SMGroup

Neural Tube Defects

Rajendra K Ghritlaharey*

Department of Pediatric Surgery, Gandhi Medical College and Associated, Kamla Nehru and Hamidia Hospitals, India

***Corresponding author:** Rajendra K Ghritlaharey, Department of Pediatric Surgery, Gandhi Medical College and Associated, Kamla Nehru and Hamidia Hospitals, Bhopal, Madhya Pradesh 462001, India, Email: drrajendrak1@rediffmail.com

Published Date: May 15, 2015

ABSTRACT

Neural tube defects (NTDs) are among the most common of all birth defects in human, affecting over 300,000 births globally each year. The worldwide incidence of NTDs ranges from 1.0 to 10.0 per 1,000 live births, and varies within the country to other part of the world. During the last few decades, there is significant decline in the incidence of NTDs all over the world; however, still the incidence is much higher in developing countries. Mandatory fortification of flour with folic acid has proved to be one of the most successful public health interventions in reducing the prevalence of NTDs affected pregnancies in many of the developed countries. More than 95% of cases of NTDs are contributed by the first affected pregnancies. NTDs occurs when the neural tube fails to close during the first few weeks of embryonic life, and are classified into two types on the basis of presence or absence of exposed neural tissues as, (a) Open Neural Tube Defects, the most common, and (b) Closed Neural Tube Defects. The exact cause of the NTDs is not known, but it is multi-factorial and multigenic. Advances in the field of diagnostics ultrasound and, magnetic resonance imaging (MRI) have dramatically changed the diagnosis of NTDs not only during post-natal, but also during anti-prenatal period. Post-natal MRI of the spine is the investigation of choice for the spinal dysraphism / spina bifida. MRI of the spine not only provides the details of the disease / defect, but at the same time also delineates the associated syringomylia, if present. Studies on prenatal repair of spina bifida / myelomeningoceles supported that prenatal repair of spina bifida reduces / reverse the severity of hindbrain herniation, preserve / improve the

neurological function, bladder and bowel functions and muscle power in lower limbs, and reduces or obviate the need for postnatal requirement of ventriculoperitoneal shunt. Fetal surgery, including repair of NTDs is available only at limited centres around the world, and having its own merits and demerits. Spina bifida is one of the commonest malformations seen in pediatric surgery practice, and it is classified as spina bifida cystica (aperta), and spina bifida occulta. Spina bifida cystica include myeloschisis, myelomeningocele, and menigocele. Myelomeningocele (MMC) is the commonest lesion and usually associated with various degrees of neurological deficits and bladder and bowel dysfunction. Spina bifida occulta means hidden split spine, and in such cases the meninges do not herniate through the opening in the spinal canal. Many of the cases of NTDs are also associated with congenital anomalies involving other system. The prognosis of the NTDs affected children depends upon the diseases itself, associated other anomalies, hydrocephalus, degree of neurological deficits, bladder and bowel dysfunction, and the treatment offered for the correction of the disease.

Keywords: Encephalocele; Fetal surgery; Menigocele; Myelomeningocele; Meningomyelocele; Neural tube defects; Neonatal surgery; Pediatric surgery; Spina bifida; Spinal dysraphism

DEMOGRAPHICS OF NEURAL TUBE DEFECTS

Neural Tube Defects (NTDs) are among the most common of all human birth defects, with the worldwide incidence varying from less than 1.0 to more than 10.0 per 1,000 births. Each year 3-4 lakh infants are born with NTDs (spina bifida and anencephaly) worldwide and more than 95% of the cases are constituted by the first affected pregnancies. In the USA, the prevalence of NTDs is 0.1 to 0.4 per 1,000 live births in African Americans, and 1 per 1,000 live births amongst white Americans, with a reported recurrence risk of 1-3%. In 1992, the USA public health service recommended that all women capable of becoming pregnant consume 400 μg of folic acid daily to reduce the incidence and the recurrence of NTDs. In a Nationwide inpatient sample database from 1988-2010 from USA, found that there were only 4034 hospitalizations for surgical repair of myelomeningocele, and concluded that the annual surgical volume of myelomeningocele repair has decreased after the introduction of public health initiatives [1-6].

In China, there were 80,000 to 100,000 pregnancies per year resulting in children born with NTDs with Northern China has the highest known rate of NTDs in the world [7]. In a study from Xian city of China conducted during 2003 to 2012 reported that the birth defects rate was 9.18% in 2003, which was declined to 7% in 2012. They further concluded that there was significant decreased in incidence of NTDs after large-scale supplemental folic acid intervention [8].

In a review conducted to determine the prevalence of pregnancies with NTDs in England and Wales between 1964 and 2004, found that there were an estimated 969 pregnancies with NTDs (168 (17%) births and 801 (83%) terminations) in England and Wales in 2004. The birth prevalence of NTDs was 3.6 per 1,000 in 1964, was decreased by 93% to 0.3 per 1,000 in 2004 [9]. In Ireland, there is no mandatory folic acid food fortification, partly due to declining NTDs rates

in recent years. In a study conducted during 2009-2011 to ascertain the incidence of NTDs in Republic of Ireland, found that during the above periods there were 225,998 total births, including 236 NTDs, giving an incidence of 1.04/1,000 births. Of all cases, 45% (n=106) had anencephaly, 49% (n=115) had spina bifida and 6% (n=15) had an encephalocoele; 78% (n=184) were live-born or stillborn and 22% (n=52) were terminations abroad. Authors also concluded that the incidence of NTDs in the Republic of Ireland appears to be increasing [10].

In India, the reported incidence of NTDs varies from 0.5 to 11 per 1,000 live births, with higher incidence from the Northern states of India; namely Punjab, Haryana, Rajasthan and Bihar. The higher incidence of NTDs is reported in women in the age group of 20-25 years in India. In a systematic review of 19 published articles reported a total of 308,387 births, among which 1310 cases of NTDs were also reported, giving an overall birth prevalence of 4.1 per 1,000. The live birth and stillbirth prevalence of NTDs was 1.3 per 1,000 births and 1.7 per 1,000 births, respectively. Amongst the NTDs; the reported prevalence of anencephaly was 2.1 per 1,000 births and spina bifida was 1.9 per 1,000 births [11-13].

In Canada, nearly 11,000 newborns are diagnosed with serious congenital abnormalities every year. The prevalence of anencephaly decreased from 2.2 to 0.4 per 10,000 total births between 1989 and 2002. Similarly, the prevalence of spina bifida in 2002 was 4.1 per 10,000 total births, down from 8.0 in 1989. There is significant decline in the prevalence of NTDs affected children born in low and high socio economic strata area since food fortification began in 1999, although children born in low socioeconomic strata areas had significantly higher rates of NTDs [14].

In an epidemiological study from Tunisia from 1991-2011, found that there were 769 stillbirths with NTDs were delivered, yielding a prevalence of 2.02/10,000. The authors also concluded that the highest frequency during winter (3.7 per 10,000 births), and nulliparous mother's were significantly more likely to have NTDs than uni or multiparous mothers [15]. In a prospective study included all neonates with NTDs (spina bifida, anencephaly, encephalocoele) born in 2009 in 32 Malaysian hospitals in the Malaysian National Neonatal Network, and reported that the prevalence of NTDs was 0.42 per 1,000 live births, being highest among the indigenous people of Sarawak (1.09 per 1,000 live births) and lowest among Malaysians of Chinese descent (0.09 per 1,000 live births). The authors further concluded that the most common type of NTDs was anencephaly (0.19 per 1,000 live births), followed by spina bifida (0.11 per 1,000 live births) and encephalocoele (0.07 per 1,000 live births). Majority of the infants with anencephaly (94.5%, n = 51), 45.8% (n = 11) with encephalocoele and 9.5% (n = 4) with spina bifida died [16]. The prevalence of NTD-affected pregnancies in South Australia was 1.95 per 1,000 births (39 cases) in 2010 and 1.91 per 1,000 births in 2009 (38 cases), the highest annual rates since 1991 [17]. In a retrospective data analysis (2006-2009) conducted in Germany to understand the economic burden of illness associated with NTDs (spina bifida and encephalocele), and found that the prevalence of NTDs ranged from 0.54 to 0.58 per 1000 enrolees for health insurance and also found that 95.4% (n=3952) were diagnosed with spina bifida [18].

