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EARLY OUTCOME ANALYSIS OF NEURAL TUBE DEFECTS PRESENTING IN NEONATAL PERIOD: OUR EXPERIENCE

Paediatric

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ABSTRACT

Background: Neural tube defects (NTDs) are congenital malformation resulting from failure of complete or partial closure of the neural tube in developing embryo.

Aims and Objectives: The aim of this study is to present our experience, management and early outcomes (one month post-operatively) of neural tube defects presenting in neonatal period at our high volume tertiary care teaching Institutions.

Materials and methods: This retrospective cohort study was conducted over a period of 10 years from January 2007 to December 2016. Medical records of neonates treated for neural tube defects were recorded in a pre-designed Performa.

Results: A total of 286 patients with clinically diagnosed neural tube defects presenting in the neonatal period were studied. Male: female ratio was 1.11. The mean birth weight was 2350g. History of peri-conceptional use of folic acid was found in 15 (5.24%) mothers. One hundred seventeen (40.90%) of the patients had multiple system involvement. Most common was orthopedic deformities. Associated hydrocephalus was appreciated in 259 (90.56%) patients. Meningomyelocele was the most common anomaly seen in 239 (83.57%), 24 (8.39%) as meningocele and 23 (8.04%) were diagnosed as having Encephalocele. Surgery with decapping and repair was performed in 277 (96.85%) of the patients. Ventriculoperitoneal (VP) shunt operation before repair of meningomyelocele was performed in 9 (3.15%) patients, while in 19 (6.64%) patients, VP shunt operation was performed after the repair of NTD's in the early (one month) postoperative period. Clinical sepsis developed in the postoperative period in twenty one (7.58%) out of 277 patients, for which antibiotics were stepped up. Thirteen patients (4.69%) died postoperatively due to sepsis and associated anomalies.

Conclusions: We present our retrospective report on neural tube defects from Indian subcontinent with accurate baseline data. Meningomyelocele was the most common type of NTD's. We recommend that folic acid supplementation should begin before marriage to raise its serum levels before the conception. Antenatal care especially antenatal ultrasonography must be contemplated as early as possible in early detection of NTDs.

KEYWORDS

hydrocephalus, meningocele, meningomyelocele, neonates, neural tube defects.

INTRODUCTION

Neural tube defects (NTDs) represent one of the most prevalent groups of birth defects with serious consequences for newborns and their families. They are congenital malformation resulting failure of complete or partial closure of the neural tube in developing embryo due to early embryonic insult. NTD's are congenital abnormalities of the central nervous system (1). The various phenotypic variations in the expression of NTDs may be classified anatomically or embryologically. They are generally classified as open or closed neural tube defects (1,2). Anencephaly, spina bifida, and Encephalocele encompasses the vast majority of NTDs. Out of these myelomeningocele is the most common anatomical type and comprises approximately 85% of anomalies of Spina bifida (2). Human NTDs are multifactorial in origin, from genetic environmental and dietary factors. The genetic origin is not yet well understood, but several non-genetic risk factors have been recognized as have prospects for prevention by maternal folic acid supplementation (3,4).

Their clinical presentation depends on the clinical type and severity. In cases of myelomeningocele the presentation is commonly a midline anomaly in the lumbosacral region. There are associated anomalies, neural malformations and malformations of the other organ systems frequently accompany NTDs. NTDs substantially are contributing to morbidity and mortality, particularly in infancy and childhood. (1,5). Thus, we aimed to present our experience, management and early outcomes (one month post-operatively) of neural tube defects at our high volume tertiary care teaching Institutions. The aim also is to analyze the complications of this disease in the current set up and to develop a basis for future research and up-gradation of facilities.

MATERIAL AND METHODS

This retrospective cohort study was conducted in the pediatric surgery department of two tertiary care teaching institutes (India) over a period of 10 years from January 2007 to December 2016.

