role in supporting bone formation. Therefore, folic acid deficiency can cause neural tube defects by decreasing the expression of TGF-β1 and IGF-1[11].

Folic acid has three physiological effects; first, as a cofactor to enzymes that synthesize DNA and RNA; second, it is necessary for the conversion of homocysteine to methionine and third, it is necessary for the methylation process in the formation of proteins. During the early formation of the fetus, the synthesis of nucleic acids and proteins are in peak condition and during this period maternal folate requirements increase sharply. When folate is insufficient, nucleic acid inhibited and cells are not able to facilitate DNA for mitosis. Cycle inhibition also resulted in the inability of DNA methylation and m-RNA of cells to synthesize amino acids and proteins including TGF-β1 and IGF-1[11,16].

This research examined folic acid and vitamin B12 levels of 6 mothers and children with NTD that has been hospitalized in Saiful Anwar Hospital Malang between September 2009 until 2013, compared with six mothers and children without

NTD. The folic acid and vitamin B12 levels are measured in Prodia Laboratory. Furthermore, the teratogen and genetic data is evaluated by history taking.

MATERIALS AND METHODS

This study was an observational cross-sectional approach and the data was taken from the patient's medical record in Saiful Anwar Hospital from September 2009 to September 2013 (3 years). This study examined folic acid and vitamin B12 levels in 6 mothers and children with neural tube defect. The results compared with six moms and children without NTD. The inclusion criteria were the subjects approved to be participated in this study and supported by signing the informed consent. The exclusion criteria were the subject of the study did not receive a blood transfusion within two months. The range of age for the mother is from 20 years old until 45 years old, for the children is from 1 years old until 6 years old.

The other etiology factors of NTD, teratogen and genetic, were asked to the subject using questioner. The teratogen factors include consumption of phenytoin, salicylate, alcohol, X-ray and fungal infection. In addition, the genetic factor is examined by comparing five generation's pedigree of subjects and controls.

RESULTS AND DISCUSSION

Table 1 shows that the mother who has a child with and without NTD has folic acid and vitamin B12 level above the minimum range. The normal range is between 7.2-19.4 ng mL^{-1} for folic acid and 211-911 pg mL^{-1} for vitamin B12 level. From the teratogen factors were asked using questioner and no mothers were exposed to teratogen. Moreover, the genetic factor was illustrated in 5 pedigrees generation and no one has a history of NTD before.

Researchers generally agree that nutritional factors are the most important etiology of neural tube defects. Less dietary folic acid in the mother during the critical period of pregnancy reported to play a role in the occurrence of neural tube defects. Approximately 70% of cases of neural tube defects can be prevented by administration of vitamin supplements[16-18].

The function of folic acid is to transfer one unit carbon in metabolism. That carbon is used in metabolic amino acid and biosynthetic purine-pyrimidine from nucleate acid. Folic acid will accelerate the separation of the cell during the closure of neural tube[19]. The vitamin B12 converse 5 mTHF to THF, which used to synthesize purine and thymine for DNA replication[20]. The age of the mother during pregnancy, too young and too old (more than 40 years old) can be a risk factor for NTD[21]. In this case report, the result odd ratio 2.5, 95% confidence interval = 0.2-87 (OR>1) so that age more than 40 years old can be a risk factor for NTD (Table 2).

Table 2 shows that children with and without NTD had folic acid and vitamin B12 levels above the minimum range 5.5-15.5 ng mL^{-1} and 211-911 pg mL^{-1}. The pattern of eating from both groups were asked by the questioner and we got that the consumption patterns among children with and without NTD have relatively similar tendencies, which was 4-5 perfectly healthy meal.

