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An Overview of Spina Bifida

Afroza Parvin, Md Mahmudul Hasan

Department of Biochemistry and Molecular Biology, Jahangirnagar University, Dhaka, Bangladesh
Email: aparvin@juniv.edu

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Abstract

A child born with untreatable birth defect encounters constant challenges in lifetime. Spina bifida is such type of defect mainly affecting neural tube. As a result, a child with spina bifida faces abnormal physical appearance to neurological dysfunctions. The incident rate of such birth defect is relatively common compared to other birth defects, therefore, an awareness among people is necessary to avoid such vulnerability. Therefore, this article provides a general outline of symptoms, types, risk factors, pathophysiology, preventive and therapeutic strategies of spina bifida which will help the general people for better understanding of the disease and be able to take precautions to combat such defect.

Keywords

Birth Defect, Neural Tube Defect, Myelomeningocele, Folic Acid, Alpha-Fetoprotein

1. Introduction

Spina bifida is a congenital spine deformity in which the meninges and a portion of the spinal cord are visible through a gap in the backbone, frequently leading to lower limb paralysis. It is a type of neural tube defect (NTD) that is associated with opening of the vertebral column which means that the neural tube fails to close properly during embryonic development (**Figure 1**). Neural tube is responsible for brain and spinal cord development [1]. Spina bifida mainly affects the lower back, but sometimes middle back or neck is also affected [2]. Apart from this common name other names include open spine, cleft spine, spinal dysraphism, and rachischisis [3].

After congenital heart defects, NTDs are considered the second most common birth disorder. Among all NTDS, Spina bifida counts almost 1/2500 new-borns worldwide [5] [6]. Around 260 babies (nearly 0.9 cases per 1000 births) are born with a NTD each year where spina bifida is found to be the most common birth

defect in Canada [6] [7]. In South America the frequency for NTD per 10,000 births is 11.7, in the United Arab Emirates is 7.7 and in central France is 0.7. Ireland and Wales are reported to have the greatest incidence (for myelomeningocele (one type of spina bifida) around 3 - 4 cases per 1000 population) of spina bifida [6] [8] [9].

Each year almost 1500 babies are born with myelomeningocele in the U. S. The incidence is found to be higher in on the east coast than west coast of the United States. In British Isles, all in all the incidence of myelomeningocele is found to be 2 - 3.5 cases per 1000 births. On the other hand, a very low incidence is found to occur in France, Norway, Hungary, Czechoslovakia, Yugoslavia, and Japan which is only 0.1 - 0.6 cases per 1000 live births.

In addition, the rate is higher for white people (1/1000) than the black people (0.1 - 0.4/1000) for live births [8] [9]. Hispanic youth has the highest incidence [6] [10], whereas Ireland immigrants are most likely to have spina bifida than do natives in USA [8] [9]. In developing countries, the rate is almost 0.4 per 1000 births [5]. The discrimination may be due to race as Caucasians are at higher risk and also due to certain environmental factors, such as, vitamins, drugs, etc [11]. In many populations, low socioeconomic status is also a risk factor of NTDs. Spina bifida occulta occurs to nearly 5% of people [12] [13]. Whereas other types of spina bifida occurrence vary significantly from 0.1 to 5 per 1000 births by countries. Within 1983-1990, 4.4 - 4.6 cases of spina bifida per 10,000 live births were reported [13] [14]. In the same year, data from state and national surveillance systems, the incidence of myelomeningocele is found to be slightly higher in females than in males (1.2:1) But in the late 20th century, the rate of myelomeningocele and other NTDs has decreased due to the availability of prenatal diagnostic and improved nutrition services among pregnant women [6].

