

Original Article

Clinical profile of neural tube defects in Sudanese children: Is malaria a risk factor?

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ABSTRACT

Neural tube defects (NTDs) are one of the most common structural malformations in human kind. It is a public health problem with great impact on the child, parents and the community at large. The aim is to study the epidemiological profile and patterns of NTDs in under five-year of age Sudanese children who attended the neurosurgical clinic at the National Centre of Neurological Sciences (NCNS), Khartoum during the period from March 2014 to December 2014. This was a prospective cross-sectional study conducted at the neurosurgery clinic in NCNS, Khartoum. A pre-set structured questionnaire was the research tool. All children under five-year of age with NTDs, who attended the Neurosurgery clinic in NCNS during the period of the study, were recruited. The data were analyzed using statistical package of social sciences (SPSS). The sample size was 71. The majority of cases were less than 6 months of age (57.7%). The female to male ratio was (1.2:1). Spinal defects were noticed to be more common than cranial defects. The spina bifida was the commonest anomaly accounting for (73.2%), whereas, encephaloceles accounted for (26.8%). The lumbo-sacral region

was the commonest site (34.6%). Hydrocephalus was the most commonly associated anomaly. NTDs were common in the young mother age group and consanguine parents. Although folic acid was taken by (69.0%) of the mothers, it was not on regular bases in the majority. Infection, particularly, malaria, during pregnancy was reported in 25.4%. Anti-malaria Sulfadoxine/Pyremethamine (Fansidar®) used by most in our cohort is an anti-folate drug and could be implicated in the etiology.

Keywords:

Spina bifida; Pattern; Epidemiology; Risk factors.

BACKGROUND

Neural tube defects (NTDs) account for the most common congenital anomalies with a high incidence compared to other congenital anomalies at birth. It affects 0.5-2 per 1000 pregnancies worldwide. It occurs because of a defect in the neurulation process. In north Russia the incidence of an anencephaly and spina bifida was 2.11/1000 compared to 1.08/1000 in Norway. The rates were the

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lowest in some African countries [1]. Two prospective hospital based studies in Sudan reported an incidence of 2.4/1000 and even higher incidence of 3.48/1000 [2]. The prevalence has fallen over recent decades in high-income countries [3,4].

The etiology is complex, with both genetic and environmental factors being implicated [5]. Ghada et al. from Sudan revealed that the incidence of NTDs was 3.48/1000; 50% of the cases were myelomeningocele, 38% were anencephaly, 10% encephalocele [6]. Although most cases are sporadic, genetic and non-genetic environmental factors are considered in its etiology. Consanguinity is a significant risk factor for the development of NTDs accounting for 20 to >50% of all marriage in some parts of Africa, Middle East and Asia [6]. Consanguinity was found to be remarkably high among Palestinian families with open NTDs [7].

Female fetus preponderance up to 3:1 for anencephaly and 2:1 for spina bifida has been observed [1,8]. Hydrocephalus is a common congenital anomaly usually associated with NTDs. Nugud et al. 2003 study from Sudan reported clubfoot as the most common association accounting for 34.9% followed by hydrocephalus 23.3% [9]. Rajab et al., in a retrospective study determined the incidence of (NTD) and congenital hydrocephalus (CH) in Oman revealed that the incidence of NTD was comparatively low (1.25 per 1000) [10]. Sphincter disturbance was reported in 14.1%, in contrast to a study done in Europe, which showed that 50% of the affected patients suffer from sphincter disturbances and anorectal anomalies with urogenital malformation [11].

There is a marked geographic variation in the rates of NTDs occurrence. It is low in African studies. Msamati BC, et al. from Malawi reported a low incidence of NTDs of 0.63/1000 [12]. Whereas, Buccimazza SS, and his colleagues showed that the NTD prevalence is low among black as compared to white population in Cape Town [13]. However, higher rates were reported from Africa as 2.6/1000 from Tanzania and 7/1000 deliveries in the middle belt of Nigeria [14,15]. Early maternal age is considered a risk factor (0.14) for mothers younger than 35 years of age ascribed to defective hyaluronate metabolism resulting in vertebral failure [16].

