ABSTRACT: Spina Bifida (SB) is a neural tube defect (NTD) due defect in neural tube, characterized by incomplete closure of spinal column. Occurrence of SB varies in different countries. In developed countries, it is about 0.4 per 1000 births, in US 0.7 per 1000 births and in Asia 1.9 per 1000 births. SB mostly occurs during first trimester of pregnancy. Variants of SB are Spina bifida Occulata, Spina bifida Cystica [meningocele and myelomeningocele], Spina bifida Manifesta and Spina bifida Aperta. Among these myelomeningocele is the most common type. Causing agents of SB may be genetic, non-genetic or environmental factors. Non-genetic factors involve anti-convulsant drugs, anti-epileptic drugs, maternal obesity, maternal diabetes and poor nutritional status (folate and vitamin B12 deficiency). Environmental factors are pesticides, nitrated compounds and air pollution. Common manifestations are brain malformations (Arnold Chiari II malformation and hydrocephalus), spinal cord abnormalities, latex allergy, breathing problems, urological abnormalities and cardio-metabolic dysfunction. Diagnostic techniques for Spina bifida are ultrasound screening, Magnetic Resonance Imaging (MRI), amniocentesis and maternal serum alpha-fetoprotein. To prevent the risk of Spina bifida, it is recommended for the mother to use 0.4mg of folic acid per day or in mothers affected with multiple pregnancies recommended dose of folic acid is 4mg per day.

Key words: Folic acid; myelomeningocele; myeloschisis; neuropore; NTD

INTRODUCTION

Spina bifida (SB) is a Latin word which means “split spine”. The most commonly occurring complex congenital malformation of CNS is spina bifida and it is associated with lifelong morbidity having a complex etiology involving environmental and genetic factors. First trimester of pregnancy is most vulnerable phase during which spina bifida usually occurs. The most common type of SB is myelomeningocele. The most common manifestations of SB are fecal incontinence, hind brain herniation (Arnold Chiari II syndrome) and hydrocephalus associated with orthopedic abnormalities like talipes, hip dislocation etc. SB varies significantly by country from 0.1 to 5 per 1000 births. On average in developed countries it occurs in about 0.4 per 1000 births, in US 0.7 per 1000 births and in India 1.9 per 1000 births.

What is Spina Bifida?

Spina bifida is neural tube defect which results due to failure of closure of neural tube. It is characterized by incomplete closure of spinal column. In SB spinal cord, its coverings and vertebral arches develop abnormally during gestation. Spina bifida is a heterogeneous disorder.

Causes of Spina Bifida

The causes of spina bifida are classified into three factors:

1. Genetic Factors
2. Non-Genetic Factors
3. Environmental Factors

1. Genetic Factors

The sequences of the coding regions revealed that patients with neural tube defects (NTDs) have missense mutation (i.e. of amino acid). Folate one carbon metabolism function is performed by enzymes which are encoded by NTD associated genes.
In these enzyme groups one enzyme is 5, 10 methylene tetrahydrofolate reductase (MTHFR), an enzyme that produces 5 methyl tetrahydrofolate which converts homocysteine into methionine. The variant MTHFR C677T, produced due to the conversion of valine to alanine at codon 222, has reduced activity of the enzyme. This mutation either in mother or fetus results in neural tube defects when folate level in mother is low. The mutations in genes of glycine cleavage system also causes neural tube defects. The mutations in glycine cleavage system genes alter the activity of glycine decarboxylase and amino methyl transferase which alters the breakdown of glycine within mitochondria, a step of folate metabolism.

2. Non-Genetic factors
The anti-convulsant valproic acid when taken by a pregnant women causes neural tube defects in a fetus. The action of valproic acid is to inhibit histone decarboxylase, which alters the functioning of proteins leading to neural tube defects. Periconceptional intake of folic acid reduces NTDs by 70%. Anti-epileptic drugs are associated with NTDs. Other factors contributing to NTDs include maternal pyrexia, maternal obesity, maternal diabetes, poor nutritional status, folate and vitamin B12 deficiency.

3. Environmental factors
The environmental factors involve following:
- Indoor air pollution
- Organic solvents
- Pesticides
- Polycyclic aromatic hydrocarbons
- Nitrates related compounds
- Air pollution

Epidemiology and Prevalence
The prevalence of SB vary in the world but on average ranges around 0.1%. There are no recent cases of SB in South Africa but previously it was reported around 0.77-6.1/1000 particularly higher in rural areas. The recurrence of NTDs is greater than 5% for a women having more than one child affected by NTDs.

Following factors contribute in the epidemiology of NTDs:
- Maternal hyperthermia is one of the early factor of pregnancy contributing in NTDs along with maternal caffeine and drug usage during pregnancy.
- The families having low socioeconomic status, there is increased risk of NTDs.
- There is increased risk of NTDs in mothers having age less than 19 years and greater than 40 years.
- Occurrence of NTDs is different in different parental races. In USA, recent studies (2003-2005), in non-Hispanic whites the prevalence for NTDs per 1,000 births was 2.0, in Hispanics was 1.96 and 1.74 for non-Hispanic blacks.