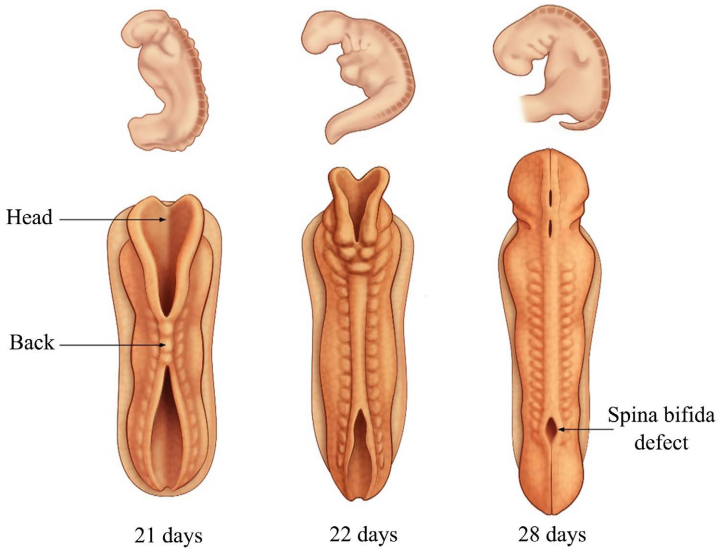

Figure 1. Spina bifida during embryonic development [4]. At day 21, spinal cord starts to develop; at day 22, opening in the spinal cord starts appearing and at day 28, clear opening in the spinal cord is observed calling spinal bifida.

2. Signs and Symptoms of the Disease

The signs and symptoms can be organized into different ways, such as, physical, neurological signs, executive and academic functions etc.

2.1. Physical Signs

Club foot, leg weakness, paralysis, hip dislocation, scoliosis, bladder, bowel, urinary incontinence, skin irritations, abnormality in eye movements are the most common physical signs for spina bifida [15].

2.2. Neurological Signs

Patients with spina bifida have smaller cerebellum that have higher lesions [16]. Cortex abnormalities may be due to neuron displacement [17]. Frontal regions of the brain are thicker whereas posterior and parietal regions are thinner with higher cortical folding [16]. Approximately in 90% of the people affected by myelomeningocele, the back part of the brain is moved to the upper neck where normal flow of cerebrospinal fluid is blocked, causing an excess of the fluid [18]. The corpus callosum is also abnormal which affects the communication between the left and right brain hemispheres [19]. Moreover, white matter tracts connecting posterior and anterior regions is less organized and tracts between frontal regions is more impaired in patients with myelomeningocele [16].

2.3. Executive Function

Many studies reports that youth with spina bifida have difficulties with executive functions such as planning, organizing, initiating, working memory, problem-solving, visual planning, abstraction etc [20] [21] [22] [23], and it is unlike that developing children do not show any improvement in executive functions as they grow older [21]. Though these patients have normal frontal lobes which are often responsible for executive functions, therefore, this dysfunction may be attributed by other parts of the brain [22]. Moreover, poor cognitive flexibility and attention problems are also observed in these children [20] [22].

2.4. Academic Skills

One study reported that around 60% of children with spina bifida had learning disability, such as, mathematical problem solving and general use of numbers in daily life [24] [25]. These difficulties may be due to the thinning of the parietal lobes and deformities of the cerebellum and midbrain that affect the functions related to mathematical skills [26]. In addition, their skills in reading are better that in mathematics [26]. As they are lack of fine motor control and working memory, they might have problem with writing too [27]. Though in elementary schools their performance is good, as the academic pressure increases, they begin to struggle as well [28].

3. Types

There are generally two types of neural tube defects (NTDs). 1) Open NTDs,

such as, spina bifida, anencephaly, and encephalocele, [29] and 2) Closed NTDs, such as, lipomeningocele, lipomyelomeningocele, and tethered cord [29] [30]. Spina bifida can be categorized into three types such as: a) occulta, b) meningocele, and c) myelomeningocele (**Figure 2**) [31].

3.1. Occulta

It is the least severe [32] and asymptomatic [33] but most common form of spina bifida where the outer part of the vertebrae is not closed enough [34]. The skin at the site usually seems to be normal, but sometimes, hair growing, dimples or birthmarks are detected [33]. Alpha fetoprotein (AFP) which is a common diagnostic tool to screen NTD in utero is not observed to be increased in this case due to the well maintained dural lining and accidentally diagnosed from spinal X-rays [35]. The prevalence is 10% - 20% of the population [36] [37]. No relationship was observed between occulta and back pain by a systematic review of radiographic research studies [38].

3.2. Meningocele

It is the least common form of spina bifida, also termed as posterior meningocele or meningeal cyst where the meninges herniate between the vertebrae. Teratoma, Currarino syndrome, tumors in sacrococcyx and presacral space are main causes of meningocele [39].

3.3. Myelomeningocele

It is the most severe form of spina bifida where the non-fused portion of the spinal cord and membrane protrude through an opening, forming a sac enclosing the meninges, nerve roots, cerebrospinal fluid, and parts of the spinal cord [40] [41]. It gets more complicated when a flattened, plate-like mass of nervous tissue grows without any overlying membrane making the baby more prone to life-threatening infections such as meningitis [42].

