The Journal of Obstetrics and Gynecology of India (May-June 2020) 70(3):195–201
https://doi.org/10.1007/s13224-020-01311-x

ORIGINAL ARTICLE

Relative Prevalence and Outcome of Fetal Neural Tube Defect in a Developing Country

Manisha Kumar[1] · Aayushi Hasija[1] · Nikita Garg[1] · Ramya Mishra[1] · S. C. Roy Chaudhary[2]

Received: 12 September 2019 / Accepted: 30 March 2020 / Published online: 18 April 2020

Abstract

Objectives To find out the relative prevalence of fetal neural tube defect (NTD) and its outcome in terms of survival at birth and beyond 2 years of age.

Methods A 10-year prospective (2008–2018) observational study was performed, which included all prenatally detected fetal NTD. Two-year follow-up was done in cases of pregnancies resulting in live birth, in terms of their survival, physical morbidity and developmental delay.

Results NTD was seen in 401/648 (62%) cases among the central nervous system malformations. More than half of the cases (54.1%) presented after 20 weeks of gestation, and 42.8% of the mothers were primiparous. Spina bifida was seen in 206 cases, anencephaly in 144, encephalocele in 43, whereas iniencephaly was seen in only eight cases. Associated anomalies were present in 51.2%. Only 19.0% cases were live-born, and merely 11% were alive beyond 2 years of age. Among types of spina bifida, lumbosacral meningomyocele was the most common (41.6%), whereas thoracic was the rarest (8.7%). After 2 years, physical disability was observed in more than half of the cases who survived.

Conclusions NTD is one of the commonest malformations with high mortality, and the physical and mental sub-normality is high among those who survive.

Keywords Fetal hydrocephalus · Central nervous system anomaly · India · Survival after birth · Spina bifida · Anencephaly · Encephalocele

Introduction

The central nervous system anomalies are the most frequently antenatally detected malformations, and the neural tube defects (NTDs) are the commonest among them [1]. Although the incidence of spinal dysraphism has significantly decreased over the last few decades, the incidence is still high in countries with poor socioeconomic status [2–4]. Neural tube defects affect 0.6 per 1000 live births in the USA and 0.5–2 per 1000 pregnancies worldwide [4]. The etiology of neural tube defects is multifactorial and can be attributed to genetic predisposition, vitamin deficiencies or teratogen exposure. Of these, low levels of folate in the maternal blood prior to conception have been implicated as the most important cause [3]. Unfortunately, poor awareness regarding folate supplementation and the high rate of unplanned pregnancy has led to underutilization of this preventive strategy, especially in low-resource settings [5].

In 1972, John Lorber published a controversial paper describing the bleak outcome of a cohort of children born

Manisha Kumar is a Professor in Department of Obstetrics and Gynecology at Lady Hardinge Medical College, New Delhi, India. Aayushi Hasija is a Senior Resident in Department of Obstetrics and Gynecology at Lady Hardinge Medical College, New Delhi, India. Nikita Garg is an Intern in Department of Obstetrics and Gynecology at Lady Hardinge Medical College, New Delhi, India. Ramya Mishra is a Resident in Department of Obstetrics and Gynecology at Lady Hardinge Medical College, New Delhi, India. S. C. Roy Chaudhary is a Director Professor and Head, Pediatric Surgery at KSCH, New Delhi, India.

✉ Manisha Kumar
manishaonly@gmail.com

[1] Department of Obstetrics and Gynecology, Lady Hardinge Medical College, Shahid Bhagat Singh Marg, New Delhi 110001, India

[2] Pediatric Surgery, KSCH, New Delhi, India

with myelomeningocele [6]. He opined that the babies with clinical features suggestive of poor prognostic significance should not be offered active treatment. Instead, he suggested that efforts should be directed to those who are most likely to benefit in the long term [6]. Over the subsequent 46 years, the outlook for the children born with myelomeningocele has changed in the developed nations, but it is virtually the same in the developing countries. Since there is no study on the outcome of cases in the existing environment, it is difficult to provide realistic counseling to the couple after its prenatal diagnosis.

