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Original Article

Epidemiology of the neural tube defects in Kashmir Valley

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Abstract

Background: Neural tube defects (NTDs) are the most common congenital malformations affecting the brain and spinal cord and have a multifactorial etiology. Genetic and environmental factors have been found to cause these defects, both individually and in combination.

Methods: A 2-year hospital-based prospective study was carried out from November 2013 to October 2015 to determine the incidence, types, demographics, risk factors, and other associated anamolies relevant to NTDs in Kashmir Valley. A detailed history of the mother was taken along with detailed clinical examination of neonate including measurement of head circumference and checking the status of fontanella, whether lax/full/bulging/or tense, type of NTD. Investigations that were done included were X-ray skull: Anterior-posterior (AP) and lateral, X-ray spine: AP and lateral, ultrasonography abdomen, magnetic resonance imaging: Spine and brain.

Results: The total number of babies with NTD's was 125 with an overall incidence of 0.503. Kupwara district was having the highest incidence (1.047) and Srinagar district the lowest incidence of NTD's (0.197). Majority of NTD's (116 cases, 92.8%) were found in the rural areas. Among the different types of NTD's, spina bifida had an incidence of 0.342 (85 cases, 68%) and anencephaly had an incidence of 0.113 (28 cases, 22.4%). There was a slight preponderance of females over males with NTD's. There were 70 females (56%) and 55 males (44%), respectively, with a male: female ratio of 0.8:1

Conclusions: The incidence rates of NTDs is very high for Kashmir Valley. Geographical distribution of NTDs at this place confirms a relationship between the socioeconomic status, educational status, maternal too young or advanced age, and environmental factors for the development of a NTD. The results of this study point to the importance establishing a health policy to prevent NTD in Kashmir Valley.

Key Words: Kashmir, meningoceles, myeloceles, myelomeningoceles, neural tube defects

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INTRODUCTION

Neural tube defects in Kashmir valley

Neural tube defects (NTDs) are the most common congenital malformations affecting the brain and spinal cord. They assume significance by virtue of their morbidity, mortality, health care expenditure, and human suffering. These defects can be categorized into two groups: Open defects and closed defects. Open defects where the neural tissue is exposed to the air (or amniotic fluid) include spina bifida (SB) cystica, which encompasses meningoceles, myeloceles, and myelomeningoceles. Myelomeningocele is a defect in the closure of the neural tube that occurs in the vertebral column. This type of defect can occur anywhere along the spinal column, but is more likely to be placed in thelumbo-sacral region. Closed defects in which the skin completely covers the neural tissue, include occult spinal dysraphism, which encompasses diastematomyelia, dorsal dermal sinus, and tight filum terminale. SB occulta refers strictly to bone fusion defects of the lower spine, generally in the lumbo-sacral region. Anencephaly is a defect in which the head end of the neural tube does not close; this results in the lack of a cranial vault and cerebral hemispheres.[7,9]

NTD's have a multifactorial etiology.[7,9,26] Genetic and environmental factors have been found to cause these defects, both individually and in combination.[9]

MATERIALS AND METHODS

The present study "Epidemiology of The NTDs in Kashmir Valley" – A hospital-based prospective study was conducted in the Neurosurgical Centre of Sher-I-Kashmir Institute of Medical Sciences (SKIMS), Srinagar, the only referral center for neurological/neurosurgical problems (hence all cases of NTDs are referred here) and at the Lal Ded Women's Obstetrical/Gynecological Disease Hospital, Srinagar; the main referral center for obstetrical/gynecological disease, situated in the center of Kashmir Valley. The study was conducted over a period of 2 years from November 2013 to October 2015.