TYPES OF NEURAL TUBE DEFECTS

Neural tube defects occurs when the neural tube fails to close during the first few weeks of embryonic life, and they are classified into two on the basis of presence or absence of exposed neural tissues as, (a) Open Neural Tube Defects, and (b) Closed Neural Tube Defects. Defective closure at anterior neuropore may result in cranial / upper level defects (anencephaly, encephaloceles) and defective closure at distal / posterior neuropore may results in spina bifida. Open neural tube defects occur when there is a failure of its closure. There is a defect in the skull or vertebrae, and occurs when the developing brain and / or spinal card are exposed at birth, and this is a more common subtypes of NTDs. Open NTDs include; anencephaly, encephaloceles, spina bifida aperta / cystica (meningocele, myelomeningocele (MMC). Myelomeningocoele is the most common amongst the open NTDs, and is the most severe birth defect with neurological, bladder and bowel dysfunctions, compatible with survival. Closed neural tube defects are rare and it occurs when the developing brain and / or spinal card are not exposed, but covered with the skin. Closed NTDs include; lipo-myelomeningocele, lipo-meningocele, tethered card, spina bifida occulta [1-4,11,16].

CAUSES OF NEURAL TUBE DEFECTS

The exact cause and the specific gene responsible for the development of NTDs are not known although, NTDs are multi-factorial, and both the genetic and environmental factors are playing an important role in the genesis of NTDs. Maternal malnutrition is an important risk factor for development of NTDs in developing countries. Folate (vitamin B_9) and vitamin B_{12} are very important in reducing the occurrences of NTDs. Importantly, a deficiency of folate itself does not lead to NTDs. Studies have shown that there were decreased maternal folate levels in NTDs affected pregnancies. Periconceptional folic acid supplementation has shown to decrease both the occurrence and recurrence of NTDs by 40% – 85%, though the exact mechanism for this protective effect remains unknown [1-5,7,11,12,14].

PRENATAL INVESTIGATIONS AND DIAGNOSIS OF NEURAL TUBE DEFECTS

With the advancement in the field of fetal therapy / surgery, an accurate prenatal diagnosis of open and closed NTDs is critical and an appropriate pre-operative diagnosis is a must. With the advancement in the field of fetal ultrasonography and other modalities, it is possible to accurately detect the NTDs well in advance, and it is possible to manage NTDs accordingly. Investigations to detect NTDs during antenatal period are; antenatal fetal sonography, antenatal fetal magnetic resonance imaging (MRI), and measurement of maternal serum alpha-fetoprotein (AFP). Measurements of the amniotic fluid AFP and amniotic fluid acetyl cholinesterase are also needed for confirmation, if fetal USG indicates NTDs. Fetal sonography is useful in detecting the NTDs, but many times it is difficult to differentiate between open and closed NTDs, which have very different prognosis. MRI is a complementary tool that can further elucidate / provide more morphological

details of spinal abnormalities and other associated CNS and non-CNS abnormalities, if present. AFP is a major serum protein in the early embryonic life, and can be leaked in the amniotic fluid from open NTDs (anencephaly and MMC), if present. Open NTDs can be diagnosed prenatal by measuring AFP in the maternal blood, and or in amniotic fluid. Maternal AFP can be measured around 15-20 weeks of gestation, and an elevated maternal serum AFP is a good predictor of open NTDs. If the diagnosis of open NTDs is doubtful or uncertain on maternal AFP measurements then amniotic fluid AFP can be obtained and measured for confirmation. An increase in AFP and presence of acetyl cholinesterase in amniotic fluid assay identify presence of open NTDs, however AFP levels fluctuates both with the gestational age and the methods of assay used. The sensitivity of the AFP varies from study to study and the methods of measurements [1,19-28].

POSTNATAL INVESTIGATIONS FOR NEURAL TUBE DEFECTS

Postnatal investigations of a child born with NTD depends upon the anatomical site, type of lesion, and associate anomalies and includes; USG of the swelling, computed tomography scan (CT scan), and MRI of lesion and head, and other investigations depending upon the associate anomalies. USG, CT scan and MRI of the head are the investigations needed for the evaluation of varieties of encephaloceles and associated hydrocephalus and other brain abnormalities, although MRI of the head is the investigation of choice. MRI of the spine is the investigation of choice for varieties of spinal dysraphism (spina bifida cystica and occulta), as this not only provides the morphological details of the defect, but at the same also delineates the associated syringomylia, if present. Other investigations may also require, if associated other system involvement are there [1,29-32].

PREVENTION OF NEURAL TUBE DEFECTS

In recent decades there is significant decreased in the prevalence and recurrence of NTDs in developed countries; however it is still high in developing countries and remains an important and preventable cause of neonatal morbidity and mortality. High-income countries have reported significant reductions in prevalence and recurrence of NTDs following folic acid supplementation and fortification. The United States Public Health Service in 1992 recommended that all women capable of becoming pregnant consume 400 μg of folic acid daily to prevent the prevalence and recurrence of NTDs. In 1996, the United States Food and Drug Administration published regulations requiring the addition of folic acid to enriched breads, cereals, flour and other grain products. In 1998, folic acid fortification of all enriched cereal grain product flour was fully implemented in the United States and Canada. This mandatory fortification of the food with folic acid helps in reducing the incidence of NTDs in USA. In Canada, food fortification is also successful in reducing the prevalence of NTDs. In a study in Canada showed that prevalence of NTDs among children born in low and high socio economic status areas declined since food fortification with folic acid began in 1999. Fortification of selected foods with folic acid has been shown to reduce the incidence of NTDs by 46% in Canada. Women with a prior history

of a birth of a NTD affected child have an increases risk for the having another NTD affected pregnancy, and if they are planning for another pregnancy, the recommendation is to consume high-doses of folic acid supplements (4 mg / day) beginning ≥ 4 weeks before conception and continuing for first 12 weeks of pregnancy. The folic acid in combination with a multivitamins supplementation has associated with a decrease in the incidence of NTDs. In a study conducted in China showed that peri-conceptional 400 μg of folic acid alone showed that there was 40% and 85% reduction in risk of NTDs in the southern and northern of China, respectively. In Xian city also there was a downward trend of birth defects including significant decline of NTDs and was observed following large scale supplementation of folic acid. In Xian city of China, during 2003 the birth defect rate was 9.18% and was declined to 7.00% in 2012. There is adequate evidence from western countries showed that maternal peri-conceptional folic acid supplementation and fortification not only prevent the first occurrence, but also prevent the recurrence of NTDs. More than 50 countries have implemented folic acid fortification of food / flour. In India at present folic acid fortification is not mandatory. In a systematic review suggested that NTDs contribute to a significant number of live births and still births in India, suggesting that pre-conceptional folic acid supplementation should be an essential of reproductive health services. Mandatory fortification of flour with folic acid has proved to be one of the most successful public health interventions in reducing the prevalence of NTD-affected pregnancies. Most developing countries have few, if any, common sources of folic acid, unlike many developed countries, which have folic acid available from ready-to-eat cereals and supplements. Expanding the number of developed and developing countries with folic acid flour fortification has tremendous potential to safely eliminate most folic acid-preventable NTDs. Studies also demonstrated the need to fortify flour and other cereal grain with folic acid in all countries of the world to prevent the prevalence and recurrence of NTDs [1,3-5,7,8,11,12,14,33-36].