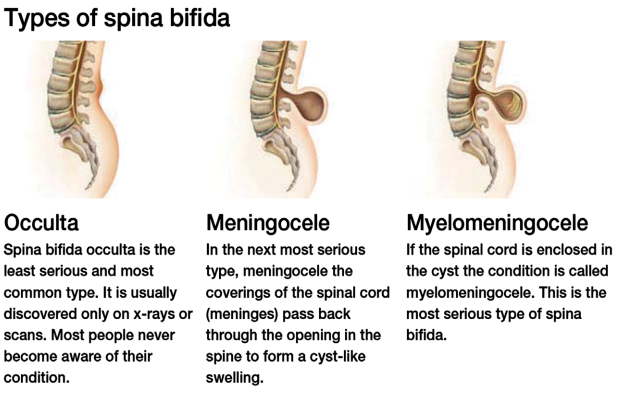

Figure 2. Types of spina bifida [43]. Three types of spina bifida are generally observed such as, occulta most common and least severe condition), meningocele (meninges pass back through the opening in the spine forming a cyst like swelling), and myelomeningocele (most severe condition where the spinal cord is enclosed in the cyst).

4. Pathophysiology

Generally, NTDs occur between the 17th and 30th day of gestation when the size of the fetus is just like a grain of rice [44]. In normal circumstances, the closure of the NTD occurs around the 23rd and 27th day after fertilization (**Figure 1**) [45]. A pregnant woman with high blood pressure, obesity, diabetes, taking some medications has the increased probability of a baby having neural tube malformation [46]. Several studies reported that folic acid deficiency is a causative factor for the pathogenesis of spina bifida [47] [48] [49]. Extensive evidence from mouse strains with spina bifida indicates that sometimes there is also a genetic basis for the condition which does not follow direct patterns of heredity as do other common genetic disorders [46].

It is well known that both: 1) genetic and 2) environmental factors function as causative agents of spina bifida. For myelomeningocele, the causes are also multifactorial, involving genetic, racial, and environmental where folic acid intake is the most important factor. Other possible causes include teratogenic effects, polygenic inheritance, chromosomal aberrations, and cytoplasmic factors [50].

4.1. Genetic Factors

In early gestation, NTD with chromosome abnormality is diagnosed in approximately 10% of infants. These associated chromosome abnormalities are mostly single-gene mutations, trisomies, and triploidy [50]. Occurrence of spina bifida is sporadic as most of the time people with no previous family history have spina bifida. Genetic pattern is found for small number of cases where there is no clear pattern of inheritance. But there is an enhanced chance of this condition in first-degree relatives (such as siblings and children) of people with spina bifida than the general population [51]. If one baby of a woman is born with spina bifida, there is about 4% risk to have another affected baby of that woman [52]. For myelomeningocele, higher risk is also found for second- and third-degree relatives of affected individuals [50].

Though in mice, mutations over 200 genes are known to be the causal factors whereas in human polygenic or oligogenic factors are mostly involved in spina bifida [53]. Mutations in multiple genes in both the mother and the baby may increase the risk of having spina bifida. The most-studied gene is *MTHFR*, which signals for a protein that processes folic acid (vitamin B9) [51]. Andrew and Nicholas in 2010 showed that two genetic polymorphisms (single nucleotide polymorphisms), (C677T and A1298C) in the *MTHFR* gene, are found to be linked with higher risk of NTDs (nearly 1.8-fold) in some races, but not all [53]. G Bassuk *et al.* in 2012 identified eight de novo copy number variations where three (*PAX3*, *PGPD8*, *GPC5*) generated copy number changes of entire genes among 128 Caucasian and 61 Hispanic patients with myelomeningocele [54]. Other genes involved in folic acid processing and the neural tube development have also been studied. But none of these genes found to be causing spina bifida [51], however, certain mutations in the gene *VANGL1* have been linked with spina bifida in some families with a history of this condition [55].