A detailed history of the mother was taken with special impetus on age, occupation: Housewife/professional worker, dietary history-fruit intake, vegetarian/nonvegetarian diet, smoking/drug addiction – type/duration, exposure to fertilizers, folic acid/vitamin intake, any other drugs, number of times conceived/abortions/intrauterine fetal deaths/previous malformations, mode of delivery, hypertension treatment/drug defaulter, diabetes – duration and type, tuberculosis, Cardiovascular (CVS) disease, epilepsy – type and duration, etc., and examination of the neonate done at Lal Ded Hospital detailed clinical examination of neonate included general physical examination, head circumference, fontanella-lax/full/bulging/tense

Type of neural tube defect

Anencephaly, encephalocele, myelomeningocele, meningocele, lipomeningocele, SB occulted, etc., site of defect: Cranial/cervical/dorsal/lumbar/sacral. Characteristics of defect: Skin covered or not/leaking or not/transilluminant or not, presence or absence of skin dimple, sinus, hemangioma, hypertrichosis, etc., spine: Normal/scoliosis/kyphosis., other associated malformations, cleft palate, cleft lip, talipes equinovarus hypospadias, etc.

Complete neurological examination of neonate with following, Investigations done were X-ray skull: Anterior-posterior (AP) and lateral, X-ray spine: AP and lateral, ultrasonography: Abdomen, magnetic resonance imaging: Spine and brain.

To gauge the most accurate epidemiological pattern of NTD's in Kashmir Valley, the patients referred from regions of the state of Jammu and Kashmir other than the valley were excluded from this study.

For statistical analysis, the total number of deliveries in different districts of the Kashmir Valley during the study period was obtained from the Department of Population Research, University of Kashmir, which was calculated on the basis of prevailing crude birth rate (taken as average of last 3 years) by the Ministry of Health and Family Welfare, Jammu and Kashmir state.

The neural tube defects were categorized into three main types:

- Anencephaly: A congenital malformation characterized by the total or partial absence of the cranial vault, the covering skin, and the brain missing or reduced to a small mass
- Encephalocoele: A congenital malformation characterized by herniation of the brain and/or meninges through a defect in the skull. Encephalocoele is not counted as a separate defect when present with SB
- SB: A family of congenital malformation defects in the closure of the spinal column characterized by herniation or exposure of the spinal cord and/or meninges through an incompletely closed spine. This definition includes meningocele, meningomyelocele, myelocele, myelomeningocele, and rachischisis. SB is not counted as a separate defect when present with anencephalus.

Disease frequency was measured by incidence rates.

Incidence rates of NTD's was calculated by the formula:

$$\text{Incidence} = \frac{\text{Number of cases that occur during a certain period of time}}{\text{Number of births during that time}} \times 1000$$

Comparisons were made with other studies conducted by various people from time to time with regards to incidence and possible risk factors.

OBSERVATIONS AND RESULTS

Kashmir Valley is topographically and geographically different from the rest of India. It is situated at an altitude of 5000–6000 feet, between 33.5° and 35° north latitudes and 74–76° east longitude. It has ten districts and a total population of 6,907,623 with a district wise distribution as shown in Table 1 (as per census of India 2011). This study was conducted over a period of 2 years from November 2013 to October 2015. The total number of babies with NTD's was 125 with an overall incidence of 0.503. Kupwara district was having the highest incidence (1.047) and Srinagar district had the lowest incidence of NTD's (0.197) as shown in Table 1. Majority of NTD's (116 cases, 92.8%) were found in the rural areas (incidence 0.572/1000 births) whereas only nine cases, i.e., 7.2% (incidence 0.197/1000 births) were from urban areas. Among the different types of NTD's, SB had an incidence of 0.342 (85 cases, 68%) and anencephaly had an incidence of 0.113 (28 cases, 22.4%). There was a slight preponderance of females over males with NTD's. There were 70 females (56%) and 55 males (44%), respectively, with a male:female ratio of 0.8:1. Majority of the patients with anencephaly, i.e., 8 (28.6%) were from Baramulla district and majority of patients with encephalocele 4 (33.3%) and SB 22 (25.8%) were from Kupwara district as shown in Tables 2 and 3. Highest number of NTD's was seen in children of primigravida (38.4%). SB and encephalocele were also most commonly seen in children of primigravida. History of a previous abortion was present in 17.6% of the mothers with children having NTD's. About 82.4% of mothers did not give history of previous abortion as shown in Table 4. Mothers of only six babies gave history of intrauterine fetal death. Of these, two had anencephaly and four had SB in present pregnancy. Mothers of three patients had history of previous malformations. One with encephalocele in present delivery had two previous babies with encephalocele. One with meningomyelocele had previous meningomyelocele and one with meningomyelocele had previous anencephaly. About 22.4% of parents gave history of consanguinity of marriage. Such history was not present in 77.6% of the parents as depicted in Table 5. About 96% of the mothers with children having NTD's, in our study, were housewives. Only 4% were professional workers. Majority of the mothers, i.e. 92 cases (73.6%) in this study consumed folic acid after 28 days of conception. None of the mothers used folic acid before conception. The socioeconomic status (SES) of patients was assessed as per the modified Prasad's classification. Majority of our patients, i.e., 93 (74.4%) were from poor and middle class. As shown in Table 6. In our study, majority of the mothers, i.e., 82 (65.6%) of the NTD affected babies were illiterate. Majority of fathers, i.e., 84 (67.2%) though literate had an educational level of undergraduate level.

