Neural Tube Defects; Clinical Patterns, Associated Risk Factors and Maternal Awareness in Khartoum State, Sudan

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Abstract

Neural Tube Defects account for one of the most common birth defects and are associated with a high mortality, morbidity and life-long disability. The main objective of this research was to determine maternal risk factors, the most common clinical presentations of neural tube defects and assess maternal awareness on folic acid supplementation and its preventive role in the occurrence of neural tube defects. This was an observational hospital-based case finding study that covered 91 patients with neural tube defects and their respective mothers conducted in the main hospitals of Khartoum state from September 2011 to February 2012. Questionnaires were filled in the form of interviews and the patients were examined to determine the clinical presentation of the neural tube defects. The results showed that experiencing any febrile illness (\(p\leq0.001\)), taking medications (\(p\leq0.001\)) during pregnancy and consanguinity (\(p\leq0.001\)) have been associated with the birth of a fetus with a neural tube defect. 42.9\% of all NTDs were myelo-meningoceles and 73.3\% of all NTDs were lumbo-sacral in location. 61.5\% of NTDs were associated with hydrocephalus and 50.5\% had lower limb weakness. Only 14.3\% of mothers were aware of the preventive role of folic acid in the development of neural tube defects. In conclusion the study emphasizes the complexity of the etiology behind neural tube defects, variability of its presentation and yet unsatisfactory awareness among Sudanese mothers about folic acid and its benefits regarding neural tube defects.

Keywords: Neural tube defects; folic acid; consanguinity, Sudan.

INTRODUCTION

Neural tube defects (NTDs) are one of the most common birth defects, affecting over 300,000 births globally each year. They exhibit a marked geographical variation, with the incidence higher in Great Britain and lower in Japan (Marks et al.1998). Indian and Eastern Mediterranean populations also have relatively high incidences of NTDs, However, unlike the Western white populations, anencephaly is more common than spinabifida (Saxena et al. 2013).

The incidence of neural tube defects (NTDs) in developing countries has been reported to be up to four-fold higher than in developed ones (Cherian et al.2005), this may be due to the absence of preconceptional counselling coupled with suboptimal antenatal care services. (Adeleye et al. 2010).

Neural tube defects (NTD) occur because of a defect in the neurulation process. Since the anterior and posterior neuropores close last, they are the most vulnerable to defects. Consequently, a majority of NTDs arise in these areas. NTDs can be classified, based on embryological considerations and the presence or absence of exposed neural tissue, as open or closed types (Dias et al.1998, Dirks et al.1999).
Over the years, epidemiologic studies have tried to determine the etiology behind NTDs. Certain genetic and environmental factors have been found to affect the occurrence of NTDs. However, there is a strong link between folic acid deficiency and the occurrence of NTDs (Salvi, 2003). To date, few specific environmental causes of neural-tube defects have been recognized, such as maternal diabetes (Becerra et al. 1990) and maternal use of some antiepileptic drugs, such as valproic acid. (Lammer et al. 1987) Other factors, including fever and hyperthermia in early pregnancy (Graham et al. 1998) and obesity (Shaw et al. 1996), have been proposed.

Treatments of NTDs depend on the severity of the complication. No treatment is available for anencephaly and infants usually do not survive more than a few hours. Aggressive surgical management has improved survival and the functions of infants with spina bifida, meningoceles and mild myelomeningoceles (Walters et al. 1997). Neural tube defects resulted in 71,000 deaths globally in 2010 (Lonzano, 2012).

In Africa, the reported incidence of spina bifida is variable, e.g. in Malawi it was 0.47/1000, in Cape Town the prevalence of NTDs was 1.74/1000, however in Sudan the incidence was 3.48/1000 which is the highest reported in Africa so far (Masmati et al. 2000, Viljoen et al. 1995, Elsheikh et al. 2009).