There is paucity of data on the outcome of NTD in the developing countries which has limited health care infrastructure and a high infant mortality rate, leaving little hope for proper care and management of children with NTDs. The problem is compounded in India as the abortion law, also known as medical termination of pregnancy (MTP) act, does not allow termination of pregnancy with fetal anomalies after 20 weeks of gestation, leaving its continuation as the only option if an NTD is diagnosed after 20 weeks.

The counseling requires information regarding the outcome not only at birth but subsequently also. The parents need to be informed about the associated physical and mental morbidity, need for surgery and impairment after surgery. The data from the developed nations are not suitable for counseling regarding the postnatal outcome in a low-resource set up. Thus, indigenous data on outcome in the existing setup are warranted for realistic counseling.

The aim of the study was to find out the relative prevalence of different types of fetal neural tube defects and its outcome in terms of survival at birth and at 2 years.

Materials and Methods

It was a prospective study, performed after ethical clearance. It included all cases of antenatally detected fetal NTDs referred to the fetal medicine clinic in the last 8 years of the 10-year study period (2008–2018). Mothers were included in the study after consents. Any defect in the closure of the spinal cord and vertebral column or skull vault was termed as NTD. Cases presented as spinal defects in the form of meningomyocele or spinal diastematomyelia, seen in the axial and coronal sections on ultrasound. Anencephaly was easy to detect with findings suggestive of the absence of skull vault and protruding eyeballs. Encephalocele was protrusion of cystic mass from a defect in the skull vault, while iniencephaly was extension of fetal head with fusion of the cervical vertebra.

After reaching a diagnosis, the mothers underwent targeted scanning to rule out other congenital malformations. When the diagnosis of major fetal anomalies was confirmed at or before 20-week gestation, termination of pregnancy was offered. If the couple desired continuation of pregnancy or when the gestational age was more than 20 weeks, genetic and pediatric surgery consultation was taken. Repeat ultrasound examinations were carried out to follow the evolution of the anomaly. All subjects were delivered at the institution. Mothers who did not deliver at our hospital were considered lost to follow-up.

The pediatrician was informed about the fetal condition at the time of delivery, so that necessary arrangement for immediate postnatal management could be planned. All live-born babies underwent appropriate tests. All cases requiring surgical intervention were referred to specialized departments for further management. Surgery for repair of meningomyocele, shunting procedure and orthopedic foot correction was done as per the requirement and availability of facilities. Pediatric examination records were maintained, and telephone interviews were conducted to track the outcome of children till 2 years of age. The outcome of babies in terms of survival and physical morbidity such as poor bladder control, limb abnormalities requiring additional medical attention, was asked for. The questionnaire concerning the developmental milestones achieved within the expected time period was also enquired for. Whether the baby underwent any surgery was also sought.

Results

In the first 8 years of study period, there were 102,216 deliveries, of which the central nervous system defects were observed in 694 cases antenatally. Out of the 648 fully followed cases of CNS defects, 401 could be attributed to NTD; 42 cases of NTD were lost to follow-up. Among the NTD cases, spina bifida was the most common (51.4%), followed by anencephaly (35.9%), encephalocele (10.7%) and iniencephaly in the rest (2.0%).

The antenatal profile of the mothers is shown in Table 1. The mean age of the mothers included in the study was 25.1 ± 3.67 years. Most of them were young and primiparous (42.8%). Of all the subjects, 84 (20.8%) had an obstetric history of one or more previous abortions. The mean gestational age at the time of presentation was 26.3 ± 8.3 weeks. In more than half of the cases (245/401, 61.1%), the women presented after 20 weeks of gestation.

