ORIGINAL ARTICLE

Prevalence and Associated Risk Factors for Neural Tube Defects in Patients at Sheikh Zayed Hospital Rahim Yar Khan

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ABSTRACT

Objectives: To determine prevalence and associated risk factors for neural tube defects in patients at Sheikh Zayed hospital Rahim Yar Khan.
Study design: Prospective study with nested case control study.
Place & duration of study: This study was conducted in paediatric unit of Sheikh Zayed Hospital, from January 2007 to December 2009.
Patients & method: All the neonates who presented to us with neural tube defects were included in the study population as cases. The cases were matched to neonates with no identified congenital anomaly, same sex & same maternal age taken as controls. The parents of all these cases & controls were interviewed and structured questionnaire form having different variables was filled.
Results: 11655 neonates were admitted during study period out of these 140 patients were having neural tube defects making the prevalence 12.01/1000 live births. Out of 140 cases 57.1% were female & 42.8% were male. The mean age of mothers in both cases and controls was 27.2years with SD 5.77 years. Factors which were strongly associated with NTD and statistically significant found were periconceptional folic acid supplementation [p<0.00, Odd ratio (OR) 0.21, 95%CI 0.11, 0.44], consanguinity of parents (p<0.01, OR 1.91, 95%CI 1.16, 3.12), maternal anemia (p<0.00, OR 2.2, 95%CI 1.36, 3.55), maternal education (p<0.00 & OR 2.2, 95%CI 1.35, 3.59) and socioeconomic status (p<0.00 OR 2.8, 95%CI 1.72, 4.52). Factors which were moderately associated with NTD included, primigravida (p>0.14 & OR 1.42, 95%CI 0.88, 2.27), maternal under nutrition (p>0.15 & OD 1.41, 95%CI 0.88, 2.27), family history (p>0.10 & OR 2.6, 95%CI 0. 8, 8.54) and history of previous affected baby (p>0.14 & OR 2.1, 95%CI 0.76, 5.74). Associated hydrocephalus was found in 72% of cases & other associated congenital anomalies in 14% of cases.
Conclusion: Lack of periconceptional folic acid supplementation, increased frequency of consanguinity, maternal health, maternal anemia, young maternal age and female sex of patients, lack of maternal education and low socioeconomic status are major risk factors for neural tube defects. Improvement in maternal education, health, socioeconomic status, proper antenatal follow up with periconceptional folic acid supplementation and avoidance of consanguineous marriage can markedly reduce this disease which has many physical & psychosocial affects on the child and parents.
Key words: Neural tube defect, folic acid supplementation. consanguinity, maternal health,

INTRODUCTION

Congenital malformations involving the coverings of the nervous system are called neural tube defects (NTD). Neural tube defects (NTD) are classified as Anencephaly, Cranium bifidum (cranial meningocele, encephalocele), spina bifida occulta, spina bifida cystica (myelomeningocele, meningocele) and sacral agenesis.

Anencephaly is a neural tube defect that occurs when the cranial end of the neural tube fails to close, usually during the 23rd and 26th days of pregnancy, resulting in an absence of a major portion of the brain and skull. Infants born with this condition are without the main part of the forebrain (the largest part of the cerebrum) and are usually blind, deaf and unconscious Infants are either stillborn or usually die within a few hours or days after birth. It is most common major CNS malformation in the western world and seen 37 times more frequently in female than in male.The recurrence rate in families can be as high as 35%[1].

Cranium bifidum includes cranial meningocele & encephalocele. In Cranial meningocele the underlying brain is normal & a meningeal sac protrudes through a skull defect. Encephalocele where a midline sac protrudes through a skull defect

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that may contain brain. The defect is caused by the incomplete closure of the cranium during development. Hydrocephalus is common[2].

Spina bifida occurs in two forms. The mildest is spina bifida occulta where the spinal cord often remains unaffected. It occurs in 5-10% of the population[2]. Individuals usually exhibit no outward symptoms & the defect often goes undetected however in some cases abnormalities of spinal cord have been described. Ectodermal abnormalities may be associated like dermal pit, a depression with a tuft of hairs and a fatty swelling[2]. The second form, Spina bifida manifesta is more physically apparent and occurs in two types, meningocele and myelomeningocele. Meningocele (approximately 4% of this group) occurs when membranes covering the spinal cord & brain push through opening and is generally not associated with any neurological deficit.