Sign and Symptoms of Spina Bifida
These include following:
- Children having SB have unrecognized pain which affects their quality of life.
- Anorexia, dysphagia, vomiting, poor feeding.
- Change in bowel or bladder function
- Headache, irritability, lethargy.
- Hoarseness or stridor, aspiration, breathe holding spell.
- Increasing head circumference with bulging anterior fontanelle.
- Sensory loss or weakness in lower extremities, deterioration of gait.
- Change in deep tendon reflexes.
- Esotropia, diplopia, paralysis of upward gaze.
- Rapidly progressive scoliosis.
- Decubitus ulcer.

Classification
Spina bifida is classified into following types:
1. Spina bifida Occulata
2. Spina bifida Cystica
3. Spina bifida Manifesta
4. Spina bifida Aperta

Spina bifida Occulata
It occurs with normal meninges and normal elements. There is no protrusion of meninges
and spinal cord and defect is covered by muscles and skin. It is of no clinical significance because it does not show any symptoms. Rarely tuft of hairs are present at defective site. In about few percent 0.8 % in 6000 cases low back pain is present.27,28

**Spina bifida Cystica**

In this type a cystic swelling is present at the site of lesion. The cystic swelling may contain meninges or both meninges and spinal cord. Spina bifida cystica has two sub-variants:28

- Spina bifida cystica with meningocele
- Spina bifida cystica with myelomeningocele

**Spina bifida Menifesta**

This type of spina bifida presents with surface manifestations such as hemangioma, hair, sinus tract, and covered or open neural elements.27

**Spina bifida Aperta**

In this type of spina bifida there is a complete aperture and there is an absence of skin at the defective site and neural tissue is exposed. It is always associated with myeloschisis. The site of spina bifida aperta is usually covered by reddish, semi-transparent, oozing membrane that merges into surrounding skin.28

**Myelomeningocele**

Failure of closure of neural tube or secondary reopening of the closed neural tube is called myelomeningocele.29 Vertebral levels of myelomeningocele are given in Table-1(a).30,31

<table>
<thead>
<tr>
<th>Classification</th>
<th>Levels of vertebrae</th>
<th>Signs &amp; Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Category</td>
<td>Higher Thoracic and Lumber</td>
<td>Lack of quadriceps</td>
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<tr>
<td>Second Category</td>
<td>Lumber (L3&amp;L4)</td>
<td>Lack of gluteus maximus &amp; gluteus medius , Tendenlenberg’s sign</td>
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<tr>
<td>Third Category</td>
<td>Higher Sacral Level</td>
<td>Weakness in Ankle Planter flexors</td>
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<td>Lower Sacral Level</td>
<td>Weakness in intrinsic muscles of foot</td>
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**Pathoembryology**

There are two distinct phases of neural tube formation primary and secondary. Primary neurulation starts on day 22 post-fertilization. Cranial neuropore closes on day 24 and caudal neuropore closes on day 26. Neural tube defects result from failure of any neurulation sequence and there are typically open defects. The most severe spinal defect is craniorachischisis. If the cranial neurulation fails then result is anencephaly.32

**Consequences**

The most commonly occurring consequences are:13,14

- Brain Malformations
- Chiari II malformation
- Hydrocephalus
- Spinal cord abnormalities
- Latex allergy
- Breathing problems
- Pressure ulcer
- Urologic abnormalities
- Cardio-metabolic dysfunction

**Brain malformations**

Abnormalities of brain include Chiari type II syndrome, agenesis of corpus callosum, hypoplasia of cranial nuclei, diffused micro structural anomalies. The common manifestations of such defects are learning disabilities including non-verbal learning disorders, attention deficit hyperactivity disorder and strabismus.14

**Chiari II malformation**

In this malformation the posterior fossa is small and brainstem is displaced to the cervical canal. This leads to compression of brainstem which may be caused by abnormal development of ventricle. Respiratory and swallowing difficulties are associated with this malformation.33 In brain defects the Chiari II malformation occurs in almost 90% cases.34 The signs and symptoms of Chiari II malformation are given in Table-1(b).

<table>
<thead>
<tr>
<th>Signs &amp; Symptoms</th>
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<tr>
<td>Dysphagia, poor or prolonged, feeding, cyanosis</td>
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<tr>
<td>Hoarseness of voice, coughing and nasal regurgitation</td>
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<tr>
<td>Aspiration with or without pneumonitis</td>
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<td>Apnea, including disordered breathing during sleep</td>
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<td>Breath holding spells</td>
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<td>Opisthotonus</td>
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**Table-I (b). Signs and Symptoms of Chiari II Malformation**

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[Table-I (a). Vertebral levels of myelomeningocele]

[Table-I (b). Signs and Symptoms of Chiari II Malformation]
Hydrocephalus
It is a diverse group of conditions resulting from impaired circulation and absorption of cerebrospinal fluid. Hydrocephalus stretches the white matter mainly corpus callosum. Hydrocephalus is associated with motor and cognitive abnormalities. Hydrocephalus occurs in about 85% patients with myelomeningocele.