The details of the delivery are given in Table 2. The mean gestational age at delivery was 29.4 ± 7.5 (11–42 weeks). The incidence of cesarean section was as low as 6.7%. The ratio of male/female was 1: 2 in anencephaly, whereas it was 1:1 in the rest. Associated defects were observed in over half of the cases (51.2%). Talipes equinovarus (TEV) was seen in 127 cases, hydrocephalus in 97 cases, omphalocele and other abdominal wall defects in 16 cases, cleft lip and palate in nine cases, and ambiguous genitalia was observed in three

Table 1 Epidemiological profile of cases with neural tube defect, diagnosed in the antenatal period ($n=401$)

Antenatal characteristics	Number of cases ($n=401$)	%
Age in years		
18–22	109	27.1
23–27	191	47.6
28–32	77	19.2
33–37	18	4.4
≥38	6	1.5
Parity		
0	172	42.8
1	122	30.4
2	71	17.7
3	21	5.2
≥4	15	3.7
Abortions		
1	52	12.9
2	27	6.7
≥3	5	1.2
Type of pregnancy		
Singletons	390	97.2
Twins	11	2.7
Gestational age in weeks		
≤20	156	38.9
21–24	53	13.2
25–28	62	15.5
29–33	61	15.2
>33	69	17.2
Socioeconomic status		
Low (income below 10,000/month)	114	28.4
Middle (income between 10 and 20,000/month)	256	63.8
High (income above 20,000/month)	31	7.8

cases. Syndromic association was observed in seven cases of encephalocele, they were Meckel–Gruber syndrome in three cases (Fig. 1), Joubert syndrome in one (Fig. 2), and amniotic band disruption sequence in three cases (Fig. 3). Karyotyping was performed in 18 cases with multiple defects, which was found to be abnormal in two (trisomy 18, unbalanced translocation).

Among 156 cases which presented at or before 20 weeks, all except two opted for termination of pregnancy (154/401, 38.4%). One could be attributed to religious reasons and the other to the history of previous three abortions preceding the present precious pregnancy. Of the 401 pregnancies, 171 (42.6%) resulted in stillbirth (Table 2). Among these stillbirths, 78 (19.5%) were ascribed to spina bifida and 13 (1.2%) to encephalocele.

Only 76/401 (19%) pregnancies constituting spina bifida and encephalocele cases resulted in live birth. The follow-up of the cases with spina bifida and encephalocele is given in Table 3. Among those with spina bifida, the defect in the lumbar/sacral region was the most common (41.6%) followed by the thoracic/cervical region (8.7%). Anterior encephalocele was seen in only three cases and was posterior in the rest 40 (10%).

On assessment of the survival of the live-born babies, it was found that 24/62 live-born with spina bifida died in the subsequent 2 years, and only 38/401 (9.4%) were alive after 2 years. Among the subjects with encephalocele, 6/401 (1.5%) survived beyond 2 years. At the end of 2 years, 44/401 (11.1%) babies were alive, of which 29/401 (7.2%) had physical disability and 16/401 (3.7%) had developmental delay. Surgery was performed in all cases with meningomyocele or encephalocele, but was not performed in spina bifida occulta and in two cases of encephalocele. Only 15 children (1.3%) had no mental or physical impairment (Table 3).

Table 4 shows the outcome of 42 cases of spina bifida who underwent surgery; 35 of them were alive after 2 years. Most of the cases underwent surgery at 2–3 months (22/42) and the rest after 6 months to 1 year of age. The timing of surgery depended upon the availability of dates by the neurosurgeon and was often delayed. Meningomyocele repair was done in all, and shunting procedure for hydrocephalus was also done in