Myelomeningocele (96% of this group) is most severe form of spina bifida where both spinal cord & surrounding membranes push though the open area in the embryo's back. Because the spinal cord itself is exposed, there is a greater potential for it be damaged. Lumber & lumbosacral regions are the most common sites of these lesions while cervical & thoracic regions are the least common sites. Certain other neurologic anomalies such as hydrocephalus and chiari II malformation accompany myelomeningocele in approximately as 84% & 90% respectively[3]. In addition, myelomeningocele have a higher incidence of associated intestinal, cardiac, and esophageal malformations as well as renal & urogenital anomalies[4].

Neural tube defects (NTD) are among the most common defects of human congenital malformations, affecting 1 per 1,000 live births in the United States. In Canada, one in every 750 babies is born with spina bifida[4]. Spina bifida and anencephaly are the most commonly reported NTDs which affect 4,000 pregnancies resulting in 2,500 to 3,000 births in the United States each year.[5,6] World wide prevalence of NTD is 1.4-2 per 1000 births[7]. In Pakistan prevalence in certain studies is 13 per 1000 birth[8].

NTD are congenital defects which have multifactorial inheritance, having a significant genetic component to their etiology that interacts with a number of environmental risk factors[9]. The risk factors associated with NTDs include deficiency of folate (2-8 fold increased risk), previous pregnancy with NTDs (30 fold increased risk), ethnicity / geographical locations, low socioeconomic status, use of anticonvulsant during pregnancy, maternal diabetes(2-10 fold increased risk), obesity(1.5-3.5 fold increased risk) and hyperthermia in 1st trimester of pregnancy(2 fold increased risk)[10,11].

The risk of recurrence following the birth of the one child with a neural tube defect is approximately 4-8%.The risk increases to at least 10% after the birth of two affected children[3]. Significant ethnic differences in prevalence exist as people of Celtic origin have the highest rate of spina bifida. Incidence is also high in Northern Ireland, the west of Scotland and south Wales. Medical evidence has confirmed that folic acid (a water soluble vitamin found in many fruits, leafy green vegetables, wholegrain breads, cereals and legumes) may prevent the majority of neural tube defects. Currently in certain countries, there has been marked reduction in NTDs, which is due to strong recommendation of folic acid supplementation in diet and particularly during pregnancy and also due to termination of NTD pregnancy[2].

As in Pakistan, the prevalence of NTD is very high as compared with developing countries and there had been limited studies conducted regarding prevalence and associated risk factors for NTD so the purpose of our study was to find the prevalence and associated risk factors for NTD in patients presenting to us in pediatrics department sheikh Zayed hospital Rahim Yar Khan.

OBJECTIVES

To determine prevalence and associated risk factors for neural tube defects in patients at Sheikh Zayed hospital Rahim Yar khan.

PATIENTS & METHODS

It is a prospective study with nested case control study which was carried out in paediatric unit of Sheikh Zayed Hospital, Rahim Yar Khan from January 2007 to December 2009. All the neonates who presented to us with neural tube defects were included in the study population as cases. The cases were matched to neonates with no identified congenital anomaly, same sex & same maternal age taken as controls. Neural tube defect patients aged above one month were excluded. The data was collected on structured questionnaire having variables like sex of patient, maternal age, gravida status, consanguinity of parents, folic acid supplementation, maternal exposure to radiation & drugs, family history, maternal health, maternal educational status, socioeconomic status, associated hydrocephalus & other congenital anomalies. NTD patients who presented during the study period were evaluated. Similar numbers of controls were taken .The mothers of these cases and controls were interviewed & questionnaire was filled.

Data was entered & SPSS (version 16.0) used to analyze the data. All controls were compared with NTD cases. Categorical variables were analyzed using the chi-square test. Risks were estimated by the odd ratio (OR), and the precision of OR was assessed by its 95% confidence interval (CI). The significant cut-off P-value was <0.05.

RESULTS

11655 neonates were admitted during study period out of these 140 patients were having neural tube defects making the prevalence 12.01/1000 live births among patients presenting at sheikh Zayed hospital . Among all NTD cases, spina bifida (n= 130), encephalocele (n=6), anencephaly (n=4). Out of 140 case 57.1 %(n= 80) were female & 42.8% (n= 60) were male which shows NTD is more common in female sex. The mean age of mothers in both case and control groups was 27.2years with st. deviation 5.77 years. Of total cases, 71.4% (n=100) of mothers were in <30 years age group and 28.6 %(n=40) in >30 years age group making NTD is more prevalent in younger age mothers. In cases 51.4% mothers were multigravida and 48.6% primigravida while in controls 60% multigravida & 40% primigravida making p>0.14 & OR 1.42, 95%CI 0.88, 2.27. 48.5% mothers were under weight in cases & 40% in controls making p value 0.15 & OD 1.41, 95% CI 0.88, 2.27. Maternal over weight was present 21% in cases compared to15% in controls with p 0.16 & OD 0.65, 95%CI 0.35, 1.19 which is not significant.

