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Etiology and Pathophysiology of the Spina Bifida

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Abstract

The spina bifida is a congenital anomaly that results in an abnormal formation of the spine and the spinal cord. The two dominant types of spinal dysraphism are based on appearance - open spina bifida if the lesion is visible and closed spina bifida if the lesion is not visible on the body surface. These conditions lead to a different spectrum of neurological effects according to the degree of neurulation disruption. The prevalence of neural tube defects has different rates among different ethnicity, geography, gender, and countries. Genetic, nutritional and environmental factors play a role in the etiology and pathogenesis of the spina bifida. Congenital anomalies in the vast majority concern children living in the early neonatal period who have important medical, social or educational needs. The lifetime cost of a child born with the spina bifida is estimated at over €500,000.

Keywords: neural tube defects, spina bifida, spinal dysraphism, etiology, pathophysiology, meningocele

1. Introduction

Spinal dysraphism encompasses congenital problems that result in an abnormal bony formation of the spine and the spinal cord. This congenital pathology is caused by the maldevelopment of the ectodermal, mesodermal, and neuroectodermal tissues. The spina bifida is a congenital anomaly that arises from incomplete development of the neural tube. It is commonly used as a nonspecific term referring to any degree of neural tube closure. The two dominant types of spinal dysraphism are based on the appearance – spina bifida aperta if the lesion is visible and spina bifida occulta if the lesion is not visible [1]. Common manifestations are meningocele, myelomeningocele, lipomeningocele, lipomyelomeningocele, myeloschisis, and rachischisis [1]. Spinal neural tube defects basically exist in two forms – open and closed spinal dysraphism. The most simple form with minimal involvement of nervous tissue is closed dysraphism (spina bifida occulta) where the vertebral defect is hidden. More severe open spinal dysraphisms (spina bifida aperta) mostly represented by meningocele or myelomeningocele result in various degrees of neurological deficit according to affected spine level, extent of lesion and amount of structures involved (**Figure 1**). In this defect there is a communication between nerve tissue and external environment leading to exposure to amniotic fluid and later leads to high risk of infection. Defect can be covered by a thin membrane. The exposed neural tissue degenerates *in utero*, resulting in

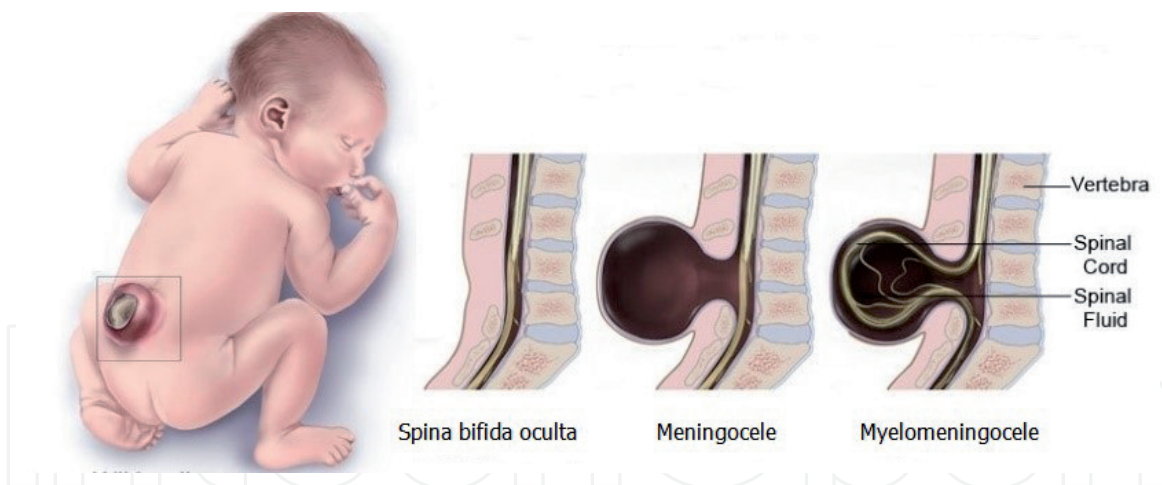


Figure 1.
Types of spinal dysraphism (public domain, source: wikipedia.org).

