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Review Article

Neural Tube Defects, Risk Factors and Prevention: A Review

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ABSTRACT

Neural tube defects are the commonest congenital malformation affecting central nervous system, it consists of closed and open spinal bifida. Neural tube defect occurs due to the failure of closure of the neural tube, leaving the spinal cord unprotected by the bony cover and open to infection and trauma. The incidence of NTD in Malaysia is about 4.2 per 10,000 life birth. 51,574 USD per patient annually was estimated to be the cost of maintaining an NTD patient. Many researches has been conducted on the prevention of NTDs during pregnancy, most of the researches are on vitamins such as folic acid and vitamin B-complex. VPA is a known teratogen used in the treatment epilepsy, fetus exposure to VPA during pregnancy can lead to congenital malformations such as facial defects and neural tube defects. These condition can be diagnosed and treated in-utero which gives a better outcome than when done after delivery. The aim of this review is to show the burden and possible prevention of NTDs. Our research group is currently working on the preventive effect of *Nigella sativa* (black cumin) seed oil on valproic acid induced NTDs. Taking the advantage of its antioxidant effect.

Keyword: Neural tube defects; risk factors; prevention; Anencephaly; Meningocele

INTRODUCTION

Neural tube defects are the commonest congenital malformation affecting central nervous system, it consist of closed and open spinal bifida. Neural tube defect occurs due to the failure of closure of the neural tube, leaving the spinal cord unprotected by the bony cover and open to infection and trauma. Neural tube defects are classified into two major forms based on the site of opening of the neural tube. The opening of the anterior neuropore leads to anencephaly, which is a type of NTD in which major part of the brain and scull are missing [1]. The opening of the posterior neuropore leads to spinal bifida, which can cystic or occult type. The cystic type can be meningocele (in which the cyst

contain only membranes) or mylomeningocele (in which the cyst contain both membranes and neural tissue). The rate of occurrence of neural tube defect one in every 1000 established pregnancies worldwide, with the range of 0.2 to 10 per 1000 pregnancies depending on the geographical location [2]. The rate for developed countries like United States is 0.5 in 1000 births, while in developing countries like Latin America it is higher (2.2 per 1000 births for Argentina and 3.1 per 1000 births for Brazil [3]. The incidence for Asia is more with China having 13.9 per 1000 births [4]. The incidence of NTD in Malaysia is about 4.2 per 10,000 life birth based on a survey in Kuala Lumpur hospital, the survey shows that Malay ethnic group is more affected than Chinese and India [5]. Neural tube defects result in both psychological and economic burdens for the patients and their families. Thus NTDs continue to be major public health issue and are gaining more attention around the world [6]. The etiology neural tube defects are multifactorial with genetic and environmental factors playing more important role. Peri-conceptional folic acid supplementation and fortification is known to prevent about 72% of NTDs [7].

Economic burden of NTDs

Children given birth to, with NTDs tends to suffer from paralysis of the lower limbs, hydrocephalus, bladder and bowel dysfunction and some cognitive impairment. All of these are often associated with lifelong medical special care and rehabilitation management [8]. There are evidence to show a substantial economic burden associated with NTDs both direct and indirect cost on the family of the NTD patients. The first year of life comes with considerable burden with high health care expenditure more than those without NTDs. Higher resources utilization continue in adolescent to adulthood, with negative impact on the work force participation for the patient and the parents or caregivers [9]. In United States direct medical cost for NTD was estimated to be 51,574 USD per patient annually in 2003 [10]. However, in Spain about 2,953.138 USD was spent on social security system direct medical cost per year on each patient with spinal bifida in 1988 [11].

Prenatal diagnosis of NTDs

Modalities are now available for diagnosis NTDs prenatally. A successful screaming that is been used is by measuring the level of alfa fetoprotein (AFP) in maternal serum and amniotic fluid, and the level of acetyl cholinesterase in the amniotic fluid. AFP is a glycoprotein that is excreted into the amniotic fluid; it is secreted by fetal liver and yolk sac. AFP can cross the placental barrier and can be found in small concentration in the maternal serum, it is considered to be abnormally elevated if the level is 2 and half times more than the normal level for gestational age [12]. Acetyl cholinesterase is an enzyme derived from neural tissue of individuals and not normally found in the amniotic fluid. It is elevated in the amniotic fluid in pregnancies with open spinal bifida [13]. Recently the use of epigenetic markers in cultured amniotic fluid stem cells and developmental proteins (Shh and BMP4) for detection of neural tube defect from amniotic fluid and maternal serum [14].