Table 2 Outcome of different neural tube defects

Variable	Total	SBf	Anencephaly	Encephalocele	Iniencephaly
Total cases	401 (100.0%)	206 (51.4%)	144 (35.9%)	43 (10.7%)	8 (2.0%)
Mean gestational age at delivery	29.4 ± 7.55 (11–42)	32.0 ± 8.3 (16–41)	25.1 ± 7.6 (11–42)	31.0 ± 8.8 (16–40)	30.8 ± 8.4 (26–40)
LSCS	27 (6.7%)	20 (5%)	0	6 (1.5%)	1 (0.3%)
Male/female	1:1	1:1	1:2	1:1	1:1
Associated defect	205 (51.2%)	134 (33.4%)	42 (10.5%)	21 (5.2%)	8 (2.0%)
Opted for termination of pregnancy	154 (38.4%)	66 (16.5%)	69 (17.2%)	16 (4.0%)	3 (0.8%)
Stillbirth	171 (42.6%)	78 (19.5%)	75 (18.7%)	13 (3.2%)	5 (1.2)
Live birth	76 (19.0%)	62 (15.5%)	0	14 (3.5%)	0

SBf spina bifida, *LSCS* lower segment cesarean section

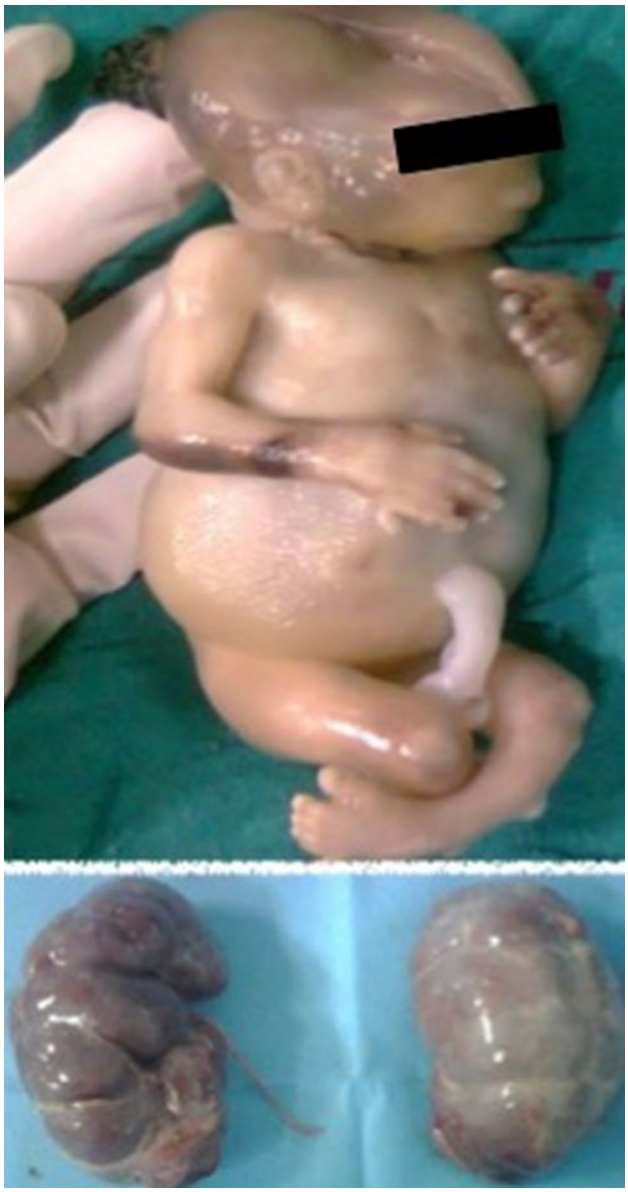

Fig. 1 Stillborn baby with encephalocele, polydactyly and enlarged polycystic kidneys suggestive of Meckel–Gruber syndrome

13 cases. Among the complications of the procedure, in 10/42 cases there was infection in the operated site and in 7/42 cases there was death in the postoperative period. Bowel and bladder incontinence was noticed in 25/35 live cases, and there was no residual defect in 10/35 live cases. Follow-up was at 6 monthly interval for most of the cases (18/35 cases) (Table 4).

