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Determination of Risk Factors Associated with Neural Tube Defects in Infants

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Abstract

Neural tube defects (NTDs) are serious birth defects of the brain and spine, NTDs is the major cause of disabilities in developing countries, there are many risk factors for this problem such as folic acid deficiency, consanguinity, genetic factors, exposure to x-ray radiation, chronic disease such as maternal diabetes and treatment of epilepsy such as valporic acid. **Material and Methods:** A descriptive cross-sectional facility-based study, the study population were all infants with NTDs who were coming to the neurosurgery clinic at the time of the study (June 2018 to September 2018) at Ibrahim Malik Teaching Hospital – Khartoum, the data were collected by questionnaire, by convenience sampling method, sample size is total coverage during the study period, data were analyzed by the computerized method Statistical Package for the Social Sciences (SPSS) version 20. **The results:** The current study revealed that most of all groups of infants were female (56%) their mean 1.56 ±. 501. The mothers whom conducted antenatal care and taking folic acid immediately after amenorrhea their mean 2.28 ± 1.29 & 3.58 ± 1.79 respectively. There is a significant relationship between early taking folic acid and mother education level p-value (. 000). 60% of children, their parent first-degree cousin, there mean 1.62 ±. 83. Previous family history of NTDs in close sibling (46%) with mean 1.62 ±. 64. Mothers having a chronic disease (Diabetes mellitus & epilepsy) the mean 2.88 ±1. 37. (82%) of mothers, not exposed to x-ray radiation, their mean 1.82 ±. 39. **Conclusion:** The majority of mothers, not taking folic acid during pregnancy**,** their awareness is poor regarding the importance of taking folic acid and their husband were related to them.

Keywords: Infants, Neural Tube Defect, Risk factors**.**

Introduction

Background:

Neural tube defects (NTDs) are the severe congenital defects of the central nervous system that begins during embryonic development and result from the failure of the formation process of neural tube closure[1]. Neural tube defects are a variety of disorders that affect the brain and spine, standardized clinical symptoms of spinal cord weakness and characterized by developmental mechanisms and the involvement of different tissue types. The labels of neural tube defects are confusing and various terms are used inconsistently in this article. Correct diagnosis and treatment are important to maximize the quality of life for these patients and prevent complications from hydrocephalus, neural bladder, and neural intestine [2].

NTDs are usually caused by prenatal events, inherited or acquired (usually between 3 and 4 weeks of gestational age), and vary from minor cosmetic irregularities to life-threatening disorders. The leading cause of infant mortality and disability worldwide[3]. Human affecting with neural tube defects represents 0.5-2 per 1000 pregnancies worldwide, with variations in incidence ranging from 0.2 to 10 per 1000 in specific geographic locations. It is estimated that more than 300,000 cases of NTD occur annually in developing countries. The problem affects the economic and social situation; the psychological impact of NTDs. It is estimated that about 2500 children are born annually with NTD in the United States[4].

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There is a strong indication that abnormal maternal metabolism contributes to a higher risk of developmental defects than to note the increased incidence of birth defects in infants born to mothers with diabetes during pregnancy[5].

Neural tube defect worldwide:

Congenital anomalies are major risk factors for infant morbidity and mortality in developing countries, and in Europe, the proportion of pregnant women with NTDs about one fetus in every 40 pregnancies. Closing the neural tube throughout the embryonic growth is a crucial step in the development of the central nervous system. The failure of this process indication to neural tube defects, including spina bifida and encephalopathy, which are among the most common birth defects around the world [6,7].

Numerous epidemiological characteristics of NTDs have been identified. In the United Kingdom and Ireland, the prevalence of NTDs declined annually from 4.5 / 1000 in 1980 to 1-1.5 / 1000 in 1990. This decline was preceded by the folic acid supplementation policy initiative. It is reported that Africans are the lowest proportion. Mexico and Northern China have high rates of NTDs. A longitudinal hospital-based study in Khartoum, Sudan showed a 2.4 / 1000 occurrence of NTDs. Another study in Omdurman found an occurrence higher than 3.48 / 1000. However, most of the mothers of the affected children in this study belonged to the tribes of West Sudan. In a retrospective study of 43 patients with NTDs from Sudan, 83.7% of Arab tribes and 16.3% of African descent[4].