The objectives of this study were: determining the clinical presentations of NTDs, determining different maternal risk factors for the occurrence of NTDs (age, consanguinity, febrile illnesses, diabetes mellitus, medications), and assessing maternal awareness on folic acid supplementation and its preventive role in the occurrence of NTDs. There is strong need to conduct this study in Sudan as NTDS are on the increase and there is gap in knowledge among mothers regarding the preventive role of folic acid supplementation.

MATERIALS AND METHODS

Study design and data collection

This was a prospective, observational, hospital based study that was conducted in the main hospitals of Khartoum state, the capital of Sudan, during the period September 2011 to February 2012. The study included all patients born with NTDs and their respective mothers. All newborns (alive and stillbirths) diagnosed as having a neural tube defect during the study period were included in the study. The dependent variable was Neural tube defects and the independent variables were age of mother, febrile illness during pregnancy, medication taken during pregnancy, maternal diabetes, family history for neural tube defects and Folic acid supplementation. Ninety one babies were included in the study. Newborns were examined by a consultant paediatrician or a senior paediatric registrar to determine the pattern of NTDs and associated anomalies. Data was obtained in the form of questionnaires, all mothers were met and personal interviews were conducted using a specifically designed questionnaire for collecting the required data.

Simple descriptive statistics, frequency distributions and cross tabulation were performed on Statistical Package for Social Sciences (SPSS) software version 17. The results were tested for association using chi-square between maternal wellbeing and NTDs. Level of significance was set on an alpha level at 0.05. Ethical clearance and approval for conducting this study was obtained from the ethical committees of the main hospitals in Khartoum state. Prior informed verbal consent was obtained from the parents of the babies participating in this study after full explanation of the study.

RESULTS

In this prospective study ninety one babies with NTDs were detected in Khartoum state during the study period. Classification of the mothers according to age showed that 40 (44%) of them were falling in the age group (26 – 35) years, whereas 36 (39.6%) were falling in the age group (15 – 25) years and 15 (16.5%) were between 36-45 years. When the mothers were classified according to their level of education, it was noticed that 23 (25.3%) of them were found to have secondary education, whereas 21 (23.1%) were found to have basic education and 19 (20.9%) were university graduates with an illiteracy rate of 13.2%. The study showed that the majority of the mothers (89.1%) were unemployed (house wives) and 47 (51.6%) of the respondents were found to have regular visits to antenatal care centers. When the respondents were inquired about experiencing any form of febrile illness during pregnancy (specially the first trimester), 27(29.7%) of them reported so. More details revealed that 10 (37%) described a flu-like illness, whereas 5 (18.5%) reported malaria. Table (1).

The study showed that only one out of the total number of subjects was found to have gestational diabetes, whereas 61 (67%) did not check their blood glucose levels during pregnancy. 26 (28.6%) of the mothers reported taking medications during pregnancy. 5 (19.2%) mentioned antiemetics, 3 (11.5%) NSAID (paracetamol / aspirin) whereas 6 (23.1%) mentioned antibiotics. Table (2). None of the respondents was found to have been exposed to any form of radiation during pregnancy. The study showed that 41 (45.1%) of the mothers were taking folic acid during pregnancy.
Table 1. Febrile illness during pregnancy.

<table>
<thead>
<tr>
<th>Illness</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flu-like illness</td>
<td>10</td>
<td>37.0</td>
</tr>
<tr>
<td>Malaria</td>
<td>5</td>
<td>18.5</td>
</tr>
<tr>
<td>Fever + skin rash</td>
<td>3</td>
<td>11.1</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>29.6</td>
</tr>
<tr>
<td>Total</td>
<td>27</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Table 2. Type of medication during pregnancy.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID* (paracetamol / aspirin)</td>
<td>3</td>
<td>11.5</td>
</tr>
<tr>
<td>Anti-emetics</td>
<td>5</td>
<td>19.2</td>
</tr>
<tr>
<td>Calcium supplements</td>
<td>1</td>
<td>3.8</td>
</tr>
<tr>
<td>Herbal</td>
<td>4</td>
<td>15.4</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>6</td>
<td>23.1</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>26.9</td>
</tr>
<tr>
<td>Total</td>
<td>26</td>
<td>100</td>
</tr>
</tbody>
</table>