neurological deficit that varies with level of the lesion. The vertebrae at the level of the lesion lacks neural arches, and so are incomplete dorsally. Spina bifida is commonly associated with several other developmental abnormalities which makes a multidisciplinary medical plan paramount to survival and positive outcomes. The spina bifida correlates with cutaneous conditions such as port-wine stain, hemangioma, hypertrichosis, fibroma pendulum, pigmentary nevus, lipoma, dermal sinus, and deviation of the gluteal furrow [2]. Motor and sensory neurological deficit is inconsistent. The result of nerve structures involvement is usually paraparesis – weakness of lower extremities which in more severe degrees leads to impaired walking or immobility. In patients with severe forms of spina bifida degree of disability strongly correlates with axial level of the lesion [3]. Long term 40-years follow-up of 117 children in the United Kingdom who underwent surgical repair during the 1960s and 1970s showed only 17% of survivors with high level of lesion (above T11) and these patients have higher risk of pressure sores and significantly lower possibility to become community walker. Survival in patients with lesion below L3 vertebra was 61%. Loss of skin sensitivity increases the risk of development of pressure sores what makes frequent skin control necessary. Incontinence of stools and urine is very frequent as well as orthopedic complications, such as contractures, talipes, dislocation of the hip joint, kyphosis and scoliosis. Patients with open forms of spina bifida often display also Chiari II malformation (herniation of the hindbrain) and hydrocephalus that could also require shunting procedure. The mobility and the need for care can be predicted from the neurological deficit. [4]. The lifetime cost of a child born with the spina bifida is estimated at over €500,000, of which 37% comprises direct medical costs with the remaining being indirect costs including special educational and caregiver needs, and loss of employment potential. The direct medical cost for spina bifida patients throughout their life is very high. The most significant amount of financial cost consumes initial diagnosis and early treatment, inpatient care and the treatment of comorbidities in adult life. The indirect lifetime cost in these patients is even higher due to great impact of their increased overall morbidity. The results from the economic evaluations demonstrate that folic acid fortification in food and pre-conception folic acid consumption are cost-effective ways to reduce the incidence of neural tube defects [5, 6]. Considering all possible medical and economic consequences of the issue of diagnosis of spina bifida, there is an emerging need for clarification of exact etiology and pathophysiological mechanisms with emphasis on possible primary prevention, as well as early and effective treatment of spina bifida and also all upcoming complications.