Risk factors of neural tube defect:

Folic acid deficiency:

NTDs have complex and multi-factor causative factors that seem to be genetics, lifestyle and environmental alike involved. Chromosomal anomalies can be associated with the NTDs, but represent only 2% to 16% of isolated NTDs. Folic acid supplements have been shown to reduce the prevalence of NTDs, leading to national public health policies for folic acid. All United State public health recommendations for the prevention of neural tube defects are based on suggested levels of folic acid intake (e.g. 400 μg / day) [8, 9, 10].

Consanguinity:

Consanguinity was a major risk factor for the development of NTDs in a Murshid report from the Al Madina city, Saudi Arabia, where 89% of spina bifida was a relative parent compared with 67% of controls ($p < .0005$). On the other hand, the risk of recurrence of siblings of children with NTDs is approximately 2-5%, representing an increase of up to 50 times as observed in the general population. As will be further elaborated, inadequate periconceptional folic acid is a major risk factor and can be universally preventable[4].

Genetic factors:

Specific causes are identified in less than 10% of the affected subjects, such as amniotic bands, some genetic defects and one with the expression of pleiotropic, chromosomal anomalies and teratogenic factors, a specific mutation known as C677T polymorphism has been observed to be more common in affected children's parents with neural tube defects[11]. Cellular studies of neuronal, mutant mouse studies, and studies of interactions responsible for the formation and embossing of the neural tube plate[12].

Maternal diabetes:

The associated risk factors with NTD include maternal diabetes. Diabetes mellitus causes NTDs, as well as other birth defects, by disorderly the expression of genes that control basic developmental processes. Oxidation, antioxidants, including vitamin E, vitamin C, a combination of antioxidants and fat, or N-acetylcysteine, may also have a protective effect on pregnancy results. It is worth noting that some data on the risk factors for the development of NTDs are from a typical system rather than humans. There is a strong indication that abnormal maternal metabolism contributes to a higher risk of developmental abnormalities than to note the increased incidence of birth defects in infants born to mothers who had diabetes during pregnancy[5].

Anticonvulsant medication:

Exposure to valproic acid during the first trimester is associated with an increased risk of congenital malformations, including heart defects, cranial abnormalities, skeletal defects, extremities, and most often neural tube defects. The mechanisms through which VPA stimulates the effects are not fully understood, though previous studies support the role of oxidative stress[13].

X-ray radiation:

The special sensitivity of the fetus to exposure to radiation, the ability of radioisotopes to bind cells, tissues and DNA raises the question of whether fetuses/newborns with congenital defects with greater exposure have been severely damaged during the period after the fallout. To date, there have been four radiological consequences over the past six decades, namely Hiroshima and Nagasaki (1945), the Marshall Islands (1952) and Chernobyl (1986) and recently Fukushima (2011). As far as Chernobyl, there has been no report of the following radiological consequences. But post- Chernobyl observations identified high rates of neural tube defects in Turkey. And then from other countries such as Bulgaria, Croatia and the Republic of Belarus. The study in the province of Turkey showed that hospital deliveries had significantly increased in cases of brain loss and opened spina bifida (5.8 per 1000 live births) in 1983- 86 period. A survey of 1204 residents of Bursa City also revealed a high prevalence of spina bifida occulta (16.3%) [14].