Furthermore, the folic acid and vitamin B12 status of children with and without neural tube defect produce t-test statistic 0.382 with probability equal to 0.711, while vitamin B12 produce t-test statistic 1.115 with probability equal to 0.305. The results of these tests indicate the probability>level of significance ($\alpha = 5\%$), thus it can be stated that the examination of children with neural tube defects

Table 1: Characteristics of the mother

	Mother who has a child with NTD				Mother who has a child without NTD			
Age (years)	<30	30.1-35	35.1-40	>40	<30	30.1-35	35.1-40	>40
Percentage	50	0	16.67	33.33	50	0	16.67	33.33
Nutritional factors								
Folic acid (ng mL^{-1})	16.3	-	25	13.2	15.6	-	18.17	13.42
Vitamin B12 (pg mL^{-1})	534	-	291	638	599	-	768	633
Teratogen factors								
Phenytoin	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Salicylate	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Alcohol	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
X-ray	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fungal infection	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Genetic factor								
In heritage	5*	5*	5*	5*	5*	5*	5*	5*

5*: From pedigree 5 generation, there wasn't history of neural tube defect, N/A: From questioner results, there wasn't history of exposure the teratogen during pregnancy, NTD: Neural tube defect

Table 2: Characteristics of the children

	Children with NTD				Children without NTD			
Age (years)	1-2	2.1-4	4.1-6	>6	1-2	2.1- 4	4.1-6	>6
Percentage	33.33	16.67	33.33	16.67	33.3	16.67	33.33	16.67
Folic acid (ng mL^{-1})	25.7	27.4	24.85	16.3	22.23	26.48	21.98	18.79
Vitamin B12 (pg mL^{-1})	677	944	609	364	890.5	913	768	757

NTD: Neural tube defect

Table 3: Different test of folic acid and vitamin B12 to NTD using the t-test

	t-test for equality of means			
	T	df	Sig. (2-tailed)	Mean Difference
Mothers				
Vitamin B12	1.313	10	0.218	154.5
Folic acid	-0.153	10	0.881	-0.34833
Children				
Vitamin B12	1.115	6.43	0.305	149.5
Folic acid	0.382	10	0.711	1.615

Sig: Significant

and without neural tube defect produce the same level of folic acid and vitamin B12 (Table 3).

Results from five case-control studies to investigate the relationship between folic acid supplementation in pregnant women with NTD births have been reported in 1988 and 1995. The study, conducted using a population of women with no previous NTD pregnancy and folic acid supplements before conception and then continued in the first week pregnancy; in some maternal and child health agencies. Mulinare *et al.*[22] in studies in Atlanta, GA, found 0.8 mg of folic acid associated with 60% decreased risk of NTD cases.

Bower and Stanley[23] evaluated the cases of spina bifida in Western Australia, reported a high intake of folate is used related to a reduced risk of neural tube defects by 75%. Instead, Mills *et al.*[24] found that there was no protective effect of folate intake is 0.8 mg through a case control study in California and Illinois. However, Werler *et al.*[25] in Boston, Philadhelphia and Toronto, showed a reduction of the provision of multivitamin related to decreased risk of NTD by 40% and Shaw *et al.*[26] in California, respectively, showed that with the addition of a multivitamin containing folic acid before conception is associated with decreased risk of NTD by 35% Shaw *et al.*[26]. Thus, the conclusion of four of the five retrospective studies showed a statistically significant reduction in the risk of NTD between 35 -75%, while one study found that the effect is not clear.

The role of maternal nutrition on fetal development has been widely known. Nutritional status of the parents can affect the quality of gametes and fertilization capacity. There are several reports that prove the enzyme metabolize polymorfisime fertilization may be associated with meiotic non-disjunction in the embryo[27]. From the observation that folic acid consumption before conception provide beneficial effects by lowering the incidence of neural tube defects as much as 50-70%[28] and reduction in NTD incidence increases with folic acid. As a result, the amount of folic acid associated with the gene has been studied in great detail. The following genes are involved in the metabolism of folate that 5,10-methylene tetrahydrofolate reductase (MTHFR), methylene tetrahydrofolate dehydrogenase (MTHFD), cystathionine β-synthase (CBS), methionine synthase (MTR), methionine synthase reductase (MTRR) and folate receptor α and β.

CONCLUSION

The results showed that folic acid and vitamin B12 of6 mothers who has children with neural tube defect and without neural tube defect had the same level. Additionally, the results of 6 children above a year with neural tube defect and without neural tube defect folic acid and vitamin B12 showed the same degree. The subjects are taken from SaifulAnwar Hospital from September 2009 until September 2013.

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