2. Epidemiology

The prevalence of neural tube defects has different rates among different ethnicity, geography, gender, and also countries. The prevalence is higher among Whites as compared to Blacks and females as compared to males [7]. Asia has more rate of neural tube defects than western countries due to low socio-economic status of eastern countries directly affecting the economic burden and negligence over the folic acid as a part of multivitamin supplementation [8]. Worldwide data show place to place-variation of the prevalence rate assumed to be due to low standard health care facilities though the exact mechanism is still unknown. The eastern Mediterranean region exhibited high variability with a swat, Pakistan having 124 cases per 10000 births. The prevalence in the African region ranges from 5.2 to 75.4 per 10000 births, the European region ranges from 1.3 to 35.9 per 10000, and American region ranges from 1.4 to 27.9 cases per 10000. Most WHO member states (120/194) did not have any data on the prevalence of neural tube defects. As the prevalence estimates vary widely, efforts need to be stepped up to monitor neural tube disorders, especially in developing countries. The folic acid supplementation and increasing the quality of the population's diet are important factors in the prevention [9]. A study from Los Angeles showed that the rate of anencephaly and exencephaly is more than spina bifida. But normally, it is supposed that the spina bifida is more common than anencephaly. Same-sex twins had a higher incidence of neural tube defects as well as higher mortality. The study verifies the same etiology between neural tube defects and monozygotic twins. The main role here is played by the common susceptibility to environmental factors [7]. The rate of neural tube defects is more common in twins than singleton and in monozygotic twins than dizygotic twins. The spina bifida most frequently affects lumbosacral spinal level. Only about 0–5% of cases occur in the cervical spine, 5–10% in the thoracic spine, 20–30% in the thoracolumbar junction, 20–30% in the lumbar, 30–50% in the lumbosacral level and 5–15% in the sacral spine [10]. Altogether cervicothoracic spinal dysraphisms are rare, with an incidence of only 1–6.5% [11]. Myelomeningocele occurs in approximately 1 in 1200 to 1400 births. 60% of those children are community ambulators, and 80% are socially continent. The incidence is not higher in any specific ethnic group, but females have a slightly higher incidence in comparison with males [12]. An increased risk of recurrence has been reported of about 3–8% after one affected pregnancy or maternal history of the defect and the risk worsens with an increasing number of affected children [13]. Researchers performed a study in northern China that showed that the recurrence risk in neural tube defects in subsequent pregnancies was 1.7%, which was higher than in the United States. The recurrence rate of neural tube defects was approximately 5-times higher than the overall prevalence in the same region of northern China [14]. The risk of recurrence in myelomeningocele was reported 2–5% in the United States. These data suggest that the genetic basis of closed defects may be same as the basis for myelomeningocele in some families [15]. Another study showed that the recurrence rate has been approximately 2–3% in consecutive pregnancies. Higher incidence rates were reported in females, increased maternal age, and lower socio-economic status. Latin Americans were the most affected population in the United States. Females are affected up to 3- to 7-times more than males [16]. The observed prevalence of the spina bifida varies globally and is largely influenced by differences in surveillance methods, prenatal diagnosis and elective termination policies, and folic acid fortification of staple foods in a given country or region. The spina bifida is more common in countries where there is no legislation providing for the mandatory enrichment of the diet with folic acid in order to reduce its prevalence. African data were scarce, but needed, as many African nations are beginning to adopt folic acid legislation [9, 17, 18]. Ultrasound screening has a major

impact on the epidemiology of the spina bifida. The prenatal detection rate of spina bifida is high, and most cases of spina bifida are isolated and have a normal karyotype [19]. Omission of elective terminations clearly underestimates prevalence and may bias risk estimations in etiologic studies. Compared with women who delivered liveborn/stillborn infants with neural tube defects, women who electively terminated neural tube defects-affected pregnancies were disproportionately white, were more highly educated, had higher incomes, and used vitamins containing folic acid more often [20]. The European network of population-based registries for epidemiological surveillance of congenital anomalies (EUROCAT), collects data on pregnancy terminations in addition to live and stillbirths, generating particularly comprehensive prevalence data for neural tube defects and other malformations. During four years (2003 to 2007), this register reports an overall prevalence of serious congenital anomalies of 23.9 per 1,000 live births. As many as 80% of children with severe congenital anomalies were born alive. The mortality of these children in the first week of life was 2.5%. The abortion was performed after prenatal diagnosis in 17.6% of cases. Congenital anomalies mainly concern newborns with specific medical and social care needs. The prevalence of chromosomal abnormalities was 3.6 per 1,000 live births. Their presence led to a 28% incidence of stillbirths or their diagnosis conditioned 48% of all terminations. The most common non-chromosomal subgroups were congenital heart defects, limb anomalies, nervous system disorders and urinary system anomalies. In 2004, perinatal mortality associated with congenital anomaly was 0.93 per 1000 births, and terminations of pregnancy following prenatal diagnosis 4.4 per 1000 births, with considerable country variation. Primary prevention of congenital anomalies in the population based on controlling environmental risk factors is a crucial policy priority, including pre-conceptional care and whole population approaches [21].