FETAL SURGERY FOR NEURAL TUBE DEFECTS

Most of the prenatally diagnosed malformations are best managed after birth by an appropriate medical and surgical therapy. Only few of the anatomical malformations may require and benefit by antenatal fetal intervention. Advancement in the field of antenatal fetal imaging, anaesthesia, tocolytic therapy, surgical techniques for hysterotomy, refinement in fetal surgical procedures, fetal and maternal monitoring, better post-operative maternal and fetal ICU care, etc help to perform fetal interventions with better outcome and a reality to benefits few of the fetuses with life threatening anatomic malformations. First human open fetal surgery in the world was performed on April 26, 1981 at division of pediatric surgery, children's hospital at the University of California, San Francisco (UCSF) by Dr. Michael R. Harrison and his team to treat advanced urinary tract obstruction. Adzick NS (2013) reported in a prospective and randomized study on in utero repair of open spina bifida (the MOMS trial; included 158 cases) has shown that fetal surgery for open spina bifida / myelomeningoceles before 26 weeks of gestation may preserve neurologic function, reverse the hindbrain herniation, and obviate the need for postnatal placement of Ventriculo

Peritoneal (VP) shunt. Other studies also supported that prenatal repair of spina bifida reduces the severity of hindbrain herniation, preserve / improve the neurological function, bladder and bowel functions and muscle power in lower limbs, and reduces the need for postnatal VP shunts. Fetal surgery for spina bifida can be executed via open fetal surgery or through fetoscopic techniques / percutaneous minimal-access fetoscopic techniques. A percutaneous minimal access fetoscopic technique for closure of spina bifida aperta is less traumatic than other techniques. Kohl (2014), reviewed 51 fetal repairs of spina bifida aperta using percutaneous minimal access fetoscopic technique, and reported that this technique for fetal repair can be performed with a high rate of technical success, regardless of the placental position. Fetal repair for NTDs is associated with significant maternal and fetal morbidity and fetal loss [1,37-43].

ANENCEPHALY

Anencephaly / acrania (Figure 1a) is a neural tube defect that occurs when the cranial end of the neural tube fails to close, and in this there is an absence of a major portion of the brain and skull. The prevalence of anencephaly varies at different geographical locations. The overall prevalence of anencephaly in the North of The Netherlands over a 5-year period (Aug 2008 – July 2013) was 5.4 per 10,000 pregnancies (n = 110), and majority of cases (69%) were detected on antenatal USG before 18 weeks' of gestation. A population-based retrospective study was performed from data of the Registry of Congenital Malformations of Alsace, France between 1995 and 2009, and found that there were only 272 cases of NTDs, of which 42% (n=113) cases were of anencephaly. In a systematic meta-analysis of birth prevalence of NTDs in India reported that the prevalence of anencephaly was 2.1 per 1,000 births. In a prospective study conducted in Malaysia to determine the prevalence of NTDs reported that the prevalence of anencephaly was 0.19 per 1,000 live births. Anencephaly can be classified into three types; (1) meroanencephaly: where there is rudimentary brain tissue and partial formation of the cranium; (2) holoanencephaly: brain is completely absent, and is the most common type, and (3) craniorachischisis: the most severe type where area cerebrovasculosa and area medullovasculosa fill both cranial defects and the spinal column. Anencephaly is also associated with other NTD and or other malformations not related to the neural tube development and are; spinal dysraphism (Figure 1b), cleft lip and palate, urinary tract anomalies, gastrointestinal and cardiac abnormalities. Gore et al, in a review of 20 fetuses of anencephaly with a gestational age of 16 to 34 weeks, reported that 16 of 20 fetuses also had other anomalies, most commonly spina bifida. Other associated anomalies were cleft palate, gastrointestinal and skeletal anomalies and genital anomalies. It is possible to accurately detect and diagnose the anencephaly on fetal USG. Vaginal USG may be necessary when the fetal head is low in the pelvis. Infants with anencephaly are either stillborn or usually die within a few hours or days after birth [1,13,16,44-49].

Figure 1a: Clinical photograph showing anencephaly.

Figure 1b: Clinical photograph showing anencephaly and associated myelocele.

MANAGEMENT OF ENCEPHALOCELES

Encephalocele is characterized by herniation of the brain, méninges, and part of the ventricles through a skull defect protruding towards exterior. Encephalocele occurs when the cranial part of the developing neural tube fails to close during the early fetal life, and reported to occur in 1-3 per 10,000 to 1 in 5,000 live births. Encephaloceles varies in size, location, and its contents. Depending upon the anatomical location of the encephalocele, it can be named as occipital (Figure 2a), anterior (Figure 2b), parietal, temporal, and vertex (Figure 2c) encephalocele. Occipital encephaloceles are the more frequently observed. Anterior encephaloces are classified as

frontoethmoidal, orbital, transethmoidal, transseller, and interfrontal types. The frontoethmoidal encephaloceles are due to the defect in the area of frontal and ethmoidal bones, and more common in the Southeast Asia. Frontal cephaloceles are often associated with median cleft face syndrome, characterized by hypertelorism and median cleft lip or palate. Depending on the content of the lesion, cephaloceles are classified as meningocele (contains meninges only), encephalocele (contains brain tissue only), encephalomeningocele (contains meninges and brain tissue), and encephalomeningocystocele (contains meninges, brain tissue and lateral ventricles). Clinically most of the encephaloceles are obvious and suspected due to the characteristic swelling, and the size of the encephalocele may vary from few cm to a giant swelling. Clinical examination consists of examination of the encephalocele / swelling (size, extend, location), size of the head for clinical suspicion of hydrocephalus or microcephaly, associated other CNS and other system anomalies. Some time the encephalocele may rupture (Figure 2d) and infected and may present with meningitis. Associated anomalies are also observed with encephalocele and are; hydrocephalus, microcephaly (Figure 2e), corpus callosum agenesis, arachnoid cyst, porencephalic cyst, single ventricle, ventriculomegaly, spinal dysraphism / meningomyelocele, and chromosomal aberrations. Most of the cases of encephaloceles are easily diagnosed on cranial views with brain protruding through cranial defect during antenatal fetal sonography. Fetal MRI serves as an accurate tool to delineate the fetal brain, and associated cranial anomalies. Postnatal diagnostic work up for encephaloceles includes; CT scans (Figure 2f), MRI of encephalocele including the head / brain to delineate not only the lesion, its contents and brain, but also detect the associated hydrocephalus, etc if present. Operative repair of the encephalocele consists of excision of the excess méninges, protruded brain tissue, watertight closure of the dural defect and approximation of the skin. Reconstruction of the skull defect may require bone graft. Operative repair for anterior encephaloceles may be executed either as a single - stage or staged - procedures. Complex anterior encephaloceles repair may require a multidisciplinary team approach. If hydrocephalus is present, it should be dealt first, followed by repair of encephalocele. Complications observed following repair of encephaloces are; post-operative meningitis, CSF leak, wound infection, hydrocephalus, etc and mortalities have also been reported following repair of encephaloceles. Prognosis of encephaloceles depends upon the size and amount of brain tissue involved in the encephalocele, associated additional anomalies of the brain, hydrocephalus and other associated anomalies [49-60].

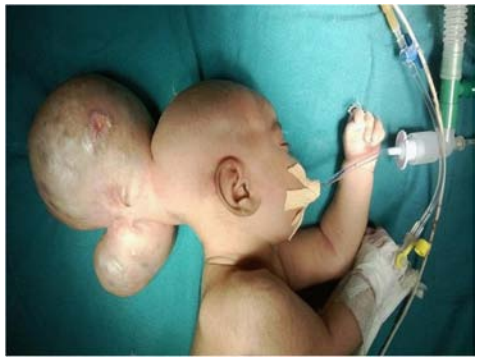

Figure 2a: Clinical photograph showing occipital encephalocele.

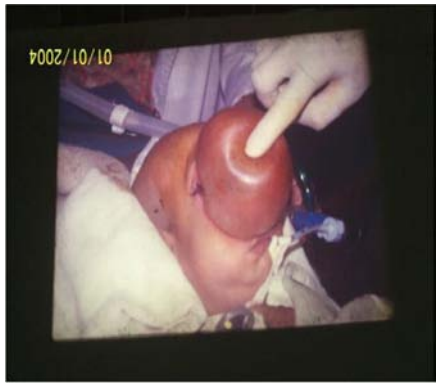

Figure 2b: Clinical photograph showing anterior / frontal encephalocele.