INCLUSION CRITERIA:

1. All patients with open NTDs presenting in the neonatal period

EXCLUSION CRITERIA:

1. Anencephaly
2. Closed NTD's including Lipomyelomeningocele and Lipomeningocele.
3. Rachischisis.
4. Anterior meningocele.
5. NTDs presenting beyond the neonatal period.

Management/Methodology:

The initial treatment was supportive and consisted with intravenous fluids to correct hypovolemia and/or acidosis; broad-spectrum antibiotics were prescribed. Adequate hydration was indicated by an hourly urine output of 1ml/Kg/hour. All patients underwent thorough assessment of their prenatal and birth history, and complete clinical examination with co-morbidities.

At the time of admission, baseline blood investigation including complete blood counts, analysis of serum electrolytes, renal and liver function tests, blood grouping and cross-matching were performed. Ultrasound evaluations for associated anomalies were performed. Radiographs were performed for associated gastro-intestinal, cardiothoracic and vertebral anomalies. Additionally ECHO (echocardiography) was contemplated when cardiac anomalies were suspected clinically.

Parental consent form for study: An Informed written consent was obtained from the patient's parents/guardian about the study. The parents were explained about the purpose of the study. It was explained that the study poses no additional or physical risk to involved participants. The parents were explained that there is no direct anticipated benefit (medical or financial) to the child. All confidential information collected about the patient would not be shared with anyone else.

The operations were performed either by a Paediatric surgeon or a senior resident under the direct supervision of a Paediatric surgeon. Postoperatively patients were given intensive care; kept nil orally till return of bowel sounds. Stitches were removed on 12th to 14th postoperative day. The patients were assessed during follow-up after discharge up to one month at weekly interval.

Pre-operative, intra-operative and post-operative (one month) medical records of children treated for neural tube defects were studied. All the

records were carefully recorded in excel sheets. The information obtained was analyzed according to objectives of the study. Charts were prepared on patients' demographic profile, clinical features, radiographic appearance, USG findings, and type of surgery and post-operative complications. All statistical data analysis was obtained with statistical package for social sciences (SPSS) version 10.0 for Windows. A "p" value of less than 0.05 was considered significant.

RESULTS:

A total of 286 patients with clinically diagnosed neural tube defects presenting in the neonatal period were studied. The clinical characteristics of the patients are summarized in Table 1.

Table 1: Clinical characteristics of the neonates with NTD's in our series

Characteristics	Frequency	Percentage (%)
Gender		
Male	150	52.45
Female	136	47.55
Birth weight (g)	Mean 2350 (1550-3950)	
Definite Peri-conceptional Folic acid use		
Yes	15	5.24
No	271	94.76
Prenatal diagnosis		
Yes	19	6.64
No	267	93.36
Frequency of Anomaly		
Meningomyelocele	239	83.57
Meningocele	24	8.39
Encephalocele	23	8.04
Total	**286**	**100**

One hundred and fifty(52.451%) of the babies were male and 136 (47.55%) were female. The mean birth weight was 2350 with range from 1550 to 3950g. History of peri-conceptional use of folic acid was found in 15 (5.24%) mothers.

Three mothers (0.78%) were found to have a history of drug usage during pregnancy. In the medical history of the mothers, one had gestational hypertension and one each had gestational diabetes and seizure disorder.

One hundred seventeen (40.90%) of the patients had multiple system involvement. More than one malformation was seen in one patient [Table 2].