3. Etiology

The development of nervous system is an embryonal process called neurulation. The primary neurulation is the first phase and includes the closure of the neural tube and thus forming brain and spinal cord. The second phase comprises formation of sacral and coccygeal segment and occurs around 26th day of gestation. Spina bifida is an incomplete closure of dorsal spinal structures and usually happens to appear between 17th to 30th postconceptional day [3]. The etiology of spinal dysraphism is multifactorial [22]. Although no clear etiology is known to result in either the open or closed forms, some regional adverse factors have been reported, primarily involving the mother at conception and early pregnancy. **Table 1** lists potential risk factors that are usually considered to be neural tube defects. Grewal et al. report in their study that maternal intake of the alcohol increased the risk for d-transposition of the great arteries, neural tube defects, and multiple cleft lip with or without cleft palate in infants. Smoking in this study was associated with a lower risk of neural tube defects [23]. Positive associations are observed between spina bifida and caffeine consumption and each caffeine source except caffeinated tea, which showed a negative association with the spina bifida. The association between caffeine consumption and anencephaly differed by maternal race and ethnicity. No dose effect of caffeine consumption was found [24]. Plasma levels of folate and vitamin B12 are independent risk factors for the occurrence of neural tube defects. This fact suggests that the enzyme methionine synthase is involved in the etiology of neural tube defects. The surprising finding is that folate and vitamin B12 levels, considered sufficient, continued to be a risk factor for an increased incidence of this defects. This finding is an incentive to re-evaluate daily doses of folate as well as

Maternal nutrition	Other maternal factors	Environmental factors
Alcohol and caffeine use	Smoking	Ambient air pollution
Insufficient folate intake	Low socio-economic status	Indoor air pollution
Low dietary quality	Infections and hyperthermia	Nitrate-related compounds
Elevated glycemic load	Pregestational diabetes	Organic solvents
Low methionine and zinc intake	Pregestational obesity	Pesticides
Low serum choline level	Psychosocial stress	Polycyclic hydrocarbons
Low vitamin B12 and C level	Valproic acid use	Disinfectant in drinking water

Table 1.
Potential risk factors for neural tube defects (according to [3]).

vitamin B12 [25]. The higher quality of the diet of expectant mothers is associated with a reduced incidence of neural tube defects. It is dietary approaches that could further reduce the risk of serious birth defects and complement existing efforts to promote the use of multivitamins during pregnancy [26]. Yazdy et al. refer that high insulin intake is risk factor for genesis of neural tube defects [27]. Results from experimental animals have suggested a role for methionine, an essential amino acid, in normal closure of the neural tube. Shaw et al. observed an approximately 30–40% reduction in neural tube defect-affected pregnancies among women whose average daily dietary intake of methionine was above the lowest quartile of intake. These reductions in neural tube defect risk were observed for both anencephaly and spina bifida, remained after adjustment for maternal race, ethnicity and education; and were observed irrespective of maternal level of folate intake [28]. Shaw et al. observed elevated risk of neural tube defects associated with lower levels of total choline, and reduced risks with its higher level [29]. In the systematic review, Ray et al. report a moderate association between low maternal B12 status and the risk of fetal neural tube defects [30]. Studies report a reduction in the risk of neural tube disorders in infants and fetuses when mothers taking zinc in the preconception period. However, it has not been established whether the combination of nutrients or zinc alone is associated with a reduced incidence of neural tube disorders [31]. Maternal hyperthermia in early pregnancy is associated with increased risk for neural tube defects and may be a human teratogen [32]. Similarly, lower socio-economic status and residence in a socio-economic status-lower neighborhood increased the risk of neural tube defect-affected pregnancy [33]. Although the excess risk for birth defects among children of mothers with diabetes mellitus is well documented, there are few data concerning the risk for specific malformations. No statistically significant differences were found among infants of mothers with gestational diabetes mellitus who did not require insulin during pregnancy. Insulin dependent diabetes mellitus is potential risk factor for malformations of central nervous system [34]. Women who experience stressful life events around the time of conception or early gestation may be at increased risk of delivering infants with certain congenital anomalies. For example, in Mexican population in the United States, the occurrence of stressful life events was associated with the risk of neural tube defects. These findings suggest that stress may increase risk in populations with poor nutritional status and poor economic resources [35, 36]. It is likely that not all malformations of the human fetus associated with valproate exposure during pregnancy have a comparable quantitative dose relationship. The reducing of the valproate dose in early pregnancy will provide more effective protection against the spina bifida and other types of fetal malformations [37]. Lupo et al. found an association between environmental level of benzene and the spina bifida. Mothers