Prevalence of NTD

Spina bifida and anencephaly, the most common forms of NTDs, occur in almost 300 000 newborns worldwide. The prevalence of NTD has declined significantly over the past three decades due to progress in the refined decision of ultrasound in a fetal uterine examination, clinical availability of serum alpha-fetoprotein measurements, termination of affected pregnancies, and folic acid supplements widely consumed by women in the reproductive age group. Shurtleff reported that the occurrence of myelomeningocele in Seattle, USA, was 0.5 per 1000 births in 1981–1982, which then dropped to 0.05 in 2001. Morris and Wald Estimates mentioned that a significant reduction in the neonatal prevalence of NTD is estimated in England and Wales in 1999. Their analyses demonstrated that the prevalence of NTD was 3.80 per 1000 live births in 1965, which steadily declined to 0.14 in 1997, that is, a reduction of 96%. Conversely, the estimated number of terminations increased considerably from 0.04 per 1000 live births in 1970 to 1.50 per 1000 live births in (1997)[15]. NTDs can be classified in "open" NTDs in which the neural tissue is exposed and "closed" NTDs with the neural tissue covered by tissue. "Open" NTDs includes craniorachischis is resulting from a total failure of neurulation with most of the brain and the entire spinal cord remaining open, anencephaly when the defect occurs in the cranial region and spina bifida cystica when the defect is localized in the lumbosacral area[16].

Significance of the Study:

There are some problems concerning with disabilities resulted from NTD, so to the best knowledge of the researcher, there are no research studies about the risk factors of neural tube defects in children done at Ibrahim Malik Hospital - Khartoum. Therefore, it is necessary to conduct this study to put the recommendation to solve this problem in the future. Also, many studies supported that NTDs are one of the major causes of mortality and disabilities in developed countries, there are suspected to be important causes of pediatric mortality and morbidity in the developing country. There is a strong need to conduct this study in Sudan as NTDS are on the increase and there is a gap in knowledge between mothers regarding the preventive role of folic acid supplementation[17].

Objective of the Study:

To assess risk factors of neural tube defects in infants at Ibrahim Malik Teaching Hospital.

Material and Methods

Introduction:

This chapter begins by presenting the research design. This is followed by the place and duration of the study, study population, data collection technique and tools, sampling method and sample size, the procedure of data collection, data management, ethical considerations, and data analysis.

Study design:

This is a descriptive cross-sectional facility-based study. The component of the study was used to determine the risk factors of neural tube defects.

Place of the study

The study was conducted in neurosurgery pediatric clinic, Ibrahim Malik Teaching Hospital-Khartoum .

Duration of the study

The study was conducted during 4 months period (from June – September 2018).

Study population

The study population for this study was all infants with NTDs who were coming to the neurosurgery clinic at the time of the study (June 2018 to September 2018) at Ibrahim Malik Teaching Hospital - Khartoum.

Data collection technique & tools

The data is prepared, collected by asking questions based on a questionnaire which filled by the researcher after asking the mothers in the study group about the risk factors of NTDs.

Sampling method & Sample size

Non-probability, convenience sampling method Sample size: total coverage of infants with NTD attending Ibrahim Malik Teaching Hospital neurosurgery pediatric clinic during the period of data collection, the data were collected from mothers of an infant.

The procedure of data collection

A letter was sent to the head of the clinic expressing a formal request to conduct the research study at the neurosurgery pediatric clinic and seeking permission to do so. Signs of agreement from the head of the clinic were provided before conducting the research study. The eligible mothers were identified from the head of the clinic considering their infants with NTD and they were invited to participate in the research study through the staff. The researcher made it very clear to mothers that their participation was voluntary.

Data management

Manual coding was used to check any error in coding. The coding manual and dummy tables were developed before entering the data. Double entry of data from researcher was done to prevent potential data entry error. The data were checked and cleaned by performing preliminary frequency distribution to enhance accuracy and reliability.

Ethical considerations

All potential mothers of infants with NTDs who participate in this study were given verbal information and verbal consent about the study and informed of their rights. They were informed that participation in the study was voluntary and that they could withdraw without explanation, and that withdrawal would have no effect on their infants. The participants were assured that their infant's progress would not be affected by their decision to participate, or not participate, in the research study.

Opportunities were provided for participants to ask questions at any time, and the researcher was freely available to answer all participant questions related to the study. All mothers were assured about the confidentiality of their responses. All information collected was confidential and was not disclosed to anyone other than the researcher. No names appeared on any results and a coding system is known only to the researcher was developed and used.

Data analysis

Data was presented using the SPSS program (version 20) in numbers, percentages, mean and standard deviation. The level of significance was adopted at $p < 0.05$.