Discussion

The present study provides the relative prevalence of NTD cases from a tertiary referral center of a populous developing country and acquaints us to the magnitude of the problem. The majority of the mothers in the study were at low risk. In more than half of the cases, the abnormality was detected in the latter half of pregnancy. Only one-fifth of the babies were delivered live. After 2 years, just over half of them were live. Surgical intervention was provided in all surviving cases; however, in most of the cases it was delayed due to lack of resources, therefore resulting in poorer outcome in two-third of the cases.

The incidence of NTDs is 2.79/1000 births in India [7]; it was estimated to be 3.9/1000 births in the present study. In our study, over half of the cases had spina bifida, and one-third of them had anencephaly. Similarly, in a study from Nigeria, 64% of cases had spinal lesions, all of which were in the lumbosacral region [8]. Associated anomalies were present in more than 50% cases, and hydrocephalus was most common; it was found to be associated in 58.8% of the children with NTD in the study by Kumar et al. [9].

Only 19% of the babies were delivered live. The probable reason for high number of stillbirths was that, in cases with associated severe hydrocephalus, cephalocentesis was done for allowing vaginal delivery, as consent for cesarean section was not given. It was due to the same reason that vaginal delivery was preferred even for cases with fetal distress in labor. Within 2 years, nearly one-third (24/62) among the live-born cases with spina bifida died. The physical disability was present in almost two-third of the surviving cases (25/38) with spina bifida. Many previous studies have also shown that most of the children who survive have multiple system involvement, severe handicap and a limited life expectancy [2, 10, 11].

Among those with spina bifida, only 20.4% could undergo surgery; no case was operated in the first month of life. Surgical intervention was delayed in most of the cases due to lack of resources. Infection was a common complication; urinary or fecal incontinence was present even after surgery in 25/35 cases who underwent surgery. In the previous study by Kuo et al., it was concluded that the delay in care was an important aspect of health care quality. The patients who suffered adverse effects following neurosurgical procedures were more likely to have had a delay in surgery [12]. In an earlier study by Shin et al., higher cervicothoracic lesions were found to be associated with a lower survival than for lumbosacral, and in the present study, none of the cases with thoracic lesions survived after 2 years [13]. In Lorber's original series, 75 of 200 (37.5%) died in the first year of life [6]. In a study by Hunt et al., the rate of mortality at the first year was 25 of 117 (21%) [14]. In the present study, nearly half of the babies with physical morbidity also had developmental delay and only 15/401 (3.7%) had minimal of no disability.

The limitations of the study were the lack of details regarding the objective absence of folic acid deficiency. The root cause of NTD is folic acid deficiency, and the fortification of food with FA and awareness among women regarding