living in census tracts with the highest benzene levels were more likely to have offspring with the spina bifida than women living in census tracts with the lowest levels [38]. Waller et al. report moderate positive association of maternal obesity with 7 of 16 categories of birth defects. The mechanisms underlying these associations are not yet understood but may be related to undiagnosed diabetes mellitus [39]. Severe obesity has been associated with larger risks of the spina bifida incidence. Underlying mechanisms that have been suggested including aberrant glucose control, oxidative stress, and metabolic syndrome [40]. Higher water nitrate intake was associated with several birth defects in offspring but did not strengthen associations between nitrosatable drugs and birth defects [41]. Cordier et al. report the association between exposure to glycol ethers and neural tube defects, multiple anomalies, and cleft lip [42]. Pesticide exposures were associated with risk of neural tube defects, especially use of pesticides at home and a peri-conceptual residence within 0.25 mile of cultivated fields [43]. Persistent organic pollutants have been associated with a wide range of adverse health effects. Elevated placental concentrations of polycyclic aromatic hydrocarbons, dichlorodiphenyltrichloroethane isomers, and α -hexachloro-cyclohexane are associated with increased risks of neural tube defects [44].

Considerable evidence points to a major genetic component in the spina bifida causation, raising the question of which genes are implicated. In animal spina bifida models more than 40 genetic strains were detected to be associated with this disorder. In some human patients were detected various genetic alterations of coding regions of planar cell polarity genes pathway and genes encoding folate metabolism. The study of folate and its association with neural tube defects is an ongoing endeavor that has led to numerous studies of different genes involved in the folate metabolism pathway, including the most commonly studied thermolabile C677T mutation in the methylenetetrahydrofolate reductase gene [3, 45, 46]. Most of observed genetic alterations are sporadic (non-syndromic), only less than 10% of cases are syndromic, connected with genetic disorders such as trisomy 13 or 18. Up to date evidence supports a theory of a multi-factorial origin of neural tube defects as a consequence of both, genetic and non-genetic factors [47]. Recent studies of mouse mutant with transformation related protein 53 showed that exencephaly susceptibility depends on the presence of two X chromosomes, not the absence of the Y chromosome. Involvement of genetic factors in etiology is supported by evidence that the risk for siblings of spina bifida patient is 2–5%, representing 20 to 50-fold higher risk compared to the general population prevalence of 1 per 1000. Relatives of 2nd and 3rd line display lower risk compared to 1st line relatives, though still increased compared to standard population risk. Woman who has child with spina bifida has approximately 3% risk for another pregnancy affected by spina bifida, risk arises to 10% after two affected pregnancies. The agreement of neural tube defects is higher in monozygotic and dizygotic twins of the same sex compared to twins of the opposite sex. Female excess among cranial neural tube defects is an epigenetic phenomenon whose molecular investigation will produce insight into the mechanisms underlying neural tube defects [3, 48]. Trisomy 18 is the most commonly associated aneuploidy with open neural tube defects. Other genetic disorders include Meckel-Gruber syndrome, Jarcho-Levin dysplasia, HARD (hydrocephalus, agyria and retinal dysplasia), trisomy 13, PHAVER syndrome (pterygia, heart defects, autosomal recessive inheritance, vertebral defects, ear anomalies and radial defects), VATER syndrome (vertebral anomalies, anal atresia, trachea-esophageal fistula and renal abnormalities), and X-linked neural tube defects among others. A significant number of fetuses with open defects are chromosomally abnormal. Although prenatal chromosome analysis should be considered in all cases, prenatal ultrasound seems effective in identifying those fetuses with an underlying

chromosomal abnormality. It is questionable how many genes in the human genome pose a risk of neural tube defects. Studies often draw conflicting conclusions due to limitations in the design of studies that affect the strength of statistical analysis. Association studies and sequencing of the entire exome or genome are a way to identify genes that affect the incidence of human neural tube defects [16, 49, 50]. If a prenatal diagnosis of myelomeningocele is suspected, karyotype and genetic consultation should be obtained. Multidisciplinary approach is necessary to treat and support this malformation which is a huge burden on the patient, family, and the society. The most of suspected etiological factors does not have strong evidence or occur less frequently. This underlines to theory of multifactorial etiology of neural tube defects.