According to Sebold *et al.* in 2005, the broad spectrum recurrence risk for lipomyelomeningocele was 0.04 (95% CI 0.01 - 0.20) considering 52 families where 25 were younger siblings and proband, and one sibling had lipomyelomeningocele [56]. When they considered all the 69 siblings, the broad spectrum recurrence risk turned to 0.043 (95% CI 0.01 - 0.12), where three had similar or related defects [56]. By Fulya and Bekir in 1994, the recurrence risk of spina bifida was approximately 0.232 as a whole, 0.328 for consanguineous parents, and 0.168 for non-consanguineous parents considering 269 cases [57]. In 1960, heritability (60% - 70%) was estimated based on affected individual among siblings of index cases in London, South Wales and Glasgow [58].

4.2. Environmental Factors

Several factors are thought to be involved such as.

4.2.1. Folic Acid

In 1980, some studies reported that folic acid intake is an effective means of primary and recurrent prevention. If the woman is supplemented with folic acid before pregnancy, the risk can be reduced by almost 70% [47] [48] [49] [59]. This is still a mystery, how or why folic acid has such reducing effect for spina bifida [60]. In 1992, in the U.S. the number of births with neural tube malformation has decreased due to the introduction of recommended folic acid [52]. Increasing levels of folic acid receptor autoimmunity is responsible for enhanced risk of NTDs in a dose-response manner [61].

4.2.2. Plant Proteins, Iron, Niacin

Risk of spina bifida increases by almost 2 - 3 times, if a woman is deficient of these essential nutrients before pregnancy [52].

4.2.3. Diabetes

A pregnant woman with diabetes has high risk to have a baby with spina bifida, then a non-diabetic woman [52]. The risk to have a child with myelomeningocele in women with gestational diabetes is lower than the risk in women with pregestational diabetes, but higher from the general population. Due to the degree of maternal metabolic control, in women with pregestational diabetes, the risk of having a child with myelomeningocele is 2 - 10-fold higher than the risk in the general population [50].

4.2.4. Obesity and Other Problems

A woman whose body mass index (BMI) is 30 or above has a higher risk of having a baby with spina bifida [52]. Apart from obesity, maternal hyperthermia (maternal fever), and maternal diarrhea are other risk factors for myelomeningocele [62] [63] [64].

4.2.5. Drugs

Women, taking some medications such as anticonvulsants that used to treat epilepsy or bipolar disorder, such as, valproate and carbamazepine, and drugs that

stimulate ovulation [62] [63] [64], are highly in risk of giving birth to infants with congenital defects, for instance, spina bifida [52].

4.2.6. Other Factors

A pregnant woman, with frequent exposure to electromagnetic fields, hazardous waste sites, disinfectants used in drinking water, pesticides, and fumonisins, is highly at risk to have a fetus with myelomeningocele [62] [63] [64].

5. Prevention

There is no single way to prevent spina bifida completely. However, decreasing incidence of spina bifida has been observed with dietary supplementation with folic acid. Cereals, dried beans, whole grains, fruits, and leaf vegetables are some common sources of folic acid [65]. Since 1998 in U.S., grain products must be enriched with folic acid. The amount of folic acid for women is 0.4 mg/day before and after three months of pregnancy which is recommended by the U.S. Food and Drug Administration [66], Public Health Agency of Canada [67] and UK [66]. But 0.4 - 0.8 mg/day is recommended by the US Preventive Services Task Force. Women of reproductive age should take approximately 0.1 mg/day [50]. Women, who are taking anticonvulsant medication, and already have a child with spina bifida, should take a higher dose of folic acid (4 - 5 mg/day) [66].

6. Tests and Diagnosis

1) Prenatal as well as 2) postnatal screening tests are essential to check for spina bifida and other birth defects.

6.1. Prenatal Diagnosis

6.1.1. Maternal Serum Alpha-Fetoprotein (MSAFP) Test

Myelomeningocele can be checked by the maternal serum alpha-fetoprotein (MSAFP) test [68]. Extremely high levels of AFP in the blood suggest that the baby might be affected by spina bifida [68] which must be followed up by two more tests – 1) ultrasound of the fetal spine and 2) amniocentesis of the mother's amniotic fluid (test for alpha-fetoprotein and acetylcholinesterase). California already has mandated AFP tests by state laws [69].

6.1.2. Ultrasound

This is an examination where high-frequency sound wave bounce is used to form black-and-white images of the body tissue on a video monitor. These images provide the information that can help to know the gestational age and multiple pregnancies which affect the AFP levels. In expert hands, ultrasound today is quite effective in detecting spina bifida and assessing its severity. Ultrasound is safe for both mother and baby [68].