*NSAID; Steroidal anti-inflammatory drugs

Table 3. Associated congenital anomalies

<table>
<thead>
<tr>
<th>Anomaly</th>
<th>Frequency</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>3</td>
<td>13.6</td>
</tr>
<tr>
<td>Respiratory</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Renal</td>
<td>1</td>
<td>4.5</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>6</td>
<td>27.3</td>
</tr>
<tr>
<td>Hernia</td>
<td>4</td>
<td>18.2</td>
</tr>
<tr>
<td>Other</td>
<td>7</td>
<td>31.8</td>
</tr>
<tr>
<td>Total</td>
<td>22</td>
<td>100</td>
</tr>
</tbody>
</table>

Regarding the timing of folic acid consumption during pregnancy, 23(56.1%) started folic acid during the second trimester and only one woman (2.4%) took folic acid preconception. Figure 1.

When the respondents were asked if they are aware that folic acid supplementation reduces the risk of developing neural tube defects, it was found that 13 (14.3%) of them were aware of that.

None of the respondents was found to have given birth to a child with a neural tube defect, however, 54 (59.4%) of the mothers reported consanguinity with their husbands and only one out of the total number of the subjects reported a positive family history of NTDs. 23 (25.3%) of the cases were diagnosed antenataly. The study showed that 61(67%) of the cases were delivered by normal spontaneous vaginal delivery whereas 30(33%) by caesarian section. The study demonstrated that 56(61.5%) of the subjects were females and 35(38.5%) were males, moreover 87(95.6%) were term and 4 (4.4%) were preterm. Classification of the babies according to the type of neural tube defect, showed that 39 (42.9%) of them were found to have myelomeningocele, 35 (38.5%) were found to have meningocele, 16(17.6%) had encephalocele and only one baby (1.1%) out of the total number had anencephaly. Examination for the location of the neural tube defect revealed that 55 (73.3%) of the cases were Lumbo-sacral whereas 10 (13.3%) were Lumbar, 8(10.8%) were sacral and only one (1.35%) in the thoracic region.

Examination for associated anomalies showed that hydrocephalus was present in 56(61.5%) of the total subjects, lower limb weakness in 46(50.5%) and foot deformity in 10(11%). Other associated anomalies outside the central nervous system are shown in table 3.
Discussion

This study was conducted in the main hospitals of Khartoum state with the main objective of determining maternal risk factors associated with NTDs. The study showed that almost 84% of the study subjects were at the age group (15-35) years which is considered to be an indication of a young generation. This result actually complements a study conducted in Omdurman Hospital in Sudan where the majority of mothers were found to be younger than 25 years of age (Elsheikhet al. 2009). The education level of the study subjects is somewhat satisfactory with an illiteracy rate of 13.2% and is expected to play an essential role in enhancing the level of knowledge and attitude of those mothers towards NTDs. 89.1% of the mothers included in this study were unemployed. This can be related to the fact that only 20.9% of them were University graduates.

The study showed that 51.6% of the respondents have attended regular antenatal care; yet this did not affect the outcome significantly. This fact may be attributed to the possibility that the antenatal care clinics they attended might have been poorly equipped and did not investigate the mothers thoroughly.

Experiencing any febrile illness and taking medication during pregnancy were found to have significant association with the occurrence of NTDs (p<=0.001). As for febrile illness the majority described acquiring a flu-like illness (37%) or malaria (18.5%). This result supports the findings of previous studies that also found fever and hyperthermia experienced in early pregnancy as a risk factor for the development of neural tube defects (Graham et al., 1998). As for medications that were used prior to the pregnancy and during the first trimester, most mothers reported taking antibiotics (23.1%) or NSAID (11.5%). Previous studies have established the direct teratogenic effect of anti-epileptic medications such as valporic acid in causing NTDs (Lammer et al. 1987). However, the role of antibiotics and NSAID have not yet been clearly established as teratogens.