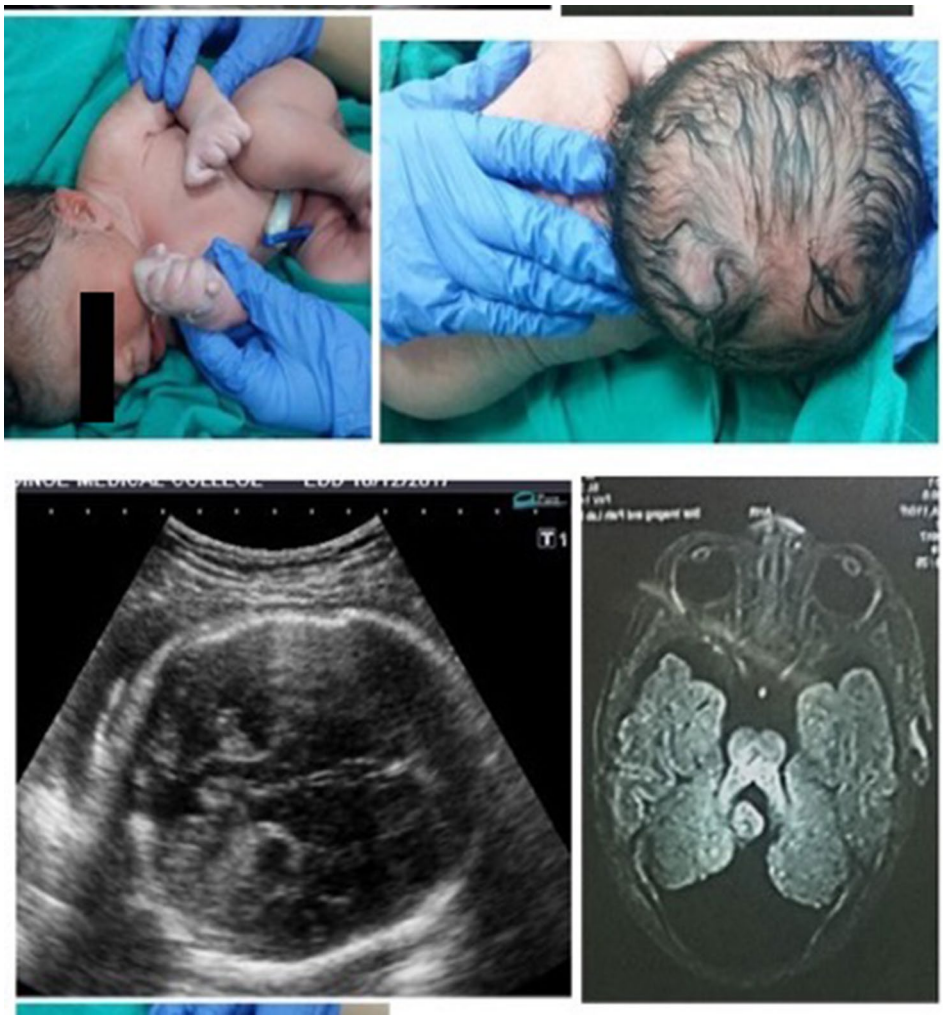

Fig. 2 Live baby with encephalocele, polydactyly and Dandy–Walker malformation on ultrasound suggestive of Joubert syndrome, confirmation by the presence of 'Molar tooth sign' on MRI

intake of FA prior to conception is necessary as it can be prevented with proper nutritional folic acid intake. Another major limitation was that the follow-up was questionnaire based and neurological examination of the babies was not done. Other weakness could be the follow-up of only 2 years, though the increase in the length of the follow-up could have increased the possibility of confounding variables like the environmental factors to bias the results. The strength of the study was the large cohort of cases with NTDs from a developing country and postnatal follow-up of cases till the period of 2 years.

The present study throws light on the outcome of cases of neural tube defects, not only at birth but at the end of 2 years. The findings show that their outcome in the present study situation is rather grim and far from the outcome data provided in literature from developed nations. Thus, the data regarding its outcome are helpful in providing realistic counseling to the couple. It also stresses upon the need for preventive measures such as periconceptional folic acid and about policy regarding ultrasound before 20 weeks of pregnancy, considering amendment of the termination of pregnancy law, and furthermore, the need for improving facilities for surgery in children with such defects.