The genotype MTHFR 677C>T and two other genes (betaine-homocystinemethyl-transferase (BHMT) 716G>A (5-Methyltetrahydrofolate-homocystine methyltransferase 501A>G genotype) in the presence of gestational diabetes (GDM) were

significantly associated with NTDs when folate was not supplemented [17].

A Chinese study of NTDs etiology revealed that the interaction between single nucleotide polymorphisms (SNPs) in folate metabolism pathway genes and environmental risk factors. A precise protective dose of folic acid against NTDs has not been determined [18]. The prevalence declined in KSA following a mandatory fortification of flour with folic acid with the minimum requirement of 1.653 gram of folic acid for each kilogram of flour [17].

This hospital based case study aimed to analyze the pattern of neural tube defects in children under five years of age and to explore the possible etiological factors.

METHODS

This was a prospective cross-sectional study conducted in the neurosurgery clinic at the NCNS in Khartoum, Sudan during the period from March 2014 to December 2014. The data were collected by filling out a pre-set structured questionnaire. All Children under five years who attended the Neurosurgery clinic in NCNS and confirmed clinically with neural tube defects were included in the study. The data were analyzed using statistical package of social sciences (SPSS).

RESULTS

The total number of patients was 71. Most of the children screened in this study were less than 6 months of age (57.7%) with no significant differences between the female and male ratio (1.23:1), accounting for (56.3%) and (43.7%) respectively. The age of the mothers ranged from 18-43 years and the most affected group were those between 18-23 years (35.2%). Beside other demographic data, consanguine marriage was noted among 69.0% of the families of the affected children, 71.4% of them were first-degree cousins (Table 1).

The majority of cases were less than 6 months of age (57.7%). The female to male ratio was (1.23:1) (Table 1). NTDs were common in the young mother age group and consanguine parents.

Some diseases such as febrile illnesses during the first trimester including malaria were recorded. Malaria was reported in 18 mothers (25.4%), 23.9% of these mothers received anti-malarial drugs. UTI was reported in 7 (9.9%) of patients. While pregnancy with hypertension

was reported in 3 (4.2%) of cases. Mothers who reported no previous illness accounted for 47.7% of the study group.

The spinal defects were noticed to be more common than cranial defects. Spina bifida and encephaloceles constituted 73.2% and 26.8%, respectively. Spina bifida cystica accounted for the most common spinal defects and was reported in 60.6%, of which 67.5% were myelomeningocele. Whereas, the rest were meningocele and spina bifida occulta (in 32.5% and 12.7%, respectively). Most of the spinal defects (34.6%) were found in the lumbo-sacral area, followed by the lumbar, sacral, dorsal, dorso-lumbar and cervical (Figure 1). Local infection was reported in 25 (48.1%) of cases. CSF leakage was reported in 25 cases (55.8%).

Occipital encephalocele accounted for (73.7%) while frontal encephalocele accounted for (26.3%). The encephalocele took different shapes as described in (Table 3). Hydrocephalus was found to be the commonest associated congenital anomaly reported in (53.8%) followed by talipes equinovarus deformity, which was present in (23.9%) of the patients. Other associated anomalies such as scoliosis, kyphosis, bone defects, undescended testicles and cardiac defects were present in 19.7% of the patients. Sphincteric disturbance was found in 14.1% of the patients.

A considerable percentage (69.0%) of mothers received folic acid during pregnancy. However, only 8% of the mothers took the folic acid on a regular basis and 53.1% of them started to take it during the first trimester.

Table 1- Demographic data.