Table 1: District wise population, births per year, distribution and incidence of neural tube defects in Kashmir Valley

District	Population	Number of births/year	Number of cases of NTD (percentage of total)	Incidence/1000 births
Anantnag	1,070,144	19,264	15 (12)	0.389
Badgam	735,753	13,244	13 (10.4)	0.491
Bandipora	385,099	6932	4 (3.2)	0.289
Baramulla	1,015,503	18,279	26 (20.8)	0.711
Ganderbal	297,003	5346	8 (6.4)	0.748
Kulgam	422,786	7610	6 (4.8)	0.394
Kupwara	875,564	15,760	33 (26.4)	1.047
Pulwama	570,060	10,261	9 (7.2)	0.439
Shupiyan	265,960	4787	2 (1.6)	0.209
Srinagar	1,269,751	22,856	9 (7.2)	0.197
Total	6,907,623	124,339	125 (100)	0.503

NTD: Neural tube defect

Table 2: Number and incidence of specific type of neural tube defects

Defect type	Number of boys (percentage of subgroup)	Number of girls (percentage of subgroup)	Total number (percentage of total)	Incidence/1000 births
Anencephaly	10 (35.7)	18 (64.3)	28 (22.4)	0.113
Encephalocele	5 (41.7)	7 (58.3)	12 (9.6)	0.048
Spina bifida	40 (47.1)	45 (52.9)	85 (68)	0.342
Total	55 (44)	70 (56)	125 (100)	0.503

Table 3: District wise distribution of specific types of neural tube defects

District	Number of cases (percentage of subgroup)			Total number of cases (percentage of total)
	Anencephaly	Encephalocele	Spina bifida	
Anantnag	1 (3.6)	0 (0)	14 (16.5)	15 (12)
Badgam	3 (10.7)	1 (8.3)	9 (10.6)	13 (10.4)
Bandipora	1 (3.6)	0 (0)	3 (3.5)	4 (3.2)
Baramulla	8 (28.6)	3 (25)	15 (17.6)	26 (20.8)
Ganderbal	2 (7.1)	1 (8.3)	5 (5.9)	8 (6.4)
Kulgam	2 (7.1)	2 (16.8)	2 (2.4)	6 (4.8)
Kupwara	7 (25)	4 (33.3)	22 (25.8)	33 (26.4)
Pulwama	2 (7.1)	1 (8.3)	6 (7.1)	9 (7.2)
Shupiyan	1 (3.6)	0 (0)	1 (1.2)	2 (1.6)
Srinagar	1 (3.6)	0 (0)	8 (9.4)	9 (7.2)

Mothers of six neonates, in our study, were smokers (hooka smoker). None of the mothers was alcoholic. Mother of only one case was having hypertension and was regularly using amlodipine. Mother of one case was having epilepsy and was on sodium valproate which she had used throughout the pregnancy. None of the mothers

Table 4: Distribution of neural tube defects with respect to maternal age groups and parity