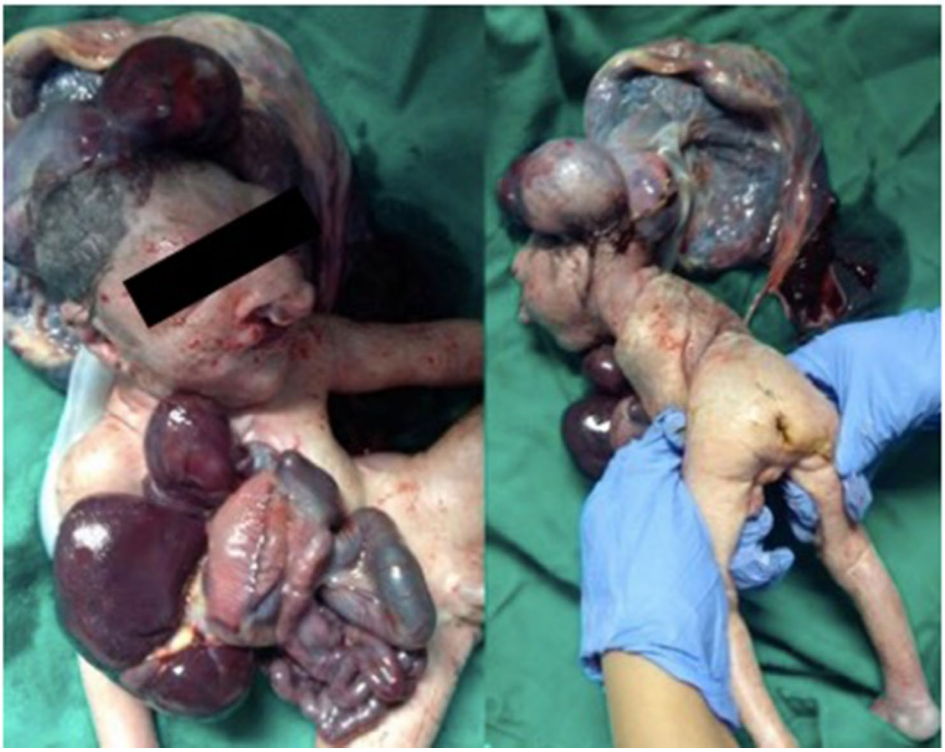

Fig. 3 Stillborn baby with amniotic band syndrome leading to disruptions in the form of facial cleft encephalocele, gastroschisis encephalocele attached to placenta

Table 3 Outcome of cases with spina bifida and encephalocele at birth and till 2 years of age

Outcome	Spina bifida ($n=206$)					Encephalocele ($n=43$)
	Total SB	Lumbar/sacral	Cervical/thoracic	Occulta	SBf with multiple anomalies	
Total cases	206 (51.4%)	167 (41.6%)	35 (8.7%)	4 (1.0%)	156 (38.9%)	43 (10.7%)
Outcome at birth						
Abortion or stillbirth	144 (35.9%)	112 (27.9)	32 (8.0)	0	111 (27.7%)	29 (7.2%)
Live birth ($n=76$)	62 (15.5%)	55 (13.7%)	3 (0.7%)	4 (1.0%)	45 (11.2%)	14 (3.5%)
Status after 2 years						
Died within 2 years ($n=32$)	24 (5.9%)	20 (5.5%)	1 (0.2%)	1 (0.2%)	21 (5.2%)	8 (2.0%)
Live ($n=44$)	38 (10.8%)	33 (8.1%)	02 (0.5%)	3 (0.7%)	24 (6.0%)	6 (1.5%)
Physical disability ($n=29$)	25 (6.2%)	23 (5.7%)	02 (0.5%)	0	10 (2.5%)	4 (1.0%)
Developmental delay ($n=16$)	13 (3.0%)	13 (3.0%)	0	0	6 (1.5%)	3 (0.7%)
Surgery among live ($n=39$)	35 (8.7%)	33 (0.5%)	2 (0.5%)	0	12 (3.0%)	4 (1.0%)
No disability ($n=15$)	13 (3.2%)	10 (2.5%)	0 (8.2%)	3 (0.7%)	0	2 (0.5%)

SB spina bifida

Table 4 Outcome of cases with spina bifida who underwent surgery

Outcome among operated cases	Number (42/206)	% 20.4%
Live after 2 years	35	17
Died after surgery	7	3.4
Reason for surgery		
Only meningomyocele repair	21	10.2
Foot deformity and meningomyocele repair	8	3.9
Meningomyocele repair and shunting	13	6.3
Only shunting	0	0
Age at surgery		
Within 1 month	0	0
2–3 months	22	10.7
6 months	6	2.9
1 year	14	6.8
Complications of surgery		
Infection	10	4.8
Skin breakdown	8	3.9
Death subsequent to operation	7	3.4
Residual defect[a]		
Fecal or urinary incontinence	25	12.1
Difficulty in ambulation	18	8.7
No residual defect	10	4.8
Frequency of follow-up in neurosurgery		
One monthly	10	4.8
6 months	18	8.7
1 year	7	3.4

[a]Some cases had more than one problems

Compliance with Ethical Standards

Conflict of interest There is no conflict of interest among authors.