Figure 2c: Clinical photograph showing vertex encephalocele.

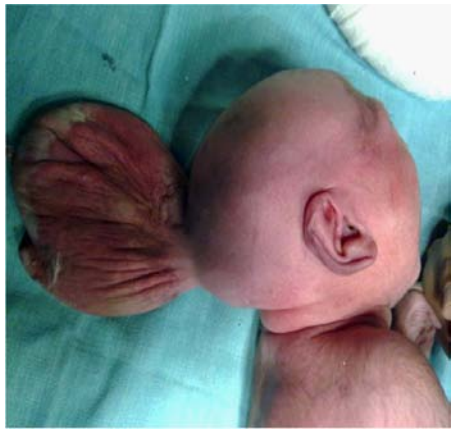

Figure 2d: Clinical photograph showing ruptured occipital encephalocele.

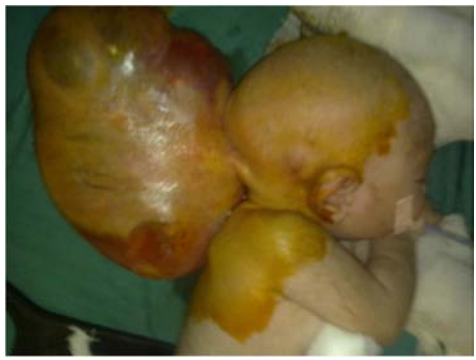

Figure 2e: Clinical photograph showing occipital encephalocele with microcephaly.

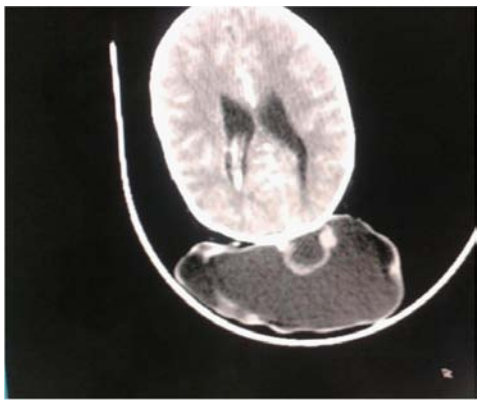

Figure 2f: Photograph showing CT scan of head of occipital encephalocele.

MANAGEMENT OF SPINA BIFIDA CYSTICA

The incidence of spinal dysraphism has significantly decreased during the last few decades all over the world, more in the developed countries; however it is still higher in the developing countries. Spina bifida is one of the commonest malformations seen in pediatric surgery

practice, and it is classified as spina bifida cystica (aperta) or spina bifida occulta. Spina bifida cystica results due to incomplete development of the neural tube mostly more caudally, and there is protrusion of the malformed neural tissue, meninges, or both through an opening in the vertebral arches, muscle, and skin. Spina bifida cystica include myeloschisis, myelomeningocele (Figure 3a), and meningocele (Figure 3b). Myelomeningocele / meningomyelocele (MMC) is the commonest lesion and usually associated with various degrees of neurological deficits of lower limbs, hydrocephalus, orthopedic problems, and bladder and bowel dysfunctions. MMC is characterized by the herniation of meninges as well as the spinal cord through a bony defect (spina bifida) and hydrocephalous is also associated with MMC in approximately four fifth of the cases. Meningocele is characterized by the herniation of meninges only through a bony defect (spina bifida) and it is well covered with the skin, and in most of the cases are not associated with neurological deficits. Open neural tube defect such as rachischisis / myeloschisis is severe malformation of nervous system and associated with severe degree of neurological deficits. Spina bifida cystica are most frequent involves the lumbosacral area (Figure 3c). Other locations are thoracic (Figure 3d), cervical (Figure 3e), sacral, and rarely may have lesions at two places in a same child. Most of the meningocele and MMC cases are located on the dorsal (posterior) aspect, but rarely may present on the anterior aspect through a vertebral defects. Spina bifida rarely also detected during adulthood.

Babies born with MMC present with characteristic swelling at the back and with neurological deficits of the lower limbs, and dysfunction / incontinenance for both urine and faeces. Many of them also have associated enlargement of the head due to associated hydrocephalus (Figure 3f). Few of the babies with MMC may have rupture of the membrane and CSF leak (Figure 3g), and may present with features of meningitis. Clinical examination consists of details examination of the lesion itself (size, location, fluctuation, trans-illumination (Figure 3h), etc), assessment of neurological deficits of the lower limbs, evaluation of bladder and bowel function ((Figure 3i), evaluation for hydrocephalus and other congenital anomalies, orthopedics and other neurological deficits. The size of the swelling varies from few cm to a large swelling. In cases of ruptured MMC, it is mandatory to look for the features of meningitis. MMC associated with neurological deficits and bladder and bowel dysfunction / incontinence need to explain the prognosis pre-operatively. Hydrocephalus is also associated with MMC in more than 80% of the cases. Other associated anomalies observed with spina bifida are; Arachnoid Chiari malformations, other CNS anomalies, talipes deformities, club foot, anorectal malformation, undescended testis, hydronephrosis. Prenatal diagnosis of spina bifida cystica is possible using antenatal fetal USG, fetal MRI, measurement of maternal serum AFP, and amniotic AFP levels. Prenatal diagnostic modalities are described in more details at “Prenatal Investigations and Diagnosis of Neural Tube Defects”. Postnatal investigations for spina bifida cystica includes; X-ray of the spine (Figure 3j), USG, CT scans and MRI of the spine and head. MRI of the spine provides the best morphological features of the lesion and also detects the syringomylia, if present. It is also mandatory to document and

detect the associated hydrocephalus, and other brain pathology. Other specific investigations are also require and depends upon the system involved with the disease.

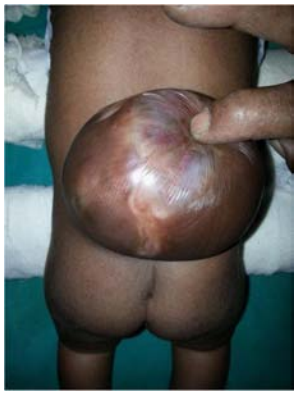

Figure 3a: Clinical photograph showing myelomeningocele.

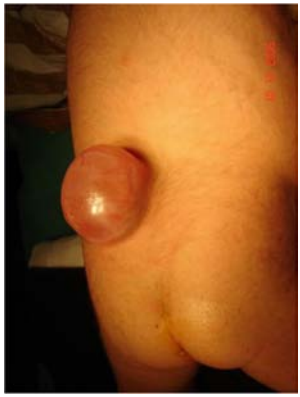

Figure 3b: Clinical photograph showing menigocele.

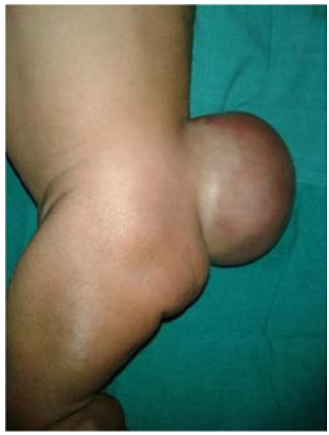

Figure 3c: Clinical photograph showing Lumbosacral myelomeningocele.

Figure 3d: Clinical photograph showing thoracic myelomeningocele.

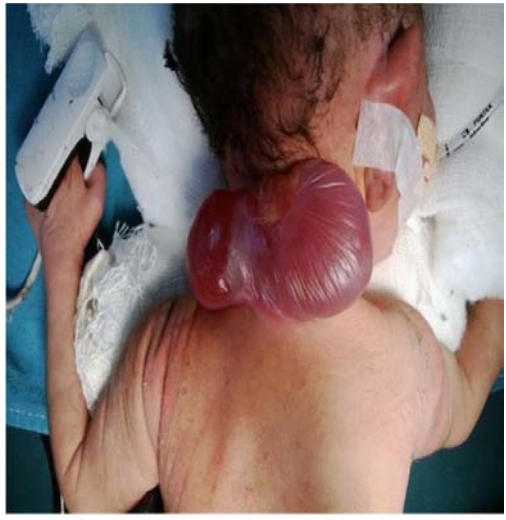

Figure 3e: Clinical photograph of cervical myelomeningocele.