	Number of cases (percentage of subgoup)			Total number of cases (percentage of total)
	Anencephaly	Encephalocele	Spina bifida	
Maternal age grouping				
15-19	1 (3.6)	0 (0)	4 (4.7)	5 (4)
20-24	14 (50)	6 (50)	34 (40)	54 (43.2)
25-29	7 (25)	3 (25)	21 (24.7)	31 (24.8)
30-34	3 (10.7)	2 (16.7)	17 (20)	22 (17.6)
35-39	3 (10.7)	1 (8.3)	9 (10.6)	13 (10.4)
Maternal parity				
Primigravida	9 (32.1)	5 (41.7)	34 (40)	48 (38.4)
Two	10 (35.7)	3 (25)	16 (18.8)	29 (23.2)
Three	4 (14.3)	1 (8.3)	13 (15.3)	18 (14.4)
Multigravida	5 (17.9)	3 (25)	22 (25.9)	30 (24)

Table 5: Distribution of neural tube defects with relation to mothers occupation mothers folic acid intake

	Number of cases (percentage of total)
Occupation	
House wife	120 (96)
Professional worker	5 (4)
Duration of folic acid intake	
Not taken	12 (9.6)
Taken within first 28 days	21 (16.8)
Taken after 28 days	92 (73.6)
Taken prior to conception	None

Table 6: Distribution of neural tube defects with relation to, previous abortions consanguinity of marriage and socioeconomic status

	Number of cases (percentage of subgroup)			Total number of cases (percentage of total)
	Anencephaly	Encephalocele	Spina bifida	
Previous abortion				
Yes	4 (14.3)	1 (8.3)	17 (20)	22 (17.6)
No	24 (85.7)	11 (91.7)	68 (80)	103 (82.4)
Consanguinity				
Present	9 (32.1)	4 (33.3)	15 (17.7)	28 (22.4)
Not present	19 (67.9)	8 (66.7)	70 (82.3)	97 (77.6)
Socioeconomic class				
Poor and middle class	19 (67.9)	8 (66.7)	66 (77.7)	93 (74.4)
High and upper high class	9 (32.1)	4 (33.3)	19 (22.3)	32 (25.6)

gave history of diabetes. Mothers of five neonates were of non-Kashmiri origin (four Bengalis and one Maharashtrian) married to Kashmiri male.

DISCUSSION

Overall incidence

The incidence of NTDs varies not only from country to country but also from region to region within a country. The incidence of NTDs, in our study, was 0.503/1000 live births. Nikkilä *et al.*[25] found the rate of SB among newborns in Sweden to diminish gradually from 0.55/1000 to 0.29/1000 during the study period of 31 years. Thunem *et al.*[31] revealed the annual birth prevalence rate of NTDs in Southern Alberta to be 1.62/1000 total births. Agarwal[1] in their study, found the incidence of NTDs in India to be 0.5–11/1000 live births. Kulkarni *et al.*[17] have found an extremely high incidence of 11.4/1000 live births in Southern India. Sharma *et al.*,[28] in four major maternity hospitals of Lucknow, found the overall incidence of NTD to be 3.9/1000 live births. Lemire[19] noted a worldwide incidence of 1.0/1000 live births for NTD's. Our findings are concordant with the previously described incidence of NTD's in some areas of India and in Sweden.

Incidence of subgroups

The incidence of various types of NTD's, in our study, was anencephaly (0.113/1000 live births), encephalocele (0.048/1000 live births), and SB (0.342/1000 live births). Thunem *et al.*[31] in their study of NTDs in Southern Alberta between 1970 and 1981 found the incidence of SB to vary from 0.17 to 1.50/1000 births (total 0.86), for anencephaly 0.20–0.94/1000 births (total 0.61) and for encephalocele 0.00–0.38 (total 0.16). Kulkarni *et al.*,[18] in their study in Southern India, found the incidence of anencephaly to be 5.10/1000 live births, encephalocele to be 0.85/1000 live births. Mathews[21] reported that the rates in 2005 for two of the most common NTD's, spina bifida, and anencephaly, were 17.96/100,000 live births and 11.11/100,000 live births, respectively. Myrianthopoulos and Melnick[24] found the total incidence of NTD's in their study to be 1.3/1000 births. The incidence of anencephaly was 0.676/1000 births, incidence of encephalocele was 0.207/1000 births, and that of SB was 0.713/1000 births. The Incidence of anencephaly, SB, and encephalocele in the year 1995 in Latin America has been reported as 0.76, 0.93 and 0.15/1000 births, respectively, and in Mexico as 1.6, 0.89 and 0.31/1000 births, respectively (congenital malformations worldwide).[8] The incidence of SB, in our study, goes in concordance with that of Latin America and Mexico but that of anencephaly and encephalocele are less than in other studies. The reason for incidence of anencephaly