Results

Table (1): showed that the frequency distribution of socio-demographic characteristics of the studied subjects, wherever the majority of the studied sample was female infants, they represented (56%) with a mean 1.56 ±. 50, half of infants sample their age less than 1 month (50%) with a mean of age 1.96 ± 1.15. The majority of mothers were aged more than 35 years old (60%), with a mean of age 2.46 ±. 73. Mother's residence, 62% from outside Khartoum, with a mean of 1.62 ±. 49. Fewer numbers of mothers were posting university level (6%) with a mean 2.36 ± 1.27.

Table1. Demographic characteristic of infants and their mothers under study. (N=50)

Items		No (%)	Mean	SD
Child age (Per months)	Less than 1 month	25 (50%)	1.96	1.15
	1-4 months	8 (16%)		
	5-8 months	11(22%)		
	9-12 months	6 (12%)		
Child sex	Male	22(44%)	1.56	.501
	Female	28(56%)		
Mother age	Less than 18	7(14%)	2.46	.734
	19-35	13(26%)		
	More than 35	30(60%)		
Mother residence	Khartoum	19(38%)	1.62	.490
	Outside Khartoum	31(62%)		
Mother educational level	Primary school	16(32%)	2.36	1.274
	Intermediate school	15(30%)		
	Secondary school	7(14%)		
	University	9(18%)		
	Post university	3(6%)		

Table (2): illustrated that, mothers' knowledge regarding risk factors of neural tube defects, 44% of mothers conducted antenatal care immediately after amenorrhea, their mean2. 28 ± 1.29. Regarding time of taking folic acid 60% of the mother not taking folic acid during all periods of pregnancy, with mean 3.58 ± 1.79. Husband-wife relationship 60% were first-degree cousin, with a mean of 1.62 ±. 83. There is equal previous family history of NTDs in close sibling and another family member (46%), with mean 1.62 ±. 64. Mothers having a chronic disease and taking continuous drugs, 28% of mothers were diabetic and 14% were epileptic mothers and 58% not having a chronic disease. 82% mother not exposed to x-ray radiation, with a mean of 1.82 ±. 39. The majority of cases were mengiomylocele (74%).

Table2. Mothers' knowledge regarding risk factors of neural tube defects

Items		No (%)	Mean & SD
Conduction of antenatal care	Immediately after amenorrhea	22(44%)	2.28±1.29
	Two weeks after amenorrhea	6(12%)	
	Three months after amenorrhea	8(16%)	
	Not conducted	14(28%)	
Time of taken of folic acid during pregnancy	Preconceive	11(22%)	3.58±1.79
	Immediately after amenorrhea	9(18%)	
	Not taking	30(60%)	
Husband-wife relationship	First-degree cousin	30(60%)	1.62±.83
	Second degree cousin	9(18%)	
	Not related	11(22%)	
Previous family history of NTDs	A close sibling	23(46%)	1.62±.64
	Another family member	23(46%)	
	Not present	4(8%)	
Mothers having a chronic disease	Diabetes meletes	14(28%)	2.88±1.37
	Epilepsy	7(14%)	
	No disease	29(58%)	
Mothers taken drugs cautiously	Hypoglycemic agent	14(28%)	2.30±.89
	Anti-epileptic drugs	7(14%)	
	Not taken	29(58%)	
Mothers' exposure to X-ray radiation during early pregnancy	Exposed	9(18%)	1.82±.39
	Not exposed	41(82%)	
Pattern of NTD	Mengiomylocele	37(74%)	1.54±1.01
	Mengiocele	4(8%)	
	Spinabifida oculta	4(8%)	
	Encephalocele	5(10%)	

Table 3: Exposed that, the presence of correlation between the mothers' educational level and taking folic acid during pregnancy, P value (.000).

Table 3. Correlation between mothers' educational level and taking folic acid during pregnancy.

Items		Did you take folic acid during pregnancy?		Significance
		Yes	No	
Mothers educational level	Primary	6	10	.000
	Intermediate	0	15	
	Secondary	3	4	
	University	8	1	
	Post university	3	0	

Table 4: Showed that there is no correlation between mother's residence and conduction of antenatal care, p-value (.23).