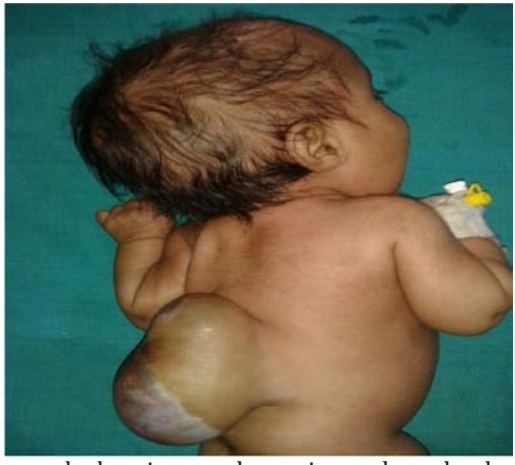

Figure 3f: Clinical photograph showing myelomeningocele and enlarged head (hydrocephalus).

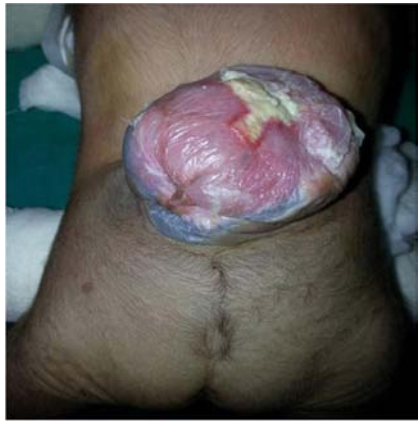

Figure 3g: Clinical photograph showing ruptured and infected myelomeningocele.

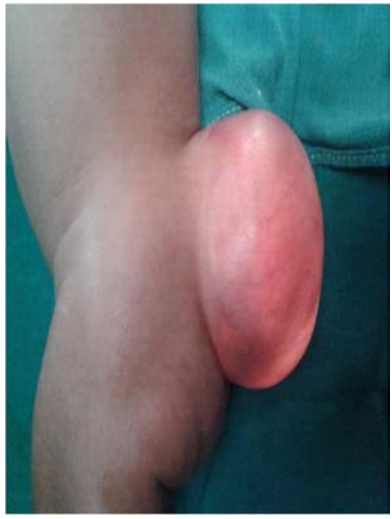

Figure 3h: Clinical photograph showing positive trans-illumination of lumbosacral myelomeningocele.

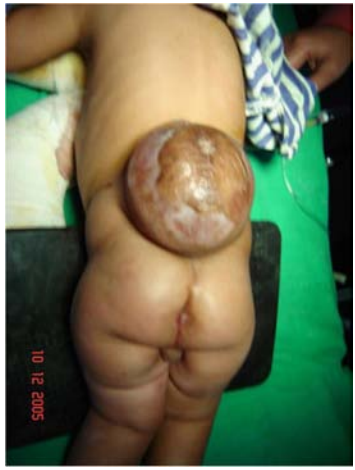

Figure 3i: Clinical photograph showing myelomeningocele with patulous anus.

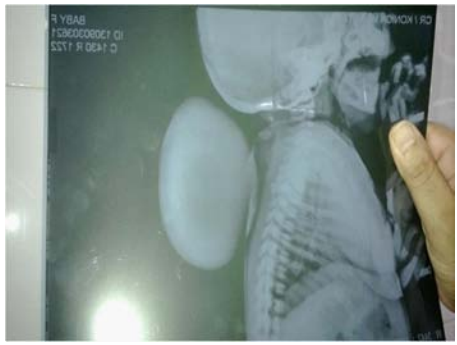

Figure 3j: Photograph of X-Ray spine of thoracic myelomeningocele.

The objective of the surgical repair for MMC is to close the neural placode, watertight closure of the dura, mobilization and midline approximation of the para spinous muscles and fascia, and skin closure. The mobilization and midline approximation of the para spinous muscles and fascia is not mandatory in all the cases of repair for MMC. In some cases during repair of large MMC, may require rotational muscle and fascial flaps to cover the defect. If hydrocephalus is detected during investigations or present with MMC, than mostly VP shunt and MMC repair can be performed at same sitting, or VP shunt surgery first followed by repair of MMC after few days to weeks. Some time hydrocephalus develops in immediate post-operative period following repair of MMC, and require an immediate shunting. Post-operative complications observed following repair of MMC are; CSF leak, meningitis, wound infection, wound dehiscence, post-operative hydrocephalus, bladder and bowel dysfunction / incontinence, limb paralysis, tethered cord syndrome. Tethered cord syndrome is an important, delayed post-operative complication reported in about 20% of the cases following the repair of MMC, and may require surgery if symptomatic. Prophylactic surgery is not advocated for asymptomatic tethered cord and detected on MRI. Spinal dysraphism is still a major public health problem, and disabling problem in the developing countries. Early closure of MMC and an aggressive placement of VP shunt for hydrocephalus, if present or develop after MMC repair helps in more survival with better social life. Management of bladder and bowel dysfunction / incontinence, care for lower limb weakness and neurological deficits, care for orthopaedic and others deformities require multidiscipline approach, and a multidisciplinary approach for managing a child with MMC probably helps for a better quality of life [1,61-72].

MANAGEMENT OF SPINA BIFIDA OCCULTA

By definition, spina bifida occulta means hidden split spine, and in the cases of spina bifida occulta the meninges do not herniate through a vertebral defect. Spina bifida occulta includes; lipo-myelomeningocele (lipo-MMC), tethered cord syndrome, and split notochord syndrome, etc. Usually the spinal cord and spinal nerves are not involved in the cases of occult spinal dysraphism. Spina bifida occulta clinically may present during infancy, childhood or during adulthood. Spina bifida occulta may be asymptomatic for years and may present latter in life as progressive

neurologic deficits secondary to traction on the conus medullaris. There may be progressive bladder and bowel dysfunction, problem in gait, sensory and motor problems in lower limbs, and tropic ulcer may be there. Skin stigmata may present with occult spinal dysraphism and are presence of hairy patches / tuft of hairs, cutaneous navi, hemangioma, lipoma, dermal sinus, etc since birth, and usually indicates the presence of underlying spinal dysraphism. Any child or person having above skin stigmata need investigation with MRI, to confirm or rule out the underlying tethered cord / spinal defect.

LIPOMYELOMENINGOCELE (LIPO-MMC)

Lipo-MMC (Figure 4) is one of the more common forms of spina bifida occulta. Patients with lipo-MMC may present with progressive neurological deterioration secondary to an inherent tethered spinal cord. CT scan and MRI are the gold standard to detect bony anomalies and cord malformations, respectively in the cases of occult spinal dysraphism, including lipo-MMC. MRI in both sagittal and coronal plains is the imaging modality of choice for the evaluation of not only the spina bifida cystica, but also for evaluation of spina bifida occulta. Lipo-MMC leading to tethered cord syndrome is one of the most common types of occult neural tube defects requiring neurosurgical treatment. An early surgical intervention of the cases of lipo-MMC and correction of the tethered cord may be beneficial in preventing further neurological deterioration. Complications may occurs following lipo-MMC operation and are CSF leak, CSF collection, wound healing problem, infection, hydrocephalus, deterioration of neurological deficits and bladder and bowel function, and renal function impairment. Teetered cord syndrome may also develop in considerable number of cases following repair of lipo-MMC and may require operation [1,73-80].

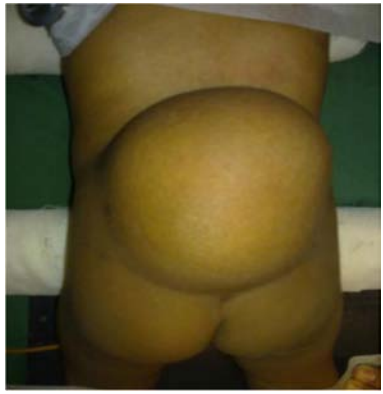

Figure 4: Clinical photograph showing lipo-myelomeningocele.