4. Pathophysiology

The development of the normal spinal cord from the second to the sixth week of pregnancy includes gastrulation and primary and secondary neurulation. During the first stage of gastrulation, the endoderm and ectoderm form a bilaminar embryonic disc (**Figure 2**). Cell division and migration lead to the formation of a mesoderm and a trilaminar disk is formed. The interaction of the notochord with the ectoderm creates a neuroectoderm. The beginning of the neural plate is in the midline and then extends in the proximal and caudal directions. The pathological effects during primary neurulation can lead to the spinal dysraphism. Part of the primary neurulation is the formation of nerve folds - the nerve groove. By joining the nerve folds, the nerve plate changes into a neural tube. Closure of the cranial and caudal openings of the neural tube represents the end of the process of primary neurulation (**Figure 3**). Disorder of the closure of the caudal neural tube causes the formation of a plaque (exposed nerve tissue). The existence of a neural plaque is a differential feature between myelocele and myelomeningocele [51]. Pluripotent cells forming the caudal end, forms vacuoles and neurons. Their cavitation leads to the formation of a central canal. Apoptosis of said cells leads to the formation of the conus medullaris, filum terminale and ventriculus terminalis. The final closure of the caudal neuropore leads to the transformation from the primary neurulation to the secondary neurulation. During secondary neurulation, the ectoderm and part of the endoderm forms the medullary cord. Two types of cells develop from the medullary epithelium - neuroblasts and spongioblasts. Neuroblasts differentiate

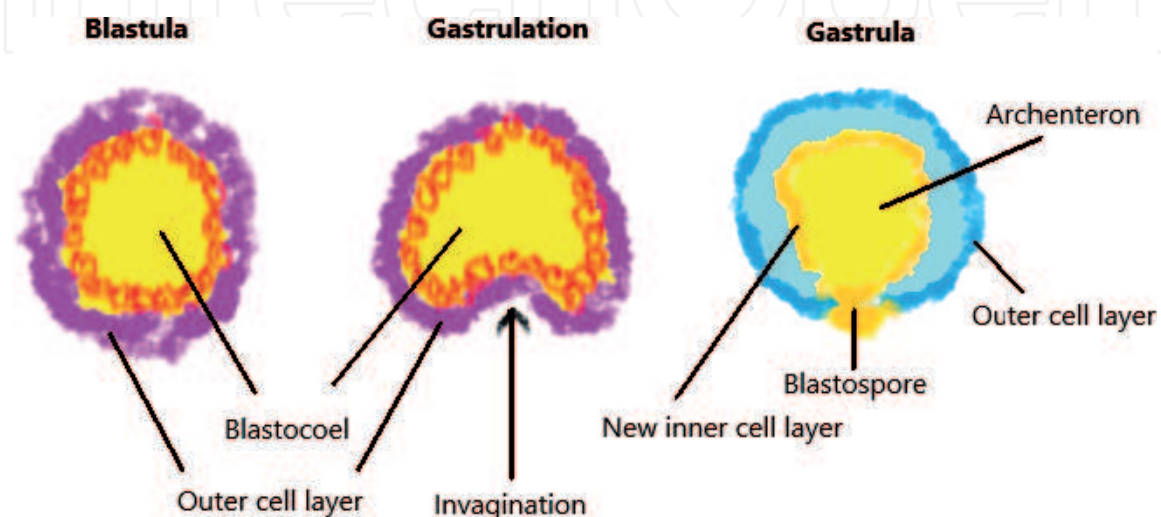


Figure 2.
The process of the gastrulation (author's archive).