Consanguinity of parents was positive 70% in cases and 54.2% in controls with p<0.01 & OR 1.91, 95% CI 1.16, 3.12 making significant risk factor for NTD. Folic acid supplementation in periconceptional period was positive 8.6% in cases & 30% in controls with p<0.00 & OR 0.21, 95%CI 0.11, 0.44 which shows significant risk factor for NTD. Maternal anemia was positive 64.3% in cases & 45% in controls with p<0.00, OR 2.2, 95%CI 1.36, 3.55 which is also significant. Exposure to drugs was positive 7.8% in cases & 6.4% in controls. Radiation exposure during pregnancy was positive 2.8% in cases & 1.4% in controls. History of previous affected baby was positive 8.5% (n=12) in cases & 4.2%(n=6) in controls with p>0.14, OR 2.1, 95%CI 0.76, 5.74.

Table 1: Results of the study

Variable	Cases n=140	Controls n=140	P value	Odds ratio(OR)	95%Confidence interval(CI)	
Sex	Male n=60(42.8%) Female n=80(57.1%)	Male n=60(42.8%) Female n=80(57.1%)	1.00	1.00	0.62	1.60
Maternal age	<30 years n=100(71.4%) >30 years n=40(28.6%)	<30 years n=100(71.4%) >30 years n=40(28.6%)	1.00	1.00	0.59	1.68
Gravida status	Primigravida n=68(48.6%) Multigravida n=72(51.4%)	Primigravida n=56(40%) Multigravida n=84(60%)	0.149	1.42	0.88	2.27
Consanguinity	Positive n=98(70%)	Positive n=76(54.2%)	0.01	1.91	1.16	3.12
Periconceptional folic acid intake	Positive n=12(8.6%)	Positive n=42(30%)	0.00	0.21	0.11	0.44
Maternal anemia (HB<11g/dl)	Positive n=90(64.3%)	Positive n=63(45%)	0.00	2.2	1.36	3.55
Maternal under nutrition (BMI<18.5kg/m^2)	Positive n=68(48.5%)	Positive n=56(40%)	0.15	1.41	0.88	2.27
Maternal overweight (BMI>25kg/m^2)	Positive n=30 (21.5%)	Positive n=21 (15%)	0.16	0.65	0.35	1.19
9-Maternal education	Uneducated n=98(70%) Primary & above n=42(30%)	Uneducated n=72(51.4%) Primary & above n=68(48.6%)	0.00	2.2	1.35	3.59
Socioeconomic status	Low n=91(65%) Middle & above n=49(35%)	Low n=56(40%) Middle & above n=84(60%)	0.00	2.8	1.72	4.52
Family history	Positive n=10(7.1%)	Positive n=4(2.8%)	0.10	2.6	0.8	8.54
Previous affected baby	Positive n=12(8.5%)	Positive n=6(4.2%)	0.14	2.1	0.76	5.74
Exposure to radiation	Positive n=4(2.8%)	Positive n=2(1.4%)	0.40	2.0	0.36	11.26
Exposure to drugs	Positive n=11(7.8%)	Positive n=9(6.4%)	0.64	1.24	0.49	3.09

The family history was positive 7.1% (n=10) in cases & 2.8% (n=4) in controls with p>0.10 (OR 2.6, 95% CI 0.8, 8.54). 70% (n=98) of mothers in cases were uneducated and 30% were primary and above while 51.4% uneducated & 48.6% primary and above in controls with p<0.00, OR 2.2, 95%CI 1.35, 3.59 showing significant risk also.Among socioeconomic status 65% of cases were belonging to low & 35% to middle& above while in control group 40% low, 60% middle & above with p<0.00,OR 2.8, 95%CI 1.72, 4.52. Associated hydrocephalus was found in 72% & other associated congenital anomalies in 14%

Table 2: Comparative results of consanguinity in cases and controls.