TETHERED CORD SYNDROME

Tethered cord syndrome may also develop in considerable number of cases following repair of menigocele, MMC, and lipo-MMC. Patients with tethered cord syndrome may present with progressive neurological deficits (weakness of lower limbs, sensory / motor problems, and muscle problems), orthopedics problems (scoliosis, gait problems, asymmetry of lower

limb, foot deformities, and back pain) and bladder and bowel dysfunction / incontinence. The most important goal for treating a symptomatic patient with tethered cord syndrome is an early untethering of the cord (tethered cord release), and an untethering operation should be performed at the earliest, irrespective of age. An early tethered cord release operation in most of the cases results in stabilization or improvement of neurological status. Untethering of the cord can improve or resolve the bladder and bowel dysfunction, and also improve the neurological deficits of the lower limbs. Complications may occur following untethering of the cord and are CSF leak, CSF collection, wound healing problem, infection, hydrocephalus, deterioration of neurological deficits and bladder and bowel function. Few of the cases following untethering may again develop tethered cord and require re-operation [1,75,81-85].

SPLIT NOTOCHORD SYNDROME

Complete cleft of the vertebral column associated with gastrointestinal tract and central nervous system anomalies is known as split notochord syndrome (SNS) and is an extremely rare form of spinal dysraphism. The name SNS was proposed by Bentley and Smith in 1960 and is also known as posterior spina bifida, combined spina bifida, neurenteric fistula, and dorsal enteric fistula. SNS is a complex malformation comprising vertebral anomalies (anterior and posterior spina bifida), central nervous system abnormalities (diastematomyelia, diplomyelia, myelomeningocele) and intestinal anomalies (fistulas, dermal sinus tract, diverticula and enteric cysts). The dorsal enteric fistula is due to the persistent connection between the endoderm and ectoderm, resulting in splitting of the notochord. About 40 cases of SNS have been reported in literature, and half of them presented with associated dorsal enteric fistula (Figure 5a). SNS is frequently associated with vertebral anomalies, duplication of spine, spinal canal, duplication of spinal cords, hydrocephalus, meningomyelocele, gastrointestinal tract anomalies (dorsal enteric fistula, imperforate anus, diverticulum, enteric cysts, atresia, intestinal duplication), and genitourinary system anomalies (penoscrotal transposition, epispadias, exstrophy of bladder). The location of the intestinal fistula varies from case to case and may be found in the distal ileum, caecum, or colon but most frequently located in large intestine. More than one-third of cases of SNS also had associated anorectal malformation, especially imperforate anus. Only one case of SNS was discovered in an adult and others were in newborn and young children and reported both in males as well in females. The exact etiology for SNS in not known, but thought to be a result of maldevelopment of notochord, neuroenteric canal and paraxial mesoderm. It is possible to detect some cases of SNS during antenatal fetal sonography, and the USG findings depend on the lesion and the associated anomalies. Pre-operative investigations are needed to identify and delineate extend of the disease and the system involved for the particular case. It includes plain x–ray of the spine (Figure 5b), USG and CT scan of the abdomen, head and spine. MRI of the spine and head also needed for better delineation of the spine and spinal cord, and brain. Other investigations are also required for evaluating genitourinary and gastrointestinal system (Figure 5c). Management of a case of SNS must be individualized and surgical approach varies from case to case as the

associated anomalies and system involved varies from case to case. Staged - procedures are advocated and needed for proper correction of these anomalies, although single - stage procedure has also been reported. Prognosis of a child with SNS depends on the associated anomalies and extends of the lesion and mostly fatal, although few survivals have also been reported [86-90].

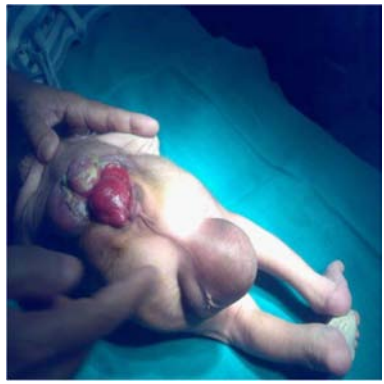

Figure 5a: Clinical photograph showing dorsal enteric fistula with MMC.

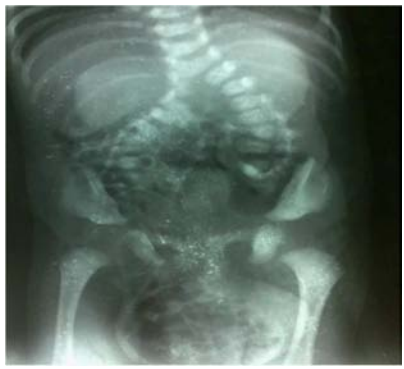

Figure 5b: Plain X-Ray spine showing splitting of spine.

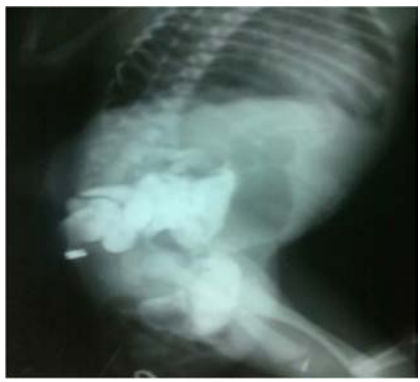

Figure 5c: Photograph showing dye study through enteric fistula (SNS).

References

1. Smith JL. Management of neural tube defects, hydrocephalus, refractory epilepsy, and central nervous system infections. In: Coran AG, Adzick NS, Krummel TM, Laberge JM, Shamberger RC, et al., editors. Pediatric Surgery. Amsterdam: Elsevier. 2012; 1673-1697.
2. Au KS, Ashley-Koch A, Northrup H. Epidemiologic and genetic aspects of spina bifida and other neural tube defects. Dev Disabil Res Rev. 2010; 16: 6-15.
3. Williams J, Mai CT, Mulinare J, Isenburg J, Flood TJ. Updated estimates of neural tube defects prevented by mandatory folic Acid fortification - United States, 1995-2011. MMWR Morb Mortal Wkly Rep. 2015; 64: 1-5.
4. Arth A, Tinker S, Moore C, Canfield M, Agopian A. Supplement use and other characteristics among pregnant women with a previous pregnancy affected by a neural tube defect - United States, 1997-2009. MMWR Morb Mortal Wkly Rep. 2015; 64: 6-9.
5. Wilson RD, Johnson JA, Wyatt P, Allen V, Gagnon A, et al. Pre-conceptional vitamin/folic acid supplementation 2007: the use of folic acid in combination with a multivitamin supplement for the prevention of neural tube defects and other congenital anomalies. J Obstet Gynaecol Can. 2007; 29: 1003-1026.
6. Kshettry VR, Kelly ML, Rosenbaum BP, Seicean A, Hwang L. Myelomeningocele: surgical trends and predictors of outcome in the United States, 1988-2010. J Neurosurg Pediatr. 2014; 13: 666-678.
7. Zhu L, Ling H. National Neural Tube Defects Prevention Program in China. Food Nutr Bull. 2008; 29: S196-204.
8. Yu M, Ping Z, Zhang S, He Y, Dong R. The survey of birth defects rate based on birth registration system. Chin Med J (Engl). 2015; 128: 7-14.
9. Morris JK, Wald NJ. Prevalence of neural tube defect pregnancies in England and Wales from 1964 to 2004. J Med Screen. 2007; 14: 55-59.
10. McDonnell R, Delany V, O'Mahony MT2, Mullaney C3, Lee B4. Neural tube defects in the Republic of Ireland in 2009-11. J Public Health (Oxf). 2015; 37: 57-63.
11. Gupta H, Gupta P. Neural tube defects and folic acid. Indian Pediatr. 2004; 41: 577-586.
12. Godbole K, Deshmukh U, Yajnik C. Nutrigenetic determinants of neural tube defects in India. Indian Pediatr. 2009; 46: 467-475.
13. Bhide P, Sagoo GS, Moorthie S, Burton H, Kar A. Systematic review of birth prevalence of neural tube defects in India. Birth Defects Res A Clin Mol Teratol. 2013; 97: 437-443.
14. Agha MM, Glazier RH, Moineddin R, Moore AM, Guttmann A. Food fortification and decline in the prevalence of neural tube defects: does public intervention reduce the socioeconomic gap in prevalence? Int J Environ Res Public Health. 2013; 10: 1312-1323.
15. Nasri K, Ben Fradj MK, Hamdi T, Aloui M, Ben Jemaa N. Epidemiology of neural tube defect subtypes in Tunisia, 1991-2011. Pathol Res Pract. 2014; 210: 944-952.
16. Boo NY, Cheah IG, Thong MK; Malaysian National Neonatal Registry. Neural tube defects in Malaysia: data from the Malaysian National Neonatal Registry. J Trop Pediatr. 2013; 59: 338-342.
17. Flood L, Scheil W, Nguyen AM, Sage L, Scott J. An increase in neural tube defect notifications, South Australia, 2009-2010. Western Pac Surveill Response J. 2013; 4: 30-39.
18. Bowles D, Wasiak R, Kissner M, van Nooten F, Engel S. Economic burden of neural tube defects in Germany. Public Health. 2014; 128: 274-281.
19. Wilson RD; SOGC Genetics Committee, Wilson RD, Audibert F, Brock JA, Campagnolo C. Prenatal screening, diagnosis, and pregnancy management of fetal neural tube defects. J Obstet Gynaecol Can. 2014; 36: 927-942.
20. Bulas D. Fetal evaluation of spine dysraphism. Pediatr Radiol. 2010; 40: 1029-1037.
21. Cedergren M, Selbing A. Detection of fetal structural abnormalities by an 11-14-week ultrasound dating scan in an unselected Swedish population. Acta Obstet Gynecol Scand. 2006; 85: 912-915.
22. Ovaere C, Eggink A, Richter J, Cohen-Overbeek TE, Van Calenbergh F. Prenatal Diagnosis and Patient Preferences in Patients with Neural Tube Defects around the Advent of Fetal Surgery in Belgium and Holland. Fetal Diagn Ther. 2015; 37: 226-234.
23. Woitek R, Dvorak A, Weber M, Seidl R, Bettelheim D. MR-based morphometry of the posterior fossa in fetuses with neural tube defects of the spine. PLoS One. 2014; 9: e112585.
24. Gat I, Hoffmann C, Shashar D, Yosef OB, Konen E. Fetal Brain MRI: Novel Classification and Contribution to Sonography. Ultraschall Med. 2014;.

