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Original Article

A Comprehensive Review Of Spina Bifida-From Embryology To Therapeutics

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ABSTRACT

This literature-based review evaluates current research on the spina bifida and its management. By reviewing studies from the past, this article indicates that Spina Bifida is a congenital defect of CNS, categorized into spina bifida anterior, spina bifida posterior and spina bifida bifidum. Generally caused due to several genetic and environmental factors. The clinical presentations depend upon category and type of spina bifida involving different pathological conditions. There are different diagnostic ways to detect spina bifida, MSAFP test is considered useful in screening SB and ultrasonography is the gold standard method in diagnosing SB. The course of treatment is determined by the type of spina bifida a person has, majority of the people with spina bifida occulta won't need surgical interventions. Various inclusion and exclusion criteria must be considered during foetal surgery. The result from this study showed that folic acid fortification led to significant decrease in the incidence of SB, but insufficient to eradicate entirely.

Keywords: Spina bifida anterior, spina bifida posterior, spina bifida bifidum, spina bifida occulta, MSAFP.

INTRODUCTION

Spina bifida comes from Latin word 'Spina' meaning "spine" and 'bifida' meaning "split" is a congenital defect of central nervous system. Although it can be survived this defect leads to lifelong disabilities to those impacted [1].

The most severe form of spina bifida is "Myelomeningocele" which is characterised by extruded spinal cord which contain cerebrospinal fluid [1]. The use of folic acid supplementation during the periconceptional period (i.e. 14 weeks before and 10 weeks after conception is a critical window with a substantial impact on fetal growth and development) reduces 50%-70% of newborn neural tube defects [2]. According to the studies conducted by Vijaya kancherla, Sowmiya Moorthie, Mathew W. Darlison, Bernadette Modell in "Estimates of global and regional prevalence of NTD for 2015: A systemic Analysis" have demonstrated an incidence rate of approx. 3.63 per 10,000 live births in U.S and incidence rate of 18.6 per 10,000 worldwide [1,3].

The neural tube starts to from early in pregnancy and closes completely by the end of the fourth week of the gestation period meaning around 28days after conception forming the basis of the future brain and spinal cord. When the vertebral column fails that protects the spinal cord fails to form leads to spina bifida [5]. Based upon the anatomical location of the defect the spina bifida is divided into three main types:

1. Spina bifida anterior
2. Spina bifida posterior
3. Spina bifida bifidum [4].

The spina posterior is further categorized into

1. Spina bifida occulta (closed form): There is non-union of the neural arch but no protrusion of the contents, skin still covers the neural tube.
2. Spina bifida cystica (open form): It is also referred as spina aperta where there is non-union of neural arch and also protrusion of the cord contents. The neural elements are exposed at the level of skin [4,6].

Based upon the histological makeup of the protruding mass the open form is classified into

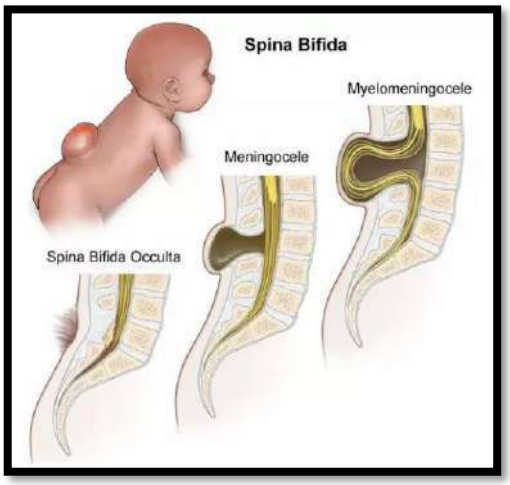
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

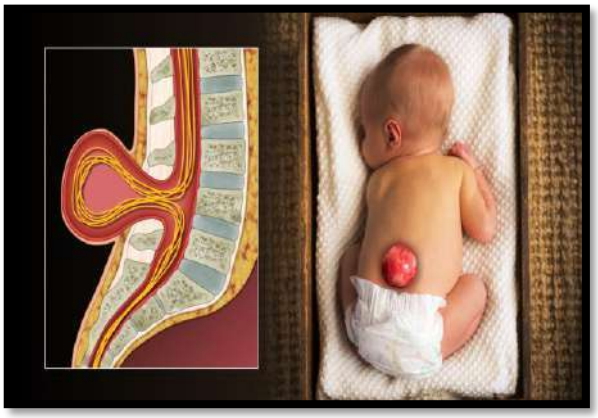
1. Meningocele: The meninges protrude through the defect and form swelling or tumour filled with cerebrospinal fluid alone.