Imaging is another known method that can be used for prenatal diagnosis for neural tube defects. Ultrasound (US) has been initially the imaging modality of choice because it is cheaper and easily assessable. However, its accuracy depends on the experience of the operator, maternal obesity and fetal position [15]. Accurate diagnosis of spinal defect can be made by ultrasound evaluation of fetal spine in all the 3 dimensions for localization of bone and soft tissue defect [16]. Magnetic resonance imaging (MRI) is now an important adjunct in the evaluation of fetal anomalies including NTDs [17].

Prevention of neural tube defect

The preventive aspect of NTDs historically started in 1970s, when Smithells and colleques [18]. Found that mothers who are carrying NTD affected pregnancies had reduced serum concentration of several vitamins such as folic acid, vitamin C and riboflavin. The authors perform an interventional study of periconceptional multivitamin supplementation with 0.36g of folic acid, to assess its effect on the prevention of NTD in women with previously affected pregnancy, which shows significant decrease in the number of recurrence [19]. A randomized control trail in Hungary, using multivitamin that contain 0.8mg of folic was

shown to have significantly prevent first occurrence of NTDs, considering that 95% of NTDs are all fist occurrence in a family [20]. A clinical trial study done in China showed a significant fall in NTD prevalence with folic acid supplementation during pregnancy [21]. The fundamental question is, what is the mechanism by which folic acid prevent NTDs. Folic acid is known to have a direct effect on the formation of neural tube in embryos, because folic acid enters one carbon metabolism which gives purines and pyrimidines for DNA replication and donation of methyl group to macromolecules in the cell, such as proteins, lipids and DNA [22]. Sildenafil citrate, which is a type 5 phosphodiesterase inhibitor popularly use in the treatment of erectile dysfunction has been found to be effective in prevention of valproic acid induced neural tube defect [23]. Studies have shown that vitamins, folic acid and drugs such as sildenafil can be used to prevent VPA induced neural tube defects. However, no research work was done to see the preventive effect of plant extracts on VPA induced neural tube defects. Our research group is currently working on the preventive effect of *Nigella satva* extract (Black cumin seed oil) on valproic acid induced NTDs.

Prenatal surgical treatment of NTDs

It has been estimated that 23% of pregnancies in which the fetus is diagnosed with neural tube defect during intrauterine life ends up in elective termination of pregnancy. Prenatal management of NTDs differs between countries, in Asia and some region in the United States more support for aggressive and intensive treatment are given than in Europe [24]. Mortality associated with spinal bifida are higher in those with brainstem dysfunction secondary to chiari II malformation, it is estimated at 35%. About 81% of the affected children have hydrocephalus that will require treatment [25,26]. Maternal – fetal surgery is a subspecialty of surgery that is directed towards correcting congenital anomalies by correcting them before birth [27]. In utero surgical repair for open spinal bifida has been in practice in many centers in United States for many years [28]. In human and mouse embryos the open spinal cord continues with the normal neurological differentiation during embryonic life, including the development of spinal sensory and motor function below the area of open spinal cord. However, as gestational age increases neurons within the area of the open NTD begin to die, which suggest that the amniotic fluid environment is toxic to the neural cells. This finding is what encourages the covering of the open neural tube during early embryonic development to prevent further neurodegeneration [29]. In-utero fetal surgery gives significant benefit for new born babies, such as improvement in spinal neurologic deficit and 50% reduction in shunt surgery for hydrocephalus. However, some complications such as premature delivery and uterine adhesion to the site of repair are associated with in-utero fetal surgery [30].

Risk factors for neural tube defect

There are both genetic and environmental risk factors that associated with neural tube defect. The environmental factors can be chemicals or radioactive elements. Anti-epileptic drugs are drugs that be used to prevent seizure, and are known to cause NTDs these drugs has to be used by epileptic mothers, during pregnancy to avoid seizure. Valproic acid is the most common anti-epileptic drug used in Malaysia [31].