25. Bredaki FE, Poon LC, Birdir C, Escalante D, Nicolaides KH. First-trimester screening for neural tube defects using alpha-fetoprotein. Fetal Diagn Ther. 2012; 31: 109-114.

26. Kooper AJ, de Bruijn D, van Ravenwaaij-Arts CM, Faas BH, Creemers JW. Fetal anomaly scan potentially will replace routine AFAFP assays for the detection of neural tube defects. Prenat Diagn. 2007; 27: 29-33.

27. Leguy MC, Tavares Sdos R, Tsatsaris V, Lewin F, Clauser E. [Assessment of AFP in amniotic fluid: comparison of three automated techniques]. Ann Biol Clin (Paris). 2011; 69: 441-446.

28. Flick A, Krakow D, Martirosian A, Silverman N, Platt LD. Routine measurement of amniotic fluid alpha-fetoprotein and acetylcholinesterase: the need for a reevaluation. Am J Obstet Gynecol. 2014; 211: 139.

29. Raja RA, Qureshi AA, Memon AR, Ali H, Dev V. Pattern of encephaloceles: a case series. J Ayub Med Coll Abbottabad. 2008; 20: 125-128.

30. Mahapatra AK. Split cord malformation - A study of 300 cases at AIIMS 1990-2006. J Pediatr Neurosci. 2011; 6: S41-45.

31. Bamba Y, Nonaka M, Nakajima S, Yamasaki M. Three-dimensional reconstructed computed tomography-magnetic resonance fusion image-based preoperative planning for surgical procedures for spinal lipoma or tethered spinal cord after myelomeningocele repair. Neurol Med Chir (Tokyo). 2011; 51: 397-402.

32. Harada A, Nishiyama K, Yoshimura J, Sano M, Fujii Y. Intraspinal lesions associated with sacrococcygeal dimples. J Neurosurg Pediatr. 2014; 14: 81-86.

33. Salih MA, Murshid WR, Seidahmed MZ. Epidemiology, prenatal management, and prevention of neural tube defects. Saudi Med J. 2014; 35 Suppl 1: S15-28.

34. Blencowe H, Cousens S, Modell B, Lawn J. Folic acid to reduce neonatal mortality from neural tube disorders. Int J Epidemiol. 2010; 39 Suppl 1: i110-121.

35. Berry RJ, Bailey L, Mulinare J, Bower C; Folic Acid Working Group. Fortification of flour with folic acid. Food Nutr Bull. 2010; 31: S22-35.

36. Bestwick JP, Huttly WJ, Morris JK, Wald NJ. Prevention of neural tube defects: a cross-sectional study of the uptake of folic acid supplementation in nearly half a million women. PLoS One. 2014; 9: e89354.

37. Lee H, Hirose S, Harrison MR. Prenatal diagnosis and fetal therapy. In: Coran AG, Adzick NS, Krummel TM, Laberge JM, Shamberger RC, et al, editors. Pediatric Surgery. Amsterdam: Elsevier. 2012; 77-88.

38. Adzick NS. Fetal surgery for spina bifida: past, present, future. Semin Pediatr Surg. 2013; 22: 10-17.

39. Kohl T, Tchatcheva K, Merz W, Wartenberg HC, Heep A, et al. Percutaneous fetoscopic patch closure of human spina bifida aperta: advances in fetal surgical techniques may obviate the need for early postnatal neurosurgical intervention. Surg Endosc. 2009; 23: 890-895.

40. Kohl T. Percutaneous minimally invasive fetoscopic surgery for spina bifida aperta. Part I: surgical technique and perioperative outcome. Ultrasound Obstet Gynecol. 2014; 44: 515-524.

41. Verbeek RJ, Heep A, Maurits NM, Cremer R, Hoving EW, et al. Fetal endoscopic myelomeningocele closure preserves segmental neurological function. Dev Med Child Neurol. 2012; 54: 15-22.

42. Kahn L, Mbabuike N, Valle-Giler EP, Garces J, Moore RC. Fetal surgery: the ochsner experience with in utero spina bifida repair. Ochsner J. 2014; 14: 112-118.

43. Grivell RM, Andersen C, Dodd JM. Prenatal versus postnatal repair procedures for spina bifida for improving infant and maternal outcomes. Cochrane Database Syst Rev. 2014; 10: CD008825.

44. Isada NB, Qureshi F, Jacques SM, Holzgreve W, Tout MJ. Meroanencephaly: pathology and prenatal diagnosis. Fetal Diagn Ther. 1993; 8: 423-428.

45. Gole RA, Meshram PM, Hattangdi SS. Anencephaly and its associated malformations. J Clin Diagn Res. 2014; 8: AC07-09.

46. Goldstein RB, Filly RA. Prenatal diagnosis of anencephaly: spectrum of sonographic appearances and distinction from the amniotic band syndrome. AJR Am J Roentgenol. 1988; 151: 547-550.

47. Fleurke-Rozema JH, van Leijden L, van de Kamp K, Pajkrt E, Bilardo CM. Timing of detection of anencephaly in The Netherlands. Prenat Diagn. 2015; 35: 483-485.

48. Timbolschi D, Schaefer E, Monga B, Fattori D, Dott B. Neural tube defects: the experience of the registry of congenital malformations of Alsace, France, 1995-2009. Fetal Diagn Ther. 2015; 37: 6-17.

49. RÄƒdulescu M, Ulmeanu EC, Nedelea M, Oncescu A. Prenatal ultrasound diagnosis of neural tube defects. Pictorial essay. Med Ultrason. 2012; 14: 147-153.