Table 2: Associated anomalies seen with NTD'S in our series

Associated anomalies	Frequency	Percentage %
Orthopedic deformities	55	19.23
Cardiac anomalies	49	17.13
Genito-urinary system disorders	37	12.94
Anorectal malformation	5	1.75
Laterality defects	4	1.40
OEIS complex	4	1.40
Omphalocele	3	1.05
Cataract	3	1.05

Most common was orthopedic deformities (pes equino-varus, scoliosis, radial limb anomalies) were found in 55 patients. Several cardiac disorders (atrial septal defect, ventricular septal defect, patent ductus arteriosus, situs inversus totalis, pulmonary stenosis) were seen in 49 patients, genito-urinary system disorders (hydronephrosis, pelvi-uretric junction obstruction, renal agenesis, ectopic kidney, multicystic dysplastic kidney, horseshoe kidney, hypospadias, undescended testes) were found in 37 patients, anorectal malformation in 5 patients, laterality defects (situs inversus, polysplenia and dextrocardia) and OEIS complex (omphalocele, exstrophy of the bladder, imperforate anus, and meningocele (spina bifida) in 4 patients each, omphalocele in 3 patients and cataract was found in three patient [Table 2].

Among 19 patients (6.64%) who were diagnosed prenatally, 15 (5.24%) were diagnosed as having meningomyelocele or meningocele and four patients (1.4%) were diagnosed as having Encephalocele [Figure 1].

Two hundred and sixty seven patients (93.36%) were diagnosed in the postnatal period. Associated hydrocephalus was appreciated in 259 (90.56%) patients.

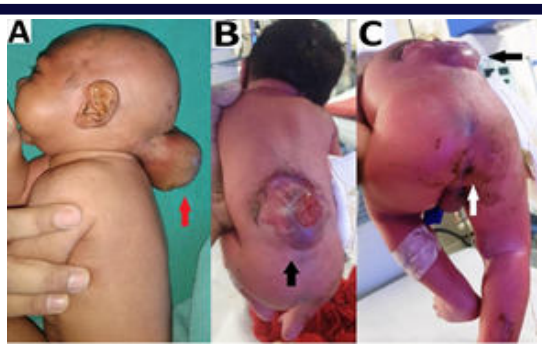

Figure 1: Photographs showing Cervical meningomyelocele (A) and Lumbar meningomyelocele (B and C).

As a result of physical examination and imaging studies (cranial and spinal ultrasonography), 239 (83.57%) of the patients were diagnosed as having meningomyelocele, 24 (8.39%) as meningocele and 23 (8.04%) were diagnosed as having encephalocele. Anatomical location of NTD's is described in Table 3. Lumbosacral was the most common type among meningomyelocele seen in 179 neonates. Among the lumbosacral sub-type, there were three (1.05%) patients with associated meningocele (double lesion); out of three, there was one patient with cervical meningocele and two with thoracic meningocele [Table 3]. Arnold–Chiari type 2 malformation was diagnosed in 105 (36.71%) of the patients with meningomyelocele.

Surgery with decapping and repair was performed in 277 (96.85%) of the patients [Figure 2]. Nine (3.15%) patients succumbed before surgery could be contemplated. The reasons for mortality were due to sepsis because of cerebrospinal fluid leakage in the sac leading to meningitis. The second most common cause was life threatening associated multiple congenital anomalies.

Ventriculoperitoneal (VP) shunt operation before repair of meningomyelocele was performed in 9 (3.15%), while in 19 (6.64%) patients, VP shunt operation was performed after the repair of NTD's in the early (one month) postoperative period. In the rest of the patients, medical management was continued.

Table 3: Anatomical location of NTD's in our series of neonates.

Type of NTD	Frequency N = 286	Percentage %
Meningomyelocele	**239**	**83.57**
A. Cervical	17	5.94
B. Thoracic	20	6.99
C. Lumbar	9	3.15
D. Lumbosacral	179	62.60
D1. Isolated	176	61.54
D2. Associated with Cervical/ thoracic meningocele (Double lesion)	3	1.05
E. Sacral	14	4.90
Meningocele	**24**	**8.39**
A. Cervical	5	1.75
B. Thoracic	5	1.75
C. Lumbar	4	1.40
D. lumbosacral	3	1.05
E. Sacral	7	2.44
Encephalocele	**23**	**8.04**
A. Occipital	18	6.29
B. Parietal	2	0.70
C. Frontal/nasal	3	1.05