Education level	Illiterate No. (%)	Basic No. (%)	High School No. (%)	High Education No. (%)	Total No. (%)
Mother education	21 (29.6)	27 (38)	13 (18.3)	10 (14.1)	71 (100)
Father education	14 (19.4)	26 (36.6)	16 (22.5)	15 (21.5)	71 (100)
Socio-economic Status	Low 45 (63.4)	Moderate 18 (13.3)	High 18 (13.3)	–	71 (100)
Mode of delivery	Normal vaginal 42 (59.15)	Assisted 8 (11.26)	Caesarian section 21 (29.58)	–	71 (100)
Parity	Primigravida 20 (28.2)	Parous 26 (36.6)	Multiparous 25 (35.2)	–	71 (100)

Table 2- Patterns of skin abnormalities overlying the NTD lesions.

Skin abnormality	No. (%)
Ulcerated Skin	06 (8.5)
Hyper pigmented	01 (5.6)
Soft	10 (52.6)
Firm	01 (5.6)
Cystic	07 (36.8)

Table 3 - Pattern of neural tube defects.

Pattern of NTDs defect	Number (%)
<i>Spina bifida</i>	52 (73.2)
Spina bifida cystica	43 (60.6)
Spina bifida occulta	09 (12.7)
<i>Encephalocele</i>	19 (26.8)
Frontal encephalocele	05 (26.3)
Occipital encephalocele	14 (73.7)

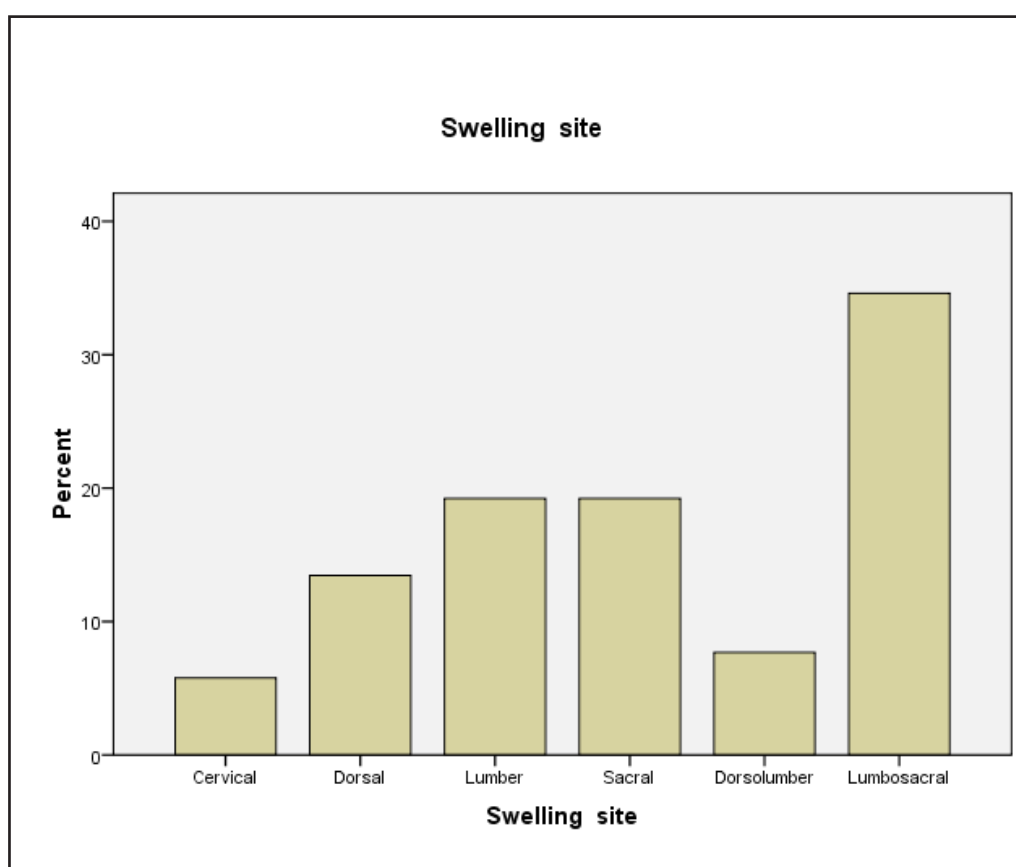


Figure 1 - The anatomical site of neural tube defects.