6.1.3. Amniocentesis

In this process, amniotic fluid that surrounds the baby is collected using a needle

from amniotic sac. Generally, in amniotic fluid there is a small amount of AFP. However, in open neural tube defect the baby's spine is skinless, as a result, the AFP leaks to the amniotic sac causing enhanced levels of AFP in the fluid. This screening is usually recommended when there is normal ultrasound report but increased levels of blood AFP [68].

6.1.4. Postnatal Diagnosis

At birth, child with spina bifida and having muscle weaknesses cause more deformities in legs, feet and hips which can be diagnosed by magnetic resonance imaging (MRI) or a computed tomography (CT) scan to view a clear image of the spinal cord and vertebrae [70].

6.2. Treatment

Though still there is no complete treatment of spina bifida, but there are a couple of strategies available through which the severity of the disease can be managed. Children with spina bifida occulta do not require treatment as it is least severe. Usually, surgery is an option to treat children with spina bifida meningocele where patients develop hydrocephalus, bladder problems or even excessive fluid in the brain that may cause ultimately mental retardation or movement disorders if untreated [71]. The most severe form of spina bifida is myelomeningocele where children may develop hydrocephalus and tethering of the spinal cord that may cause loss of muscle function in legs, bladder and bowel. In this case, surgery may require restoring the function. Children with bladder function problems can be cured by catheterization to drain urine [3]. So, treatment depends on signs, symptoms and severity of the diseases [72].

6.2.1. Surgical Options

1) Prenatal surgery: To minimize the severity of the diagnosed spina bifida, prenatal surgery is recommended where during week 19 to 25 after fertilization, the uterus is opened and repaired the spinal cord of the fetus [72].

2) Postnatal surgery: In this surgery, spinal cord and exposed tissues are replaced into the neonate's body just within the 2 days of birth. If later problems with bone development occur, such as scoliosis, another surgery might be needed for the correction. Other option is to use a back brace to correct scoliosis [72]. To remove the fluid from the brain, a special tube named shunt is used which is fitted by surgery [71].

6.2.2. Therapeutic Options

1) Physical therapy: To prevent muscle weakening of the lower limb and to make individual independent, physical therapy is essential, for example, muscles get stronger if one uses leg brace. An electrical or a manual wheelchair is useful for a complete paralyzed person. The manual one is more useful to maintain the fitness and upper-body strong. To resolve learning problems, computer and specialized software may be useful [72].

2) Occupational therapy: By this therapy, the child will learn the everyday activities effectively, for instance, dressing up, eating, cleaning etc. which will help to enhance self-esteem and independency [72].

3) Medications: In myelomeningocele, for neurogenic bladder dysfunction treatment, medications, such as, alpha-adrenergic antagonists, Tricyclic antidepressants, anticholinergics etc. are frequently used along with some bladder emptying techniques to prevent upper urinary tract complications [73].

7. Advanced Research to Treat Spina Bifida

In 2017, a unique therapy, which is a combination of both surgery developed by fetal surgeon Diana Farmer of UC Davis Health and a cellular treatment with canine placenta-derived mesenchymal stromal cells (PMSCs) developed by scientists Aijun Wang and Dori Borjesson, director of the Veterinary Institute for Regenerative Cures at the University of California, was applied to a pair of English bulldog puppies with spina bifida which is a significant step for both human and dog. They successfully cured spina bifida except the incontinence problems. Diana Farmer later successfully did a prenatal surgery of lamb with pre-diagnosed walking problems combined with human PMSCs and later the lamb was born without any noticeable disability. So, they expect that their research outcomes will help to eradicate spina bifida of both human and dog and associated bladder, bowel, and urinary incontinence in near future [74].

8. Ethical Issues

There are some religious and spiritual issues arise when research conduct with human participants. So, it is important to give emphasis on certain points such as maintenance of confidentiality, spread of research finding following appropriate mechanisms, avoidance of stigmatization, identification of vulnerable communities, and development of special protection [75].

9. Overall Outlook

The life expectancy of people with spina bifida has increased to adulthood which was only 12 months almost 50 years ago and now they have normal intelligence and independent life as well. In U.S., help and supports are available for nearly 1666,000 people. Some organizations provide information, support as well as research programs about spina bifida which are provided by the National Institute of Neurological Disorders and Stroke (NINDS) [76].

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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