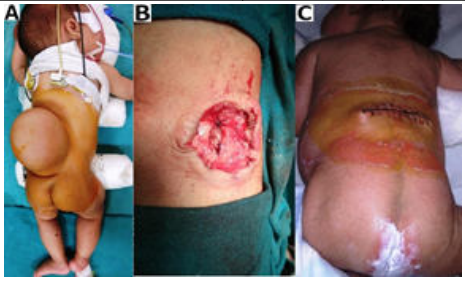

Figure 2: Intraoperative photographs showing patient positioning

for excision of a large lumbosacral meningomyelocele (A), completion of decapping of the sac and repair of duramater. Photograph showing 5th Postoperative day following repair of meningomyelocele (C).

Antibiotic treatment was started at the time of admission in those with cerebrospinal fluid leakage in the sac and peri-operatively in others. It was continued postoperatively in all the patients in the study. Clinical sepsis developed in the postoperative period in twenty one (7.58%) out of 277 patients, and meningitis in 9 (3.25%) patients for which antibiotics were stepped up. Surgical site infection was present in twenty nine (10.47%) neonates. All were discharged after treatment with appropriate antibiotics. Thirteen patients (4.69%) died postoperatively due to sepsis and associated anomalies. The median time of hospitalization was 8 days, ranged between 4 and 21 days.

DISCUSSION

Neural tube defects (NTDs) are preventable congenital malformations of the central nervous system in the majority of cases. Worldwide, roughly 300 000 children are born with NTDs each year (1). The incidence of NTDs has been reported to be 0.89–0.93 in 1000 live births in the European countries, 0.62–13.8 in the Arab countries, and 0.53 in the USA (6,7,8).

Anencephaly is a fatal congenital developmental abnormality of NTD'S due to failure of the fusion of cranial end of the neural tube that develops between days 22 to 25th of fetal life. This results in exposure of malformed brain. Approximately 60% fetuses die before birth and none survives beyond two weeks post-natally (9). Spina bifida results from failure of posterior vertebral arches to fuse.

In patients with lumbosacral spina bifida, problems include motor and sensory dysfunction in the lower extremities, anal and urethral sphincter failure, and neurogenic bladder. Especially, most patients with thoracic and lumbosacral spina bifida have an increased probability of hydrocephalus and Arnold–Chiari type 2 malformation. Arnold–Chiari type 2 malformation accompanies meningomyelocele at a high rate with 65% to 71.4% in recent studies (10,11). Associated malformations significantly increase the morbidity and mortality in the neonatal period and the 1st year of life (12).

NTDs occur early in pregnancy, within the first 4 weeks, by that time, most females would not even know they are pregnant. The neural tube is generated by the processes that shape, bend, and fuse the neural plate, and fusion in the dorsal midline progressively seals the neural tube as it forms. Neural tube will eventually form the brain and spinal cord. NTDs are defined as failure of the developing neural tube to close properly during the development, exactly between 24 and 26 days of gestation (2,3). When there is a failure at the cephalic end of the neural tube to close, anencephaly occurs. Similarly, if the neural tube remains open at the caudal end, Spina bifida results (2,3). Also if there is an error during primary neurulation, the result is spina bifida cystica (meningocele and meningomyelocele), while errors of secondary neurulation result in various forms of spina bifida occulta.

The risk factors implicated for the development of NTDs are environmental, genetic, pharmacological and dietary factors. Forty five years back, Richard Smithells et al. observed that ladies who gave birth to offspring with NTDs had low levels of folic acid in their serum and red blood cells (4). This research led to a clinical trial of peri-conceptional 4 mg folic acid supplementation in subsequent pregnancy for women who already had an affected child. Consequently, folic acid treatment significantly reduced the rate of NTDs in any pregnancy (5). Presently, 0.4 mg of folic acid is recommended for all women before conception and for the first 12 weeks of a pregnancy.