DISCUSSION

The age of the patients ranged from 0-60 months, 57.7% of these cases were less than 6 months, this agrees with a previous prospective study from Sudan [5]. Although most of the families lived in rural areas, the results indicated that, mothers were aware about the defects and sought medical advice at earlier age. A considerable number of parents in this study received different levels of education.

Contrary to many worldwide studies that showed female predominance, this study and that of Nugud et al. 2003 from Sudan showed no significant gender difference with female to male ratio of (1.23:1) [1,8,9]. This disagreement may be due to the small numbers of patients and to the short duration of these studies.

The pattern of defects reflected a high rate of spina bifida compared to encephalocele. Similar to some African studies, spina bifida cystic was more common than spine bifida occulta, however it does not agree with others [8,11,12]. Myelomeningocele was more common than meningocele, this was in agreement with Nugud et al., study, but didn't not agree with a prospective follow up study from Iran, which showed a high prevalence of meningocele compared to myelo-meningocele [9,17]. The occipital encephalocele is more common than frontal encephalocele. This finding agrees with a retrospective study from Uganda [18].

Hydrocephalus and clubfoot were common congenital anomalies usually associated with NTS [9]. In this study, 59.2% of the NTD cases were associated with hydrocephalus, followed by clubfoot, which disagreed with Nugud et al. study from Sudan reporting clubfoot as the most common association in 34.9% followed by hydrocephalus 23.3% [9]. Sphincter disturbance was present in 14.1% unlike a European study, where sphincteric disturbances and anorectal anomalies with urogenital malformations were more prevalent [11].

Infection, particularly, malaria, during pregnancy was reported in 25.4%. A considerable group of the affected mothers received anti-malaria drugs in the 1st trimester, mainly Sulfadoxine/Pyremethamine (Fansidar[®]) that is an anti-folate drug. This was not previously reported from Sudan and it was not a finding, to our knowledge, in other similar reports on risk factors of NTDs [19].

The genotype MTHFR 677C>T was significantly associated with NTDs with synergistic effects when there was no folate supplementation and also in the presence of gestational diabetes [16]. Genotyping is not currently widely available or affordable in Sudan.

No case of maternal diabetes or maternal epilepsy was detected in this study unlike previous study of Nugud in which maternal diabetes was reported in 9% of cases [9].

Early maternal age is considered a risk factor (0.14) for mothers younger than 35 years of age ascribed to defective hyaluronate metabolism resulting in vertebral failure [16]. The mother's age range in this study was between 18-45 years old. Maternal education state naturally plays a role in seeking prenatal services. In this study 38.0% of the mothers received basic education, so poor maternal education if coupled with low social-economic status (63.4%) could contribute as risk factors for NTDs.

Although there was no conclusive evidence of relationship between consanguine marriage and NTDs, more than 69% of the children in this study were products of consanguine marriage and 71.4% were first-degree cousins [1,3]. Little or no attention is currently paid to the prevention of CNS congenital anomalies in much of the low- and middle-income countries of the world. In the Sudan, folic acid is supplemented but on interrupted bases, and it is not a trend in the preconception period, therefore the need is urgent for folic acid supplementation for all women of childbearing age through appropriate food fortification.

CONCLUSION

Neural tube defects are common in Sudan. Hydrocephalus was the most commonly associated anomaly. Consanguine marriage is a potential risk factor for NTDs development and is prevalent in Sudan. Poor folate intake and maternal febrile illnesses are risk factors. Further larger studies would better explore Malaria as a risk factor.