The fact that the majority of the mothers were not screened for any form of diabetes may be attributed to the affordability of the investigations and poor antenatal care. Diabetes cannot be considered as risk factor among this group of mothers, since only one was a diabetic and most respondents didn’t have their blood glucose checked. As mentioned before, diabetes is a well-established risk factor for the development of NTDs (Becerra et al., 1990), regardless of the inconclusive results of this study.

Our study showed insignificant association between consumption of folic acid and development of NTDs (P =0.345). Almost half (45.1%) of the respondents reported taking folic acid, however, 56.1% of the mothers who did take folic acid took it in their 2nd trimester, moreover 70.1% of the mothers did not take folic acid regularly during their pregnancy due to poor compliance. It can be clearly concluded that the true potential of folic acid in preventing NTDs cannot be accurately assessed in this group of mothers. This makes it difficult to draw any conclusions about the role of folic acid in the development of NTDs. Regardless, most of the studies advocate the use of folic acid during pregnancy as a form
of primary prevention of NTDs, Folic acid taken by women at least four weeks prior to conception and throughout the first trimester of pregnancy, or periconceptional intake, has been associated with up to 80% reduction in the incidence of NTDs. (Czeizel et al.1992). A 19% reduction in NTD birth prevalence occurred following folic acid fortification of the United States food supply. However, factors other than fortification may have contributed to this decline (Honeinet al.2001).

Almost 86% of the study subjects were not aware that folic acid supplementation reduces the risk of developing NTDs. This was found to be the universal state of the mothers regardless of their educational status. This is in agreement with the Nigerian study where most of the respondents did not know the beneficial effect of Folic acid in reducing the risk of NTDs (Lawalet al.2014).

In our study consanguinity has been found to be a risk factor for the development of NTDs (p=<0.001). 59.4% of the mothers were indeed related to their husbands and 49.5% of them were direct first degree relatives. This may indicate the complex genetic role behind the etiology of NTDs. This is in agreement with a study done in India where NTDs were significantly higher among babies born to parents of consanguineous marriage (P=0.01) (Mahadevanet al.2005).

Our study showed that 56(61.5%) of the subjects were females and 35(38.5%) were males, with females more affected that males. This is in agreement with many other studies, however no genuine explanation could be offered for this gender preponderance. (Masmati et al.2000, Gaigi et al.2000, Viljoen et al.1995).

In this study 56(61.5%) of all NTDs were associated with the presence of hydrocephalus, which is similar to many other previous studies (Nielsen et al.2006, Cate et al.2002, Northrup et al.2000). Almost half (50.5%) of all fetuses with NTDs suffered from lower limb weakness and this is usually permanent in most cases. 24.2% of NTDs were associated with other anomalies, most were musculoskeletal in origin (27.3%). This clearly shows that NTDs are almost always associated with other anomalies of one form or another increasing the morbidity and mortality of NTDs.

**Conclusion**

Neural tube defects account for one of the most common birth defects. Experiencing any febrile illness, taking medications during pregnancy and consanguinity have been associated with increased risk of birth of a fetus with a neural tube defect. The study emphasizes the complexity of the etiology behind neural tube defects, variability of its presentation and yet unsatisfactory awareness among Sudanese mothers about folic acid and its beneficial role in preventing neural tube defects.

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**References**


Elsheikh GE and Ibrahim SA (2009). Neural Tube defects in Omdurman Maternity Hospital, Sudan. Khartoum Medical Journal; 2: 185 -190

Lawal TA and Adeleye AO (2014). Determinants of folic acid intake during preconception and in early pregnancy by mothers in Ibadan, Nigeria. The Pan African Medical Journal; 19:113