2. Meningomyelocele: In meningomyelocele there is protrusion in the meninges with cerebrospinal fluid and also in spinal nerves or spinal cord or both.

3. Myelocele: In myelocele there is no swelling but the spinal cord spread out in the midline of the surface of back like a flat plate [4].

Spina bifida is associated with several developmental disorders like minimal impairment to severe neurological symptoms which include motor and sensory disabilities, bladder and bowel dysfunction and orthopaedic problems such as foot deformities, contractures and scoliosis [6].





ETIOLOGY:

Due to incomplete closure of spinal elements which include the pedicles, laminae, facets, transverse processes, and spinous processes the spinal cord and spine does not form properly leading to spinal dysraphism [7].

Spina bifida is caused by series of genetic variants and their interaction with environmental factors.

[A] Genetic factors:

i. MTHFD1: Methylene tetrahydrofolate dehydrogenase also referred as "C1-THF synthase" is a nicotinamide adenine dinucleotide phosphate (NADP) dependent cytoplasmic enzyme. It acts as 10- formyl, 5,10-methenyl, 5,10-methylene derivative. MTHFD1 plays important role in folate metabolism, it is a key enzyme which catalyses three sequential reactions, converting tetrahydrofolate into 5,10-methylene tetrahydrofolate [8,9]. Genetic variation in the MTHFD1 gene i.e. excess of MTHFD1 "Q" allele or overexpression of "QQ" homozygotes in the mothers is associated with increase in the genetically determined risk of NTDs and may be associated with decreased embryo survival [9,10].

ii. MTHFR: This gene is responsible for the production of methylenetetrahydrofolate reductase enzyme involved in the conversion of 5,10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, which is a co-substrate for homocysteine remethylation to methionine which is important for making DNA and proteins. Acute leukaemia, neural tube abnormalities, colon cancer, and occlusive vascular diseases are all influenced by genetic variations in this gene, and mutations in this gene are linked to methylenetetrahydrofolate reductase deficiency [11].

iii. MTR5: The enzyme 5-methyltetrahydrofolate-homocysteine methyl transferase is encoded by MTR gene. This enzyme catalyses the last stage of methionine biosynthesis and is also referred to as "cobalamine-dependent methionine synthase". The fundamental cause of methyl cobalamin deficiency (vit B12) complementation group G has been found to be due to mutations in MTR [12].

iv. MTRR: The enzyme methionine synthase reductase which is a member ferredoxin-NADP (+) reductase (FNR) family is encoded by MTRR

gene. This enzyme reactivates methionine synthase responsible for folate metabolism and cellular methylation. Homocystinuria megaloblastic anaemia result from mutations in this gene [13].

Women are more likely to give birth to a child with a neural tube abnormality if they have insufficient folate, excessive plasma homocysteine, or low vit B12 [8].

[B] Environmental factors:

i. Numerous chemicals, widely disparate medicinal medications, environmental pollutants, infectious agents, solvents, and other substances have been identified as cause of spina bifida in some case reports and epidemiologic research.

ii. The prevalence of NTD is said to be greatly increased by maternal hyperthermia, the use of valproate by epileptic women during pregnancy, nutritional excess and deficiency, and chronic maternal illness (such as DM).