REFERENCES

1. Salih MA, Murshid WR, Seidahmed MZ. Classification, clinical features, and genetics of neural tube defects. *Saudi Med J* 2014; 35:S5-S28.
2. Salih MAM. Genetic Disorders in Sudan. In: Teebi AS, editor. *Genetic Disorders among Arab Populations*. 2nd ed. New York (NY): Springer 2010; 575-612.
3. Wallingford JB, Niswander LA, Shaw GM, Finnell RH. The continuing challenge of understanding, preventing, and treating neural tube defects. *Science* 2013; 339:1222002.

4. Hamamy H. Epidemiological profile of neural tube defects in Arab countries. *Middle East Journal of Medical Genetics* 2014; 3:1-10.
5. Dirks PB, Rutka JT. The neurogenetic basis of pediatric neurosurgical conditions. In: Albright L, Pollack I, Adelson D, eds. *Principles and Practice of Neurosurgery*. New York: Thieme Medical Publishers; 1999: 23-4.
6. Zlotogora J. Genetic disorders among Palestinian Arabs: Effects of consanguinity. *Am J Med Genet* 1997; 68:472-475.
7. Little J, Elwood JM. Epidemiology of neural tube defects. In: Kiely M, editors. *Reproductive and Perinatal Epidemiology*. Boca Raton (ELA): CRC Press Inc; 1991; 251-336.
8. Nugud A, Arbab M, Osman TM. Pattern of neural tube fusion defects in Sudan. *Saudi Med J* 2003; 24:S54.
9. Rajab A, Vaishnav A, Freeman NV, Patton MA. Neural tube defects and congenital hydrocephalus in the Sultanate of Oman. *J Trop Pediatr* 1998; 44:300-303.
10. Msamati BC, Igbigbi PS, Chisi JE. The incidence of cleft lip, cleft palate, hydrocephalus and spina bifida at Queen Elizabeth Central Hospital, Blantyre, Malawi. *Cent Afr J Med* 2000; 46:292-296.
11. Buccimazza SS, Molteno CD, Dunne TT, Viljoen DL. Prevalence of neural tube defects in Cape Town, South Africa. *Teratology* 1994; 50:194-199.
12. Kinasha AD, Manji K. The incidence and pattern of neural tube defects in Dar es Salaam, Tanzania. *Eur J PediatrSurg* 2002; 12:S38-S39.
13. Airede KI. Neural tube defects in the middle belt of Nigeria. *J Trop Pediatr* 1992; 38:27-30.
14. Barber RC, Lammer EJ, Shaw GM, Greer KA, Finnell RH. The role of folate transport and metabolism in neural tube defect risk. *Mol Genet Metab* 1999; 66:1-9.
15. Liu J, Qi J, Yu X, Zhu J, Zhang L, Ning Q, et al. Investigations of single nucleotide polymorphisms in folate pathway genes in Chinese families with neural tube defects. *J Neurol Sci* 2014; 337:61-66.
16. Centers for Disease Control and Prevention (CDC). Use of dietary supplements containing folic acid among women of childbearing age--United States, 2005. *MMWR Morb Mortal Wkly Rep* 2005; 54:955-958.
17. Safdar OY, Al-Dabbagh AA, Abuelieneen WA, Kari JA. Decline in the incidence of neural tube defects after the national fortification of flour (1997-2005). *Saudi Med J* 2007; 28:1227-1229.
18. Warf BC, Stagno V, Mugamba J. Encephalocele in Uganda: ethnic distinctions in lesion location, endoscopic management of hydrocephalus, and survival in 110 consecutive children. *J Neurosurg Pediatr*. 2011; 7(1):88-93.
19. Salih MA, Murshid MR, Mohamed AG, Ignacio LC, de Jesus JE, Baabbad R, et al. Risk factors for neural tube defects in Riyadh City, Saudi Arabia: Case-control study. *Sudan J Paediatr* 2014; 14(2):49 - 60.