Valproic acid and risk of NTDs

Valproic acid is an anti-epileptic drug that is frequently used worldwide as the first line treatment for migraine headache, bipolar disorder and seizure disorder. VPA is a known teratogen; fetus exposure to VPA during pregnancy can lead to growth retardation and congenital malformations such as facial dysmorphism, neural tube defects, urogenital, heart and skeletal malformations [32]. More attentions are given to VPA because it is more teratogenic than all the antiepileptic drugs and it is the drug of choice for epilepsy in young ladies of child bearing age [33,34]. Some registry studies recently done found that maternal treatment with VPA during pregnancy has great risk for somatic birth defects in offspring compared to other antiepileptic drugs that are in use. The rate of malformation for VPA mono therapy is about 6-11% depending on the dosage [35,36]. VPA is a histone deacetylase inhibitor; it is presently in clinical trials as an anticancer agent [37]. Its properties as an anticancer agent differ for different cell types and these include: growth arrest through arrest of cell cycle and decreased proliferation, apoptosis and anti-angiogenesis [38]. Microarray studies of VPA

intake during pregnancy have demonstrated an increase in the expression of genes responsible for growth-arrest, such as gadd45b and gas5 in the head region of the embryo. These suggest that neural tube defects may arise from inhibition of cell growth and induction of apoptosis in the neuroepithelial cells [39]. Additionally, a study previously shows that embryonic p53 protein expression increases just 3 hours after maternal VPA administration, this was localized to the embryonic somites [40]. Some previous studies on VPA, shows that VPA increases reactive oxygen species (ROS) formation. Reactive oxygen species (ROS) induces DNA double strand breakage in an in vitro study [41]. ROS can cause macromolecular damage to some components like lipids, proteins, and DNA and alteration in embryonic signaling pathways, in the cells [42].

Genetic risk factors for NTDs

More than 100 mutant mouse genes are known to disrupt neurulation, many of them shows multiple developmental anomalies other than NTDs, but few of them have provided insight into the regional signals for neural tube closure [43]. Evidence for genetic for genetic bases of NTDs is an increase recurrent risk of 2-5% for sibling of an index case compared to 0.1% risk in the general population. Women with two or more affected pregnancies have a risk of about 10% of more recurrence [44]. The prevalence of NTD is higher in same sex twins than in different sex pair, which is consistent with a pronounced genetic component. Presentation of NTD as multiple cases in families is very rear, but instead a sporadic pattern is usually recorded [2]. Two main gene pathways have yielded good result with regards to NTDs causation, they are; Planar cell polarity pathway and folate one carbon metabolism pathway.

The genes that encode enzymes which catalysis mitochondrial one carbon metabolism have been shown to cause NTDs. The gene MTHFDIL for mitochondrial 10-formyl-THF synthesis is associated with increased risk of NTDs [45]. Two genes, *AMT* and *GLDC*, encoding enzymes (aminomethyltransferase and glycine dehydroxylase) of the glycine cleavage system harbor various mis-sense genomic changes in NTD cases but not in unaffected controls [46]. The gene *GLDC*, these variants diminish enzyme activity, indicating a functional effect on folate metabolism. Each of these enzymes greatly affects flux of formate from the mitochondrion into the cytoplasm, which accounts for roughly 75% of one-carbon units entering folate metabolism [47]. Surprisingly, in folate complete dietary conditions the mitochondrial enzymes encoded by the genes *Mthfd1l* and *Amt* caused NTDs in knockout mice [46]. But exencephaly occurs in *Shmt1* null embryos in folate deficiency conditions [48]. The above findings indicate that neural tube closure is principally sensitive to change in the mitochondrial contribution to folate metabolism.

At the inception of neurulation, the embryo go through lengthening and narrowing of the disc shaped neural plate to ensure that neural folds are adequately close together for closure to start [49]. The elongation of the neural plate and the underlying tissue need a lateral to medial displacement and intercalation of cells, called convergent extension [50]. Indications of possible role of planar cell polarity pathway in human NTDs is from the discovery that genes in this pathway bring about NTDs in mouse mutants. Mutations in the trans-membrane proteins encoded by *Fzd3/6, Celsr1*, *Vangl2* and *Ptk7* all lead to craniorachischisis, which is a severe form of NTD yielding an open neural tube from midbrain to lower spine [2].

CONCLUSION

Neural tube defect remains one of the commonest categories of birth defect known worldwide. Imminent eradication of NTDs was predicted by the preventive effect of folic acid. However, the clinical severity and uncertainty on the outcome of repair in NTDs make researchers to focus on the improvement of primary prevention and prenatal diagnosis and treatment. In this review we provide evidence that NTD has worldwide incidence with not much work done on it in Malaysia. The burden of NTDs is very high and can impact on the economy of affected patients house hold and the country at large. The condition can be diagnosed and treated in-utero which gives a better outcome than when done after delivery. Our research group is currently working on the preventive effect of *Nigella sativa* (black cumin) seed oil on valproic acid induced NTDs. Taking the advantage of its antioxidant effect.

CONFLICTS OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this paper.

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