EPIDEMIOLOGICAL STUDIES: [15,16]

According to epidemiological research conducted in the early 1990s, maternal folate level is essential for appropriate neural tube closure during embryogenesis. The ground breaking investigations shown that the incidence and recurrence of NTDs may be considerably decreased by raising maternal folate levels. In response to these findings, the US Food and Drug administration required folic acid fortification of all cereal and grain products in January 1998. In the US, 2 out of every 10,000 live babies had SB by 2005. Between 1995-1996 and 2003-2004, the birth prevalence of SB in the US dropped by almost 23%, demonstrating the significant benefits of folic acid fortification in diet. Therefore, folic acid fortification led to a notable decrease in the incidence of SB, but it was insufficient to eradicate it entirely. This implies that the genesis of SB involves variable other than maternal folic acid insufficiency [15].

CLINICAL PRESENTATION:

The symptoms of spina bifida occulta includes:

- A dimple or depression in the lower back.
- A small area of black hair.
- Deposits of soft fat.
- Deep purple macular lesions are known as post-wine nevi.

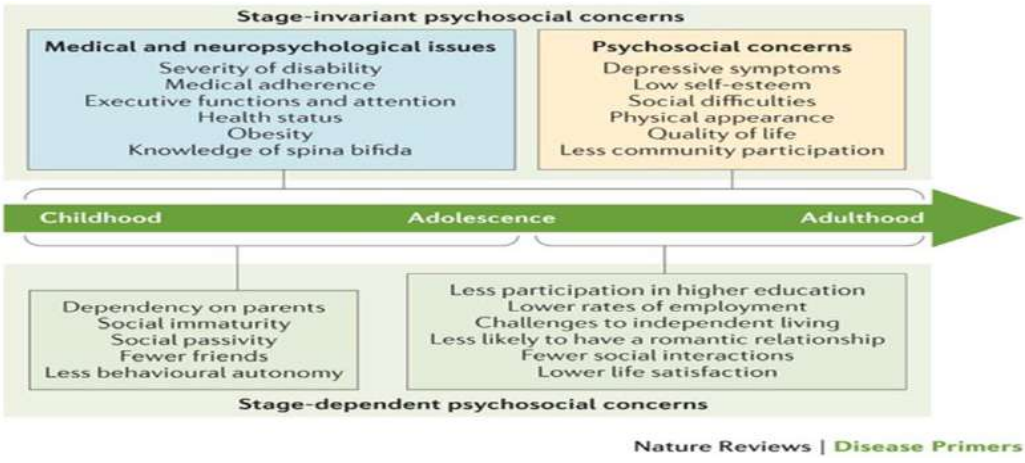
The symptoms of spina bifida meningocele include:

- A sac-like cyst that extends beyond the vertebrae.

Depending on the extent of the lesion, bowel and bladder incontinence may be present, although neurological impairments are uncommon in cases of occulta and meningocele.

More severe deficits are caused by spina bifida myelomeningocele:

- Spastic or flaccid paralysis.
- Scoliosis, hip dislocation, hip dysplasia, club foot, and hip/knee contracture.
- Hypotonia of the trunk.
- Delayed automatic postural reactions [17].



DIAGNOSIS:

Spina bifida is typically identified during prenatal screenings, which are a routine aspect of prenatal care, prior to the birth of the child.

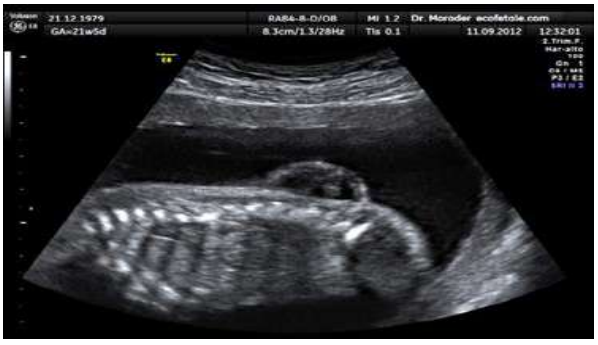
A. Blood tests:

- Maternal serum alpha-fetoprotein (MSAFP) test: An AFP test is a blood test that measures the level of alpha-fetoprotein (AFP) in the blood when pregnant. The test is usually done between 15-20 weeks of pregnancy. AFP is a protein mostly made in developing baby's liver. Usually, some AFP passes from the baby into the mother's blood. Under certain medical conditions baby's body release more or less AFP than usual. This leads to higher or lower AFP levels in the mother. This may be the sign that the baby has increased risk of a health problems such as neural tube defects, down syndrome, Edwards syndrome [18].