Folic acid is a coenzyme that plays a major role in metabolic processes. Folic acid is a substance which is essential for synthesis of intracellular nucleotides used in DNA synthesis and for the methylation reactions i.e. methionine synthase activity taking place in the cell. Methionine synthase converts homocysteine into methionine. This enzymatic step requires methylation, provided by folic acid, and if this does not ensue, homocysteine levels increases and which further prevents the neural tube closure and NTDs (5). Since the neural tube is formed in the early stages of pregnancy sufficient folic acid must be available in the milieu in the peri-conceptional period. It has been revealed that folic acid deficiency causes NTDs and use of peri-conceptional folic acid decreases NTD recurrence by 50% to 70% (9).

Only 5.24%, of the mothers of our neonates had used folic acid. Therefore, families should be explained that they should use folic acid along with Vitamin B12 very early in the peri-conceptional period to decrease NTD's recurrence in subsequent pregnancies. This study points out to the fact that folic acid is not the only factor responsible for all NTD's. Also, as per a recent research folic acid is more effective in reducing the occurrence of isolated spina bifida compared to non-isolated spina bifida i.e spina bifida with associated malformations (13,14).

Other risk factors associated are hot tub use, obesity, and exposure to certain medications that are folic acid antagonistic, such as methotrexate and trimethoprim and anti-epileptics drugs like valproic acid and carbamazepine (15). In our study only one patient was on medicines for gestational diabetes and obesity and also only one was on anti-epileptics drugs.

Current antenatal screenings with maternal serum alpha fetoprotein and ultrasonography has allowed prenatal diagnosis of NTDs, but in Indian subcontinent, the facilities are limited in the rural setting. By the time NTD's are diagnosed prenatally it is beyond the legal period for medical termination of pregnancy (15).

The male to female ratio in Nigerian was of 1.1:1 (16). Male predominance with male to female of 1.2:1 was also observed by a British research group, which is similar to our series (17). Japanese reported a male to female ratio of 1:1.1, which is in contrast to our findings (18).

Myelomeningocele remains the most common anatomical type of NTD's which was also found in our series with 83.57% of the total anomalies. Anatomical location of NTD's in our series was roughly similar to other reports (16). Surgical closures of NTD's were done post-natally within the first 48 hours of admission, with the exception of 3.15% cases requiring VP shunt before sac repair.

In NTDs, associated morbidity in other organ systems usually accompanies central nervous system anomalies. The patients need long term follow up and cooperation of different clinical branches including pediatrics, pediatric surgery, neurosurgery, urology, physical therapy and rehabilitation. Raising awareness of the families of babies who are diagnosed in the early prenatal period about the prognosis is paramount (15,16).

Folic acid supplementation is provided to reduce NTD's risk which represents a major public health problem. NTDs are a heterogeneity group of malformations and research suggests that primary prevention may be accomplished ideally by multiple interventions, with use of supplementary micronutrients alongside folic acid. This would provide added advantage to reduce risk (19,20).

The main limitation of this study was that follow up was performed for a period of only one month owing to resource constraints and also that the data was only from one paediatric surgery unit. However, the data was collected consistently by the senior author.

CONCLUSIONS:

We present our retrospective report on neural tube defects from Indian subcontinent with accurate baseline data. The incidence of NTDs was high in which meningomyelocele was the most common condition. The cause of high NTDs was mostly due to inadequate maternity facilities. In most cases of NTDs no definite risk factor was identified. Although first trimester folic acid supplementation can decrease the prevalence, but we recommend that folic acid supplementation should begin before marriage to raise its serum levels before the conception. As in our geographical area, most of the pregnancies are planned. Females who had medical disease e.g. epilepsy, the disease should be controlled, and drugs should be reevaluated before pregnancy and preferably before marriage. Antenatal care especially antenatal ultrasonography must be contemplated as early as possible in early detection of NTDs.

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