Table 4. Correlation between mother's residences and conduction of antenatal care

Items		Did you conduct antenatal care?		Significance
		Yes	No	
Mothers residence	Khartoum	11	8	.23
	Outside Khartoum	23	8	

Discussion

Neural tube defect is the main cause of mortality, morbidity, and disabilities in infants, lack of knowledge regarding the risk factor of neural tube defects are present. Otherwise, an adequate knowledge is necessary to prevent recurrence of NTDs. So the existing trends in researches emphasize the importance of investigating knowledge regarding the problem. The present study aimed to assess the risk factors of neural tube defects in infants. The current study found that 28% of mothers included in the study reported that they had never received ante-natal care, this means that early conduction is very important for doctor prescription of folic acid because the problem occurs in the 1st. 4 weeks of gestation, which supported by[18]. Whom mentioned that the development and closure of the neural tube is completed 28 days After pregnancy. If the neural tube fails, the embryo develops a neural tube. However, some writers also support the possibility of some NTD resulting from the temporarily closed neural tube re-opening[19]. 60% of mothers didn't take folic acid at whole period of pregnancy, so folic acid is crucial to the health of DNA as it is needed for a process called methylation, a gene may not function without proper methylation this supported by[20].

The time of taking folic acid is inaccurate time, so only 22% of mothers received folic acid preconceive of the total number. Preconception supplement with folic acid substantially decreases the risk of occurrence and recurrence of NTD. There is accumulating evidence indicated that folic acid taken by mothers only 0.4mg around the time of conception prevents the development of NTD in a genetically susceptible embryo and during the earliest days of pregnancy[21]. This is primary prevention, which emphasizes the importance of focusing on the search for potentially treatable or avoidable environmental trigger factors. Mothers awareness is very important regarding taking folic acid, and health care provider should discuss nutrition, which content, folic acid during pregnancy and the benefit of taking folic acid through media and advertisement. 60% of husband, wife relationship was first-degree cousin. Recent evidence supports consanguinity is of genetic importance because close relatives have a greater chance of carrying the same alleles than unrelated people. Descendants of relatives' combinations are likely to inherit alleles of identical symmetry from the offspring of unrelated parents[22]. Presence of NTD in sibling and family, 46% of the mothers mentioned that there is NTD in their close sibling, 46% in another family member and 8% not having a previous family history, so families who had children with NTD the possibility of having subsequent children with anomaly is higher than those in the general population[23].

Mothers having a chronic disease and taken drugs cautiously, 28% having diabetes mellitus, 14% having epilepsy and 58% haven't. The abnormally high glucose level in maternal blood lead to increased glucose transported to the embryo, and is responsible for teratogenicity effecting, excess glucose metabolism disturbs the neural tube formation. Regarding drugs, insulin therapy had been considered the gold standard for management because of its efficiency in achieving tight glucose control and the fact that it does not cross the placenta[24].

Valporic acid is an effective, widely used anti-epileptic drug, unfortunately, it is used in pregnant women associated with NTD in the offspring. This supported by[25] Whom mentioned that. Since 1982, various case reports and studies have been reported implicating that valproic acid increased the risk of NTDs in offspring of VPA treated pregnancies. Few of mothers took x-ray radiation during 1st 4 weeks of pregnancy due to different fracture (18%) and 82% haven't. According to the American College of Radiology, no single diagnostic x-ray has a radiation dose significant enough to cause adverse effects in a developing embryo or fetus[26]. Focusing on the pattern of NTD to ensure the presence of this problem. The majority of these problems (74%) were mengiomylocele comparatively of a study done by[27]. Whom mentioned that Lumbosacral myelomeningocele was the most common type of NTD in our region. There is a significant relationship between early taking folic acid and mother education level p-value (. 000). There is no significance between the conduction of antenatal care and mother residence p-value (. 23).

Conflict of Interest

The author declared that she did not receive any financial support for this work, and there is no conflict of interest related to this study.

Conclusion

The majority of mothers, not taking folic acid during all periods of pregnancy, and also they are first- degree cousin husband-wife relationship. The high percentage of mothers, not having a chronic disease and not exposed to x-ray radiation. There is the presence of correlation between the mothers' educational level and taking folic acid during pregnancy.

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