to be less, in our study, could be that anencephaly is not compatible with life and most of the babies with it die immediately after birth. As our study was hospital based conducted at the Department of Neurosurgery, SKIMS, and Lal Ded Hospital for Obstetrics and Gynecological Diseases, cases of anencephaly delivered at other places in the valley must not have survived to be referred to us.

Male:female ratio

In our study, there was a slight preponderance of females over males with NTD's in total (male:female ratio of 0.8:1) as well as in sub groups. This is in concordance with the study of Jorde *et al*.,[15] who in their study, found a male:female ratio of 0.67. Whiteman *et al*.,[34] in their study of 694 cases of NTD in Oxfordshire, England, also found that female offspring were more than twice as likely as males to harbor an NTD.

Maternal age

In our study, we found that most of the NTD's 54 (43.2%) including the subgroups of NTD's i.e., 14 patients (50%) of anencephaly, 6 patients (50%) of encephalocele, and 34 (40%) patients of SB occurred in mothers of younger age group (20–24 years). A number of studies have reported maternal age risk for NTD's to be U-shaped, i.e., highest among youngest and oldest women, while other studies have found risk to decrease with increasing age or the reverse.[16,22] In concordance with our study, Vieira and Castillo Taucher[33] in a meta-analysis study of maternal age as risk factor for NTD's, found increased risk associated with mothers of 40 + years and mothers younger than 19 years. The detected effect was stronger for SB than for anencephaly. Frey and Hauser[13] also reported increased risk of NTD's in older or very young mothers. Whiteman *et al*.,[34] in their study, found most of mothers (46.9%) with NTD affected baby to lie in the age group 20–24 years and only 6.2% in the age group 30 or more than 30 years. Strassburg *et al*.[29] observed that advanced maternal age was a stronger risk factor for SB than for anencephalus but no increased risk was observed among teenage mothers.

Parity

In our study, the highest number of NTD's was found in primigravidas 48 cases (38.4%) followed by multigravidas 30 cases (24%). This is in concordance with the study of Little and Elwood[20] who in their study found a U-shaped pattern of NTD risk, i.e. risk being higher for the lowest and highest order of births. Whiteman *et al*.[34] in concordance with our study also found most of the mothers with NTD affected pregnancy were primigravida (35.2%). Only 17.2% mothers in their study had three or more previous deliveries. Elwood *et al*.[11] also reported a modest increase in NTD risk in mothers of parity three or more and an increased risk in primiparous mothers.

Prior abortions

In our study, 82.4% of mothers did not give history of previous abortion. Whiteman *et al*.[34] in concordance with our study also found that 77.1% of the mothers with NTD affected babies did not have previous history of abortions. Little and Elwood[20] and Myrianthopoulos and Melnick[24] reported higher rates of prior spontaneous abortions in women with NTD-affected pregnancies. Mathews *et al*.[21] in their study also found a significant excess of spontaneous abortions when the preceding pregnancy was compared with the succeeding pregnancy.

Consanguinity

About 77.6% of the cases of NTD, in our study, were a product of nonconsanguineous marriage. In concordance with our study, Asindi and Al-Shehri,[2] in their study, in the Assir region of Saudi Arabia found that consanguinity rates were not high among parents of newborns with NTD than in the general population. In some studies, higher NTD rates have been found where the parents are related Little and Elwood.[20]

Occupation of mother

In our study, 12 (96%) mothers were housewife. Although a number of studies have shown an increased risk of NTD's in mothers with occupation like cleaning, healthcare,[6] agriculture and janitors,[5] none of the mothers, in our study, was having such an occupation. Little and Elwood[20] did not find a consistent link with maternal occupation and maternal exposures. Thulstrup and Bonde,[30] in their study, also found no convincing evidence linking occupational exposure during pregnancy and birth defects including NTD's.