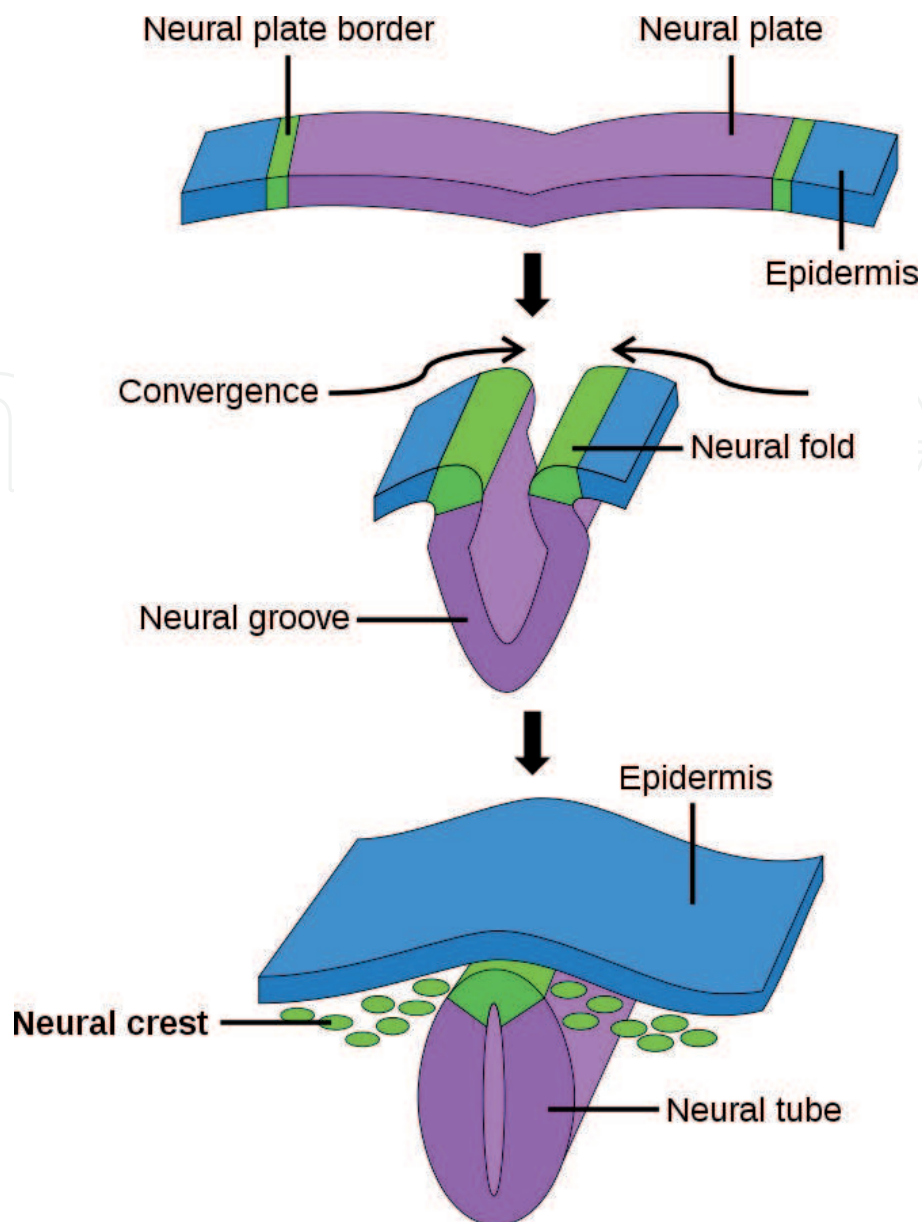


Figure 3.
The process of primary neurulation (public domain, source: wikipedia.org).

into different types of neurons. Ependymal cells, astrocytes and oligodendrocytes differentiate from spongioblasts. The wall of the occluding medullary tube is formed by a layer of cylindrical pluripotent neuroepithelial cells. Towards the cavity, the cells are interconnected by connecting complexes. The luminal surface of the neuroepithelium forms the inner border membrane. From the environment, the neuroepithelium is bounded by a basement membrane, which forms the outer border membrane. As the cells proliferate, the medullary tube wall thickens, making the neuroepithelium multilayered cylindrical. In the area of the future spinal cord, it is possible to histologically distinguish the inner ventricular zone (the primitive ependymal layer), the middle intermediate zone (the future gray matter) and the outer marginal zone (the future white matter). The primitive medullary tube has a thin wall and a wide lumen. Later, the wall is roughened and the lumen has the shape of a slit in cross-section oriented ventrodorsally (the future central canal). On both sides, the cavity is inserted into the wall in the form of a longitudinal notch - sulcus limitans. This incision divides the lateral walls of the neural tube into ventral basal and dorsal alar plate. Neuroblasts of the basal plate become motor neurons, whereas sensory neurons form in the alar plate. In the future spinal cord, unlike the lateral walls, the dorsal and ventral walls do not participate in active cell