Spinal cord abnormalities
Spinal cord abnormalities include both loss of sensory and motor function. Loss of sensory sensation leads to ulcers and loss of motor function leads to musculoskeletal abnormalities. The spinal cord fixation is referred to as tethered spinal cord resulted from variety of conditions mainly from repaired myelomeningocele. The consequences of spinal cord abnormalities are given in Table-I(c).

Latex allergy
Latex allergy is hypersensitivity to latex due to the presence of IgE antibodies. There is a suggestion of genetic association between spina bifida and latex allergy. More than 50% of children who have myelomeningocele develop latex allergy. In cases of spina bifida the percentage of latex allergy is 20-40%. The first case of latex allergy was reported in 1989.
Breathing problems
Breathing problems are commonly associated with spina bifida which includes upper airway obstruction, vocal cord palsy, apnea and hypoventilation and severe sleep disordered breathing. These problems may be fatal and can cause death.54-59

Pressure Ulcers
Children with spina bifida are at a great risk of suffering from pressure ulcers. Pressure ulcers require long and complex treatments. Support surfaces, positioning, nutrition and supplements are used for treatment of pressure ulcers.60-63

Urologic abnormalities
Urologic abnormalities associated with spina bifida are vesicoureteral reflex (21-25%), cryptorchidism (10-30%), bladder exostrophy (6.8%), hypospadias (0.1%), unilateral renal agenesis (2-8%), ureteropelvic junction obstruction (1-3%), multicystic dysplastic kidney (7-13%) and horseshoe kidney (2-7%).64-74

Cardio-Metabolic Dysfunction:
People having SB have increased body mass index (BMI) and percent body fat than that of people without SB. Young adults and children having SB have decreased muscular strength and aerobic fitness in addition to having increased body fat.75-78 Persons having SB tend to have decreased physical activity which leads to obesity in these patients and hence causing cardio-metabolic disease.79

NTD screening techniques
NTD screening techniques are of two types:
1. Non-invasive diagnostic methods
2. Invasive diagnostic methods

1. Non-invasive diagnostic methods
Ultrasound screening
For the detection of fetal abnormalities including NTDs, ultrasonography is the non-invasive screening technique of choice because of its detection sensitivity, safety and cost optimality. According to Society of Obstetricians and Gynecologists of Canada (SOGC), ultrasound should be offered to all pregnant women during the second trimester and it is safer than amniocentesis diagnostically because amniocentesis causes infection or spontaneous abortion.80-82 During ultrasound, visible feature in second trimester includes abnormal skull shape (lemon sign), cerebellar abnormalities (banana sign) and abnormality in the lower limb movement.81

Fetal MRI (Magnetic Resonance Imaging)
During 23 and 32 weeks of gestation, for the proper imaging of the subarachnoid space and fetal brain, fetal MRIs are usually performed. MRI provides us good contrast between the soft tissue regardless of maternal obesity, fetal life and oligohydramnios.80,83

Maternal serum AFP (alpha fetoprotein)
Maternal serum alpha fetoprotein (MSAFP) screening is conducted during the second trimester between 15 and 18 weeks of gestation.84

2. Invasive diagnostic methods
Amniocentesis
Amniocentesis is usually performed between the 15th and 20th gestational weeks for the detection of genetic mutations and NTDs.80,84

Treatment and management
The management and treatment of SB involves surgery, ventricoperitoneal shunt, bladder and urinary tract management and fetal surgery with stem cells. The surgery is conducted within 48 hours of birth to close the child back to minimize the spread of infections, otherwise that can result in meningitis. A ventricoperitoneal shunt is needed for the treatment of almost all the neonates with thoracic level lesion, 85% of lumbal level lesion and 70% of sacral level lesion.13 Posterior fossa decompression surgery is conducted in severe cases.85 Shortly after birth orthopedic deformities are treated which require long term follow-up. Urinary tract management involves intermittent catheterization, pharmacological drugs and surgery.86 Bowel management involves suppositories, laxatives or antegrade colonic or traditional enemas.13,87 To monitor fetal heart function intra-operative echocardiography is
used. Stem cell surgery is done which enhances the neural crest cell differentiation.  

Prevention
The mother is administrated with folic acid containing multi-vitamin which reduces the risk of SB. It is recommended for the mother to take 0.4 mg of folic acid per day or in affected women to take 4 mg per day.

Role of Folic Acid
The exact mechanism by which folic acid prevents SB remains unclear but some studies show that exogenous folic acid play role in embryonic cell proliferation by enhancing the pyrimidine and purine synthesis. Or through its role in regulation of epigenetic modifications (methylation) of DNA. The role of folic acid is explained in Figure 1.

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REFERENCES


SPINA BIFIDA


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**AUTHORSHIP AND CONTRIBUTION DECLARATION**

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