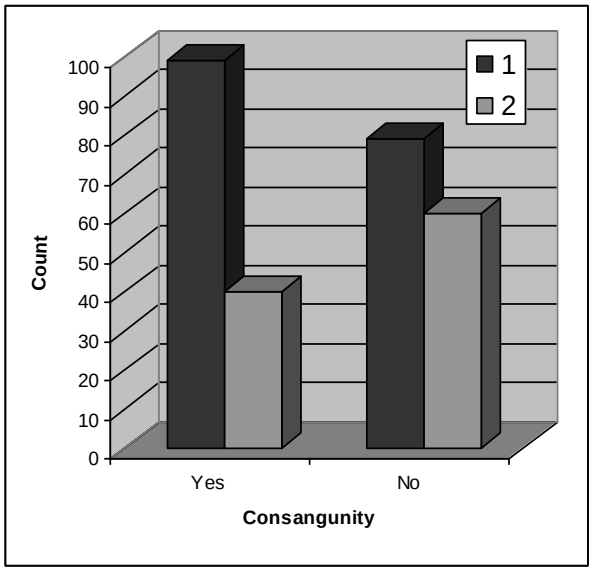
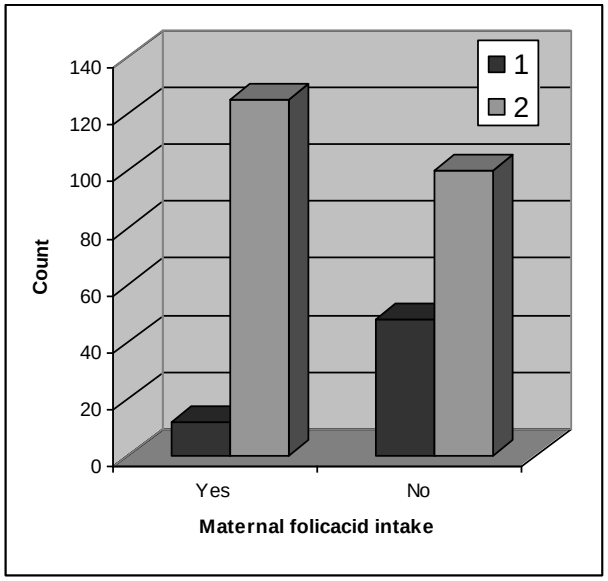


Table 3: Comparative results of folic acid intake in cases and controls



DISCUSSION

Neural tube defects are the commonest structural congenital anomalies. Its incidence varies in different geographical & ethnic areas because of multifactorial etiology. The prevalence of NTD in our study is 12.01/1000 live births The prevalence in our country in some studies is 13.09 per 1000 live births[8] in Peshawar and 7.8 per 1000 live birth in Rahim Yar khan[12] which is very high as compared to prevalence world wide (1.4-2 /1000 births)[7] or in developed countries like USA (1 /1000 births).The results of our study are comparable to other local studies. The reasons for high prevalence in our country is because of presence of many risk factors like lack of periconceptional folic acid supplementation ,consanguinity of parents, maternal malnutrition ,low socioeconomic status, lack of education regarding etiology of NTD & its prevention.

NTD is more common in female gender as is evident from our study showing male to female ratio 1:1.3 which is comparable to other studies conducted in Iran & in Pakistan where 2/3rd of affected newborn were female.[12,13,14].

Maternal age in our study has moderate influence on NTD as 71.4% of cases are in less than 30 years age group and 28.4% in above 30 years age group, which is also comparable with other study[12]. The association of NTD with primigravida was 48.6% while in multigravida it was 51.4%. The effect of maternal parity in certain studies showing more risk with primigravida mother[15] while in our study it is slightly more with multigravida which is statistically not significant.

Consanguinity has been proved statistically one of the major risk factor in our study as 70% in cases compared to 54% in controls with p value <0.05 and this result is comparable to many local as well as international studies[16,17,18]. This is preventable and definite associated risk factor which can be resolved by creating awareness and providing marital & genetic counseling.