50. Kiymaz N, Yilmaz N, Demir I, Keskin S. Prognostic factors in patients with occipital encephalocele. Pediatr Neurosurg. 2010; 46: 6-11.

51. Mahapatra AK, Agrawal D. Anterior encephaloceles: a series of 103 cases over 32 years. J Clin Neurosci. 2006; 13: 536-539.

52. Alexiou GA, Sfakianos G, Prodromou N. Diagnosis and management of cephaloceles. J Craniofac Surg. 2010; 21: 1581-1582.

53. Gao Z, Massimi L, Rogerio S, Raybaud C, Di Rocco C. Vertex cephaloceles: a review. Childs Nerv Syst. 2014; 30: 65-72.

54. Aojanepong C. Purse-string closure for frontoethmoidal encephalomeningocele. J Craniofac Surg. 2011; 22: 1584-1590.

55. Hoving EW. Nasal encephaloceles. Childs Nerv Syst. 2000; 16: 702-706.

56. Boonvisut S, Ladpli S, Sujatanond M, Tisavipat N, Luxsuwong M. A new technique for the repair and reconstruction of frontoethmoidal encephalomeningoceles by medial orbital composite-unit translocation. Br J Plast Surg. 2001; 54: 93-101.

57. Nasu W, Kobayashi S, Kashiwa K, Honda T. Secondary craniofacial reconstruction of huge frontoethmoidal encephalomeningocele after primary neurosurgical repair. J Craniofac Surg. 2008; 19: 171-174.

58. Agthong S, Wiwanitkit V. Encephalomeningocele cases over 10 years in Thailand: a case series. BMC Neurol. 2002; 2: 3.

59. Kasprian GJ, Paldino MJ, Mehollin-Ray AR, Shetty A, Williams JL, et al. Prenatal imaging of occipital encephaloceles. Fetal Diagn Ther. 2015; 37: 241-248.

60. Sepulveda W, Wong AE, Andreeva E, Odegova N, Martinez-Ten P. Fetal Cephalocele: First-Trimester Sonographic Spectrum In A Review Of 35 Cases. Ultrasound Obstet Gynecol. 2014;.

61. Agrawal A, Sampley S. Spinal dysraphism: A challenge continued to be faced by neurosurgeons in developing countries. Asian J Neurosurg. 2014; 9: 68-71.

62. Ulsenheimer MM, Antoniuk SA, Santos LH, Ceccatto MP, Silveira AE. Myelomeningocele: a Brazilian University Hospital experience. Arq Neuropsiquiatr. 2004; 62: 963-968.

63. Ugwu RO, Eneh AU, Oruamabo RS. Neural tube defects in a university teaching hospital in southern Nigeria: trends and outcome. Niger J Med. 2007; 16: 368-371.

64. Aygün C, Kurucu S, Çakmak-Çelik F, Dağçınar A, Tanyeri B, et al. Experience of a tertiary care center on 100 newborns with neural tube defects. Turk J Pediatr. 2013; 55: 359-364.

65. Arts MP, de Jong TH. Thoracic meningocele, meningomyelocele or myelocystocele? Diagnostic difficulties, consequent implications and treatment. Pediatr Neurosurg. 2004; 40: 75-79.

66. Kıymaz N, Yılmaz N, Güdü BO, Demir I, Kozan A. Cervical spinal dysraphism. Pediatr Neurosurg. 2010; 46: 351-356.

67. Durmaz R, Arslantaş A, Ozön YH, Tel E. Double meningocele. Case report. Turk J Pediatr. 2000; 42: 331-333.

68. Oner AY, Uzun M, Tokgöz N, Tali ET. Isolated true anterior thoracic meningocele. AJNR Am J Neuroradiol. 2004; 25: 1828-1830.

69. Shastin D, Selvanathan SK, Tyagi AK. A rare case of anterior sacral meningocoele presenting as cauda equina syndrome. Br J Neurosurg. 2014;.

70. Ramdasi RV, Nadkarni TD, Goel AH. Congenital meningocoele presenting in an adult. J Craniovertebr Junction Spine. 2014; 5: 134-136.

71. Idris B. Factors affecting the outcomes in children post-myelomeningocoele repair in northeastern peninsular malaysia. Malays J Med Sci. 2011; 18: 52-59.

72. Lien SC, Maher CO, Garton HJ, Kasten SJ, Muraszko KM. Local and regional flap closure in myelomeningocele repair: a 15-year review. Childs Nerv Syst. 2010; 26: 1091-1095.

73. Wang HH, Wiener JS, Ross SS, Routh JC. Emergent care patterns in patients with spina bifida: a case-control study. J Urol. 2015; 193: 268-273.

74. Torre M, Guida E, Bisio G, Scarsi P, Piatelli G. Risk factors for renal function impairment in a series of 502 patients born with spinal dysraphisms. J Pediatr Urol. 2011; 7: 39-43.

75. Herman JM, McLone DG, Storrs BB, Dauser RC. Analysis of 153 patients with myelomeningocele or spinal lipoma reoperated upon for a tethered cord. Presentation, management and outcome. Pediatr Neurosurg. 1993; 19: 243-249.

76. Sutton LN. Lipomyelomeningocele. Neurosurg Clin N Am. 1995; 6: 325-338.

77. Segal LS, Czoch W, Hennrikus WL, Wade Shrader M, Kanev PM. The spectrum of musculoskeletal problems in lipomyelomeningocele. J Child Orthop. 2013; 7: 513-519.

78. Rossi A, Cama A, Piatelli G, Ravegnani M, Biancheri R. Spinal dysraphism: MR imaging rationale. J Neuroradiol. 2004; 31: 3-24.

79. Patnaik A, Mahapatra AK. Complex forms of spinal dysraphism. Childs Nerv Syst. 2013; 29: 1527-1532.

80. Sarris CE, Tomei KL, Carmel PW, Gandhi CD. Lipomyelomeningocele: pathology, treatment, and outcomes. Neurosurg Focus. 2012; 33: E3.

81. Kushel' IuV, ZemlianskiĂ MIu, Khit' MA. [Tethered cord syndrome in different types of spina bifida in children]. Zh Vopr Neirokhir Im N N Burdenko. 2010; : 19-23.

82. Hudgins RJ, Gilreath CL. Tethered spinal cord following repair of myelomeningocele. Neurosurg Focus. 2004; 16: E7.

83. Garg K, Tandon V, Kumar R, Sharma BS, Mahapatra AK. Management of adult tethered cord syndrome: our experience and review of literature. Neurol India. 2014; 62: 137-143.

84. Tseng JH, Kuo MF, Kwang Tu Y, Tseng MY. Outcome of untethering for symptomatic spina bifida occulta with lumbosacral spinal cord tethering in 31 patients: analysis of preoperative prognostic factors. Spine J. 2008; 8: 630-638.

85. Frainey BT, Yerkes EB, Menon VS, Gong EM, Meyer TA. Predictors of urinary continence following tethered cord release in children with occult spinal dysraphism. J Pediatr Urol. 2014; 10: 627-633.

86. Ghritlaharey RK, Malik R. Split notochord syndrome with dorsal enteric fistula in a male neonate: a case report. J Clin Diagn Res. 2009; 3: 1797-1800.

87. Dindar H, Kanmaz T, Cakmak M, Savaş C, Yücesan S.. The split notochord syndrome with dorsal enteric fistula, meningomyelocele and imperforate anus. Turk J Pediatr. 1999; 41: 147-150.

88. Agangi A, Paladini D, Bagolan P, Maruotti GM, Martinelli P. Split notochord syndrome variant: prenatal findings and neonatal management. Prenat Diagn. 2005; 25: 23-27.

89. Srivastava P, Gangopadhyay AN, Gupta DK, Sharma SP. Split notochord syndrome associated with dorsal neuroenteric fistula: A rare entity. J Pediatr Neurosci. 2010; 5: 135-137.

90. Mirza B, Sheikh A. Split notochord syndrome with neuroenteric fistula. J Pediatr Neurosci. 2011; 6: 87-88.