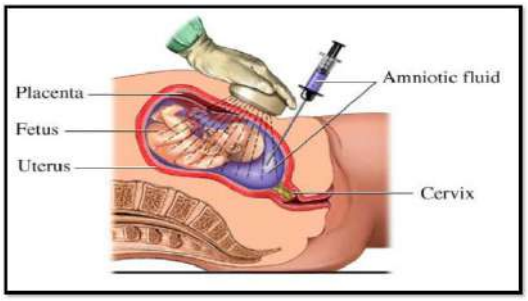
- Triple screen test: It is a blood test that measures three things called Alpha- fetoprotein, human-gonadotropin and unconjugated estriol. This test is usually done between the 16th and 18th weeks of pregnancy. It may also be done between 15th and 22nd week of pregnancy [19,20].

B. Ultrasound: Using ultrasound medical professionals may view and photograph the foetus while it is still inside the mother's womb. Spina bifida is frequently detectable by ultrasonography [20].

C. Amniocentesis: In this procedure the physician extracts a portion of the amniotic fluid that surrounds the embryo in the embryo in the womb using a long needle. If the fluid has high levels of AFP, it may indicate spina bifida in the foetus [20].



Ultrasonography of pregnant woman with spina bifida foetus



Amniocentesis procedure

PATHOGENESIS:

- When a lesion occurs, spina bifida (SBA), also known as spina bifida cystica typically apparent at birth as exposed neural tissue with or without a projecting sac.

- Spina bifida aperta (SBA) is also known as myelomeningocele or myeloschisis.

- When the main neural tube does not fully close, the spinal cord protrudes from the spinal canal into a fluid filled sac, a condition known as myelomeningocele.

- A cleft spinal cord with the margins flushes with the defect is known as myeloschisis, which is caused by the main neural plate's inadequate closure.

- The placement of the lesion along the neuraxis determines the degree and severity of the neurological impairments.

A. Meningocele: In contrast to myelomeningocele, which is characterized by neural matter clearly herniating at the site of the open lesion, meningocele is frequently described as a less severe variant of myelomeningocele in which the spinal cord is not found in the sac and embryologist describe it as lacking neural matter in its herniated sac. Therefore, in terms of embryogenesis, it is still up for debate whether meningocele is an open (aperta) or closed (occulta) abnormality. Nonetheless, radiologists imaging data has conclusively identified meningocele as spina bifida occulta.

B. Myelomeningocele: Myelomeningocele (MMC) is typically linked to hydrocephalus, ventriculomegaly, and type II chiari hindbrain malformation. The downward migration of the cerebellar vermis into the cervical vertebral canal known as chiari type II malformation. Ultrafast fetal MRI is used to diagnose it prenatally and is frequently symptomatic. 90% of patients develop hydrocephalus as a result of this abnormality, which results in obliteration of the fourth ventricle and extension of the brain stem, which obstructs the circulation and cerebrospinal fluid. About 82% of patients require treatment for this associated hydrocephalus, which entails draining cerebral fluid through a subcutaneous shunt into the peritoneum or another bodily cavity.

C. Spina bifida occulta: The second main kind of NTD is spina bifida occulta (SBO), in which the lesion site is not revealed. Spina bifida occulta includes spinal dorsal dermal sinus tract, lipomyelomeningocele and lipomeningocele. These conditions can manifest phenotypically as dysplastic skin, a hair tuft, vestigial tail and other types of spinal dysraphism that lack a pathogenic representation when the vertebrae develop abnormally, resulting in the absence of neural arches. In children or adults who are otherwise healthy and normal, tethering of the spinal cord inside the vertebral canal can cause symptoms such as pain, weakness and incontinence [21].

MANAGEMENT:

The type of spina bifida a person has determined their course of treatment.

1. Surgery is necessary for both meningocele and myelomeningocele soon after birth in order to seal the wound and stop infection. Myelomeningocele frequently causes hydrocephalus in infants, necessitating the use of a shunt to drain the fluid.