In our study 8.6% of mothers in cases had periconceptional folic acid supplementation in comparison to 30% in controls which is a very important risk factor and statistically significant with p value <0.00. There is a strong correlation between incidence of NTD & maternal nutrients especially in relation to folic acid intake. Different studies showing reduced risk of NTD even up to 70% with folic acid supplementation in the peri-conceptional period. The centre of Disease control (CDC) claims that 75% of spina bifida can be prevented by folic acid supplementation (400ug daily). It has been proved by a set of studies showing folic acid deficiency as important factor & its supplementation has role in

prevention[19,20]. Certain randomized controlled trial from Hungary found daily multivitamin supplement containing 0.8mg folic acid was effective in reducing the occurrence of NTD in first births[2]. U.S. public health service recommends that all women capable of becoming pregnant consume 400 micrograms of folic acid daily. Because approximately 50% of pregnancies in the United States are unplanned and the neural tube develops before most women know they are pregnant, it was also recommended that women consume this amount of folic acid routinely[11].The supplementations of folic acid in the diet of women of child bearing age will markedly reduce the incidence of this disease as has been seen reduction of 30% in NTD births in US with mandatory wheat flour fortification and upto 50% and 70% reduction in Canada and Chile respectively with even higher amounts of folic acid added to flour than in US.[2] The estimated number of NTD affected pregnancies in the USA declined from 4000 in the period 1995-1996 to 3000 in1999 to 2000 (Center for disease control and prevention, 2004). Apart from folic acid supplementation, early diagnosis of NTD and advising early termination of affected pregnancies with this lethal anomaly will help in decreasing the existing prevalence rate at birth.

Maternal health is also a significant factor in the etiology of NTD as is evident from certain studies. Maternal overweight & obesity has association with congenital malformations like NTD[21]. In our study 48.5% of mothers were underweight (BMI<18.5kg/m$^{2)}$ in cases & 40% in controls while 21.5% were overweight (BMI 25-30 kg/m^2) in cases compared to 15% in controls, the association of over weight mother with NTDs in our study is less as compared with underweight which possibly explain poor maternal intake of food and especially folic acid. Maternal anemia in our study is also a significant risk factor as proved statistically with p<0.00 and has been favoured by certain other studies[12.]

Maternal education & socioeconomic factors have inverse influence on NTD as level of education & socioeconomic status is low, the risk of NTD is high as proven from large scale study conducted in China & in other countries[22,23,24,25]. The results of our study are comparable to these studies. Lack of awareness of potential benefits of folic acid supplementation during periconceptional period, failure of access to medical care and failure to take green leafy vegetables in diet could be related with uneducation & low socioeconomic status.

Although women with previous history of NTD birth have 10-30 times increased risk for next NTD birth however the majority (95%) of NTD pregnancies occurs in women without previous NTD births in certain studies[26]. In our study history of previous affected pregnancy was only in 8.5% which suggest majority of patients are 1st born which is comparable with other studies[8]. Thus the prevention of the 1st occurrence is of real public health importance[27.] Family history of NTD is one of the strongest risk factors for these disorders. The risk for NTD in the siblings of affected persons ranges from 3% to 8% and is increased to 10% after the birth of two affected children. The recurrence risk is consistently higher than that of the general population for second or third degree relatives of affected persons[11].In Australia it is recommended by National health and medical research council for women with a close family history of NTD should have 4mg periconceptional folic acid supplementation2. The results of family history in our study is 7.1% positivity in cases compared to controls as 2.8% resulting in p>0.1 but OR is 2.6.

Exposure to radiations & drugs are also risk factors for NTD particularly anticonvulsants like valproic acid or carbamezepine having inutero exposure. The risk with valproic acid is 1-2%.[11] but in our study the nature of drugs taken by mothers were not known and it accounted for 7.8% in cases compared to 6.4% in controls which are not statistically significant.

Hydrocephalus is associated in 70-85% of cases of myelomeningocele which is resulting due to chiari ii malformation. In our study we found hydrocephalus in 72% of cases and certain other congenital anomalies in 14% of cases.

CONCLUSION

Lack of periconceptional folic acid supplementation, increased frequency of consanguinity, maternal underweight, maternal anemia, young maternal age, female sex of patients, lack of maternal education and low socioeconomic status were found major risk factors for neural tube defects. Improvement in maternal education, health, socioeconomic status, proper antenatal follow up with periconceptional folic acid supplementation and avoidance of consanguineous marriage can markedly reduce this disease which has many physical & psychosocial affects on the child and parents.

Our study provides new light regarding still high prevalence of this disease in our country which needs urgent steps regarding its prevention & enforces the public health programmer for conducting education programmes for health professionals and for general public for NTD awareness, its preventive steps and early diagnosis of NTD and advising early termination

of affected pregnancies, will help in decreasing the existing prevalence.

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