Socioeconomic status

Majority of the cases, i.e., 93 (74.4%), in our study, belonged to low or middle class families. The SES of the families was assessed by modified Prasad's classification. This finding goes in concordance with other studies where increased incidences of NTD's have been found in families of low SES. Blanco Muñoz *et al*.,[4] in their study, in a Mexican population found increased risk of anencephaly in mothers of low SES. Mutchinick *et al*.[23] found a significantly greater frequency of bricklayers among fathers of anencephalic children than among fathers of healthy children. They attributed this difference to the low socioeconomic level associated with this occupation. Elwood and Elwood[10] found an association between living in socially deprived areas and anencephaly. However, Strassburg *et al*.[29] found no association between SES and the incidence of anencephaly or SB.

Educational status of parents

Majority of the mothers, i.e., 82 (65.6%), in our study, were illiterate and majority of fathers, i.e., 84 (67.2%) though literate were undergraduates. In concordance with

our study Grewal *et al*.,[14] in their study, found women who did not graduate from high school and lived in low-SES neighborhoods exhibited a significantly higher risk for NTD pregnancy than women with high school or higher education who lived in the same neighborhood. Farley *et al*.,[12] reported that risk estimates for NTD's ranged between 1.8 and 2.3 for mothers with less than a high school education. However, Rouhani *et al*.[27] and Velie and Shaw *et al*.[32] found no association between risk of NTD's and educational level of the mother.

Folic acid intake

Majority of the mothers, i.e., 92 (73.6%), in our study, had taken folic acid after 28 days of conception. Only 12 (9.6%) of the mothers had consumed folic acid within 28 days of conception and none before conception. In patients who have a family history of an NTD, folic acid taken orally on a daily basis is shown to lower the occurrence and recurrence of NTD's in their own offspring and in their relatives. The Medical Research Council (Group MRCVSR 1991)[26] was the first to prove conclusively that when women who had had a previous child affected by an NTD took 4.0 mg of folic acid daily, beginning 3 months prior to conception, there was a 70% reduction in the recurrence in subsequent offspring. Berry *et al*.[3] demonstrated a 79% reduction in occurrence in North China (an area of high incidence) but only 40% in South China (where there is a low incidence) when the women took 0.4 mg of folic acid periconceptually. Since none of the mothers, in our study, had taken folic acid preconceptually, and there is no existing program of fortification of food with folic acid in the valley, counseling of such mothers and implementing food fortification with folic acid will further decrease the incidence of NTD's in the valley.

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Conflicts of interest

There are no conflicts of interest.

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Commentary

Study of the "Prevalence of Neural Tube Defects in India" is important as a higher incidence is presumed to occur compared to the western world, and a wide variation in various regions within the country has been reported. The prevalence rate all over India is reported to be 6.63/1000 births, the highest being reported from the northern states of Punjab, Uttar Pradesh, and Bihar.[5] A more recent systematic review has shown the overall pooled birth prevalence of 4.5/1000 births.[1]

The majority of the studies included in these reviews are hospital-based except a few community-based study in North India (Balrampur, Uttar Pradesh) which showed a prevalence of 8.2/1000 births.[2] Higher incidences have also been noted in a survey at a hospital in another North Indian City, Rohtak, Haryana, earlier (18.2/1000).[4]

Kashmir is further north of Haryana and this may partly explain the higher incidence in the accompanying paper. The detailed analysis of various districts in the Kashmir valley is a unique feature of this study. Although this study is based on hospital-based statistics, this relatively isolated geographic area with limited health facilities has made the study almost a community-based survey. The study also shows that the majority defects occurred in the rural area, in relatively lower socioeconomic group, especially in young mothers. Most mothers took folic acid for several weeks into pregnancy, but none took folic acid before conception. Maternal malnutrition has been suggested as the main cause in India and suggested strategies including food fortification, vitamin supplementation, and dietary modification.[3]

Although India has witnessed a substantial decrease in infant mortality attributed to infectious diseases and malnutrition, significant reduction in neural tube defects has not been seen in many areas, emphasizing further the need for greater attention to this problem.

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