2. To avoid further health issues including paralysis and bowel and bladder issues, children with closed neural tube defect may require surgery.

3. Spina bifida occulta patients typically don't require therapy [22].

Prevention is essential the cornerstone of treatment for NTDs like spina bifida. To avoid NTDs, women of reproduction age should take folate supplements. To assist reduce incidences, the U.S started requiring folic acid fortification of cereals. Women with a history of NTD or a previous pregnancy should take 4mg of folic acid supplements, while those who are attempting to conceive should take 0.4mg of folic acid daily prior to conception. The majority of people with spina bifida occulta won't need to have the problems surgically corrected. Nonetheless, a number of surgical procedures may be able to lessen the neurologic consequences of open NTDs. An intrauterine repair may be attempted in a small number of individuals in order to avoid further issues. The foetus must be between 19 and 25 weeks, old, have a T1-sacrum lesion, and have an Arnold Chiari malformation in order to be eligible for this dangerous procedure. These operations have demonstrated sufficient cerebellar relocation, increased leg function and ambulation, and a markedly decreased requirement for future ventriculoperitoneal shunt insertion. However, intrauterine repair has a considerable risk, which includes a higher chance of preterm birth and serious problems for the mother.

Numerous consequences and after effects must be watched for and treated throughout the newborn stage. In order to limit the danger of infection or damage to any exposed defect and to avoid substantial neurologic deterioration, early closure within 72hrs is advised. After the defect is closed, patients with hydrocephalus frequently need a ventriculoperitoneal shunt. Arnold Chiari malformations are frequent and frequently need to be repaired, however when patients are ill, the risk of this procedure being successful is high. Since several organ systems may be impacted, long-term care calls for an interdisciplinary approach. The syndrome frequently manifests as neurogenic bladder and intestines. Usually associated with neurogenic bladder, detrusor-sphincter dys-synergia can result in renal failure of left untreated.

Patients may need occasional catheterization for long-term care, and biennial renal ultrasounds are recommended for surveillance. Additionally, patients have neurogenic bowel, which is brought on by inadequate sphincter control and diminished feeling. For proper control patients need to learn a regular

bowel regimen that include digital stimulation, motility medication and short softness.

Weakness, flaccidity, spasticity and contractures are just a few of the many motor involvement symptoms that children with NTDs may exhibit. Patients with severe contracture that affect their ability to walk, clean their hands, or posture themselves may benefit from tendon lengthening operations. Rocker bottom, calcaneous, and equinovarus abnormalities are among the typical foot malformations seen with NTDs. For severe spaticity and/or contractures, splinting, passive stretching, and serial casting might be helpful [07].

When to consider fetal surgery?

Under following conditions fetal surgery is considered.

1. Myelomeningocele which also include myeloschisis-defect located between the lower thoracic (chest) area of the spine and the sacrum.
2. Chiari II malformation- usually diagnosed by MRI and fetal.
3. Normal fetal karyotype by amniocentesis, including size, shape and chromosome count.
4. At referral, the gestational age ranged from 19-25-6/7 weeks (5-7 months).
5. The mother is at least 18yrs old.

Under following conditions fetal surgery is not recommended

1. Twins, triplets and other multiple gestations.\
2. Mother -specific contraindications to surgery or anaesthesia include severe asthma, heart problems, and unwillingness to receive a blood transfusion.
3. If severe hypertension (high blood pressure) has been discovered in the mother.
4. Pregestational diabetes that is insulin-dependent (high blood sugar even before pregnancy).
5. HIV and hepatitis B or C in the mother are examples of infectious illness.
6. Severe obesity is defined as BMI of above (grade 3 obesity) or greater than 35 with morbidity associated with obesity. Maternal BMIs between 35 and 40 will be assessed individually.
7. Fetal kyphosis (spinal curvature) level of the defect greater than or equal to 30.
8. Additional prenatal issues, such as a heart condition or an intracranial haemorrhage, that are unrelated to spina bifida.
9. Cervix shortening (uterine opening) dilation of the cervix or less than 20mm.

Early labour with the present pregnancy [23].

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