Ethical Approval The research involves human participants, and ethical clearance has been taken from institute's ethical committee.

Informed Consent Informed consent was taken from the participants before conduction of the study.

References

1. Hans JTD, Martin L, Akira H. Clinical neuroembryology: development and developmental disorders of the human central nervous system. 2nd ed. Heidelberg: Springer; 2014.
2. Greene ND, Stanier P, Copp AJ. Genetics of human neural tube defects. Hum Mol Genet. 2009;18:R113–29.
3. Hunter A. Brain and spinal cord. Oxford Monogr Med Genet. 2006;52:715.
4. Mahapatra A. Spinal dysraphism controversies: AIIMS experiences and contribution. Indian J Neurosurg. 2012;1:4–8.
5. Busby A, Abramsky L, Dolk H, et al. Preventing neural tube defects in Europe: a missed opportunity. Reprod Toxicol. 2005;20(3):393–402.
6. Lorber J. Spina bifida cystica. Results of treatment of 270 consecutive cases with criteria for selection for the future. Arch Dis Child. 1972;47(256):854–73.
7. Kandasamy V, Subramanian M, Rajilarajendran H, et al. A study on the incidence of neural tube defects in a tertiary care hospital over a period of five years. J Clin Diagn Res JCDR. 2015;9(7):QC01–4.
8. Adeleye AO, Olowookere KG. Central nervous system congenital anomalies: a prospective neurosurgical observational study from Nigeria. Congenit Anom (Kyoto). 2009;49(4):258–61.
9. Kumar R, Singhal N. Outcome of meningomyelocele/lipomeningomyelocele in children of northern India. Pediatr Neurosurg. 2007;43(1):7–14.
10. Netto JM, Bastos AN, Figueiredo AA, et al. Spinal dysraphism: a neurosurgical review for the urologist. Rev Urol. 2009;11:71–81.
11. Thompson DN. Postnatal management and outcome for neural tube defects including spina bifida and encephalocoeles. Prenat Diagn. 2009;29(4):412–9.
12. Kuo BJ, Vissoci JR, Egger JR, et al. Perioperative outcomes for pediatric neurosurgical procedures: analysis of the National Surgical Quality Improvement Program-Pediatrics. J Neurosurg Pediatr. 2017;19(3):361–71.
13. Shin M, Kucik JE, Siffel C, et al. Improved survival among children with spina bifida in the United States. J Pediatr. 2012;161(6):1132–7.
14. Hunt GM. Open spina bifida: outcome for a complete cohort treated unselectively and followed into adulthood. Dev Med Child Neurol. 1990;32:108–18.

About the Author

Dr. Manisha Kumar is Professor (OBGYN) and in-charge of fetal medicine in Lady Hardinge Medical College, New Delhi. She is chairperson fetal medicine subcommittee of AOGD. Her area of interest includes antenatal ultrasound, fetal autopsy and genetic counselling. She has received FOGSI USV Genetic and fetal medicine award, Corion award and Rajat Ray award FOGSI. She has keen interest in research and has been the PI of Preeclampsia Screening project of ICMR, and she is part of WHO-SEARO project for stillbirth, ICMR Project on respectful mother care. She is PI of placental research project funded by GIA-ICMR and DBT-funded establishment of NIDAN Kendra (Genetic Lab) at LHMC. She has more than 40 publications in indexed journals to her credit.