proliferation. The cells of these parts are mainly involved in the formation of ependyma. The medullary cord separates, gradually condenses and is subject to cavitation. The cavitation combines to form a single tube. The disorder of secondary neurulation is mostly limited to the spinal cord and conditions the formation of closed neural tube defects (neural tissue is not exposed). Factors playing role in etiology of spina bifida, such as genetic, environmental and nutritional factors have mostly effect on neurulation causing its disruption, preventing closure of neuro-pores and neural folding. Effect of etiological insults is different, disrupting various phases of neural tube formation, but the result in all factors is alike, causing abnormal neurulation [8]. The essential step in pathogenesis of spina bifida is non-union of dorsal spinal structures, in severe forms it is failure of embryonic neural tube closure. Immature neural tube remains uncovered or is covered only by a thin membrane what causes direct exposure of the developing and open neural tube to the amniotic fluid. After relatively normal initial development, neuronal differentiation of bifid neuroepithelium and development of spinal motor and sensitive functions in whole extent including levels below the lesion, with the progression of gestation, destructive effect of exposure of the developing spinal cord to the amniotic fluid manifests as necrosis of neurons and micro-hemorrhagic changes of the spinal cord [3]. Pathological examination of the spinal cords of stillborn human fetuses with myelomeningocele demonstrate varying degrees of neural tissue loss at the site of the defect, but normal-appearing dorsal and ventral horns proximal of the lesion. Recently produced experimental evidence suggests that secondary traumatic injury and degenerative changes, acquired in utero, to the openly exposed neural tissue may be primarily responsible for the massive neurological deficit associated with myelomeningocele. In myelomeningocele as the severe degree of spina bifida the defect consists of dorsally opened vertebral arch, as well as dorsal defect of dura mater that is laterally attached to the dermal layer and defect in layer of pia mater which is fused to the epidermis. The unclosed spinal cord is directly exposed without any covering to the amniotic fluid and later to the surrounding environment. On the surface of spinal cord is only membrane - the abnormal arachnoid sac – which is unable of providing protection against traumatic injury caused by toxic exposition. Another insult to the nervous tissue can occur during passage through the birth canal in case of vaginal delivery leading to further hemorrhage and abrasion. The devastating role of secondary insult to the exposed nervous tissue underlines the presence of dorsal and ventral parts of the spinal cord with developed nerve roots and ganglia, what is evidence of preexisting appropriate early embryogenic development. This finding emphasizes the role of early in utero surgery in protection from secondary injury caused by prolonged exposition of the unprotected neural tissue to the amniotic fluid and in preservation of neurological functions [52, 53]. Regular sonographic observations of human fetuses with myelomeningocele show progressive deterioration of leg movements during pregnancy [54]. Experimental data on fetuses with the spina bifida aperta strongly indicate that a discrepancy exists between the occurrence of prenatal leg movements and the spinal location of the meningomyelocele on the one hand, and between the occurrence of pre- and postnatal leg movements [55]. In hemimyelocele, half of the dysgraphic spinal cord is not covered by the dura mater and is exposed to the intrauterine environment. The correlating lower limb shows a motor or sensitive deficit, while the function of the other lower limb is normal or only slightly altered [56]. Staged series of animal fetuses with myelomeningocele have demonstrated gain of neurological function even after the lesion has formed, followed by loss of this function. This finding correlates with a progressive loss of spinal cord tissue integrity. Stiefel et al. studied the development of neuronal connections and neurological function of mice during fetal and neonatal stages in a

genetic model of exposed lumbosacral spina bifida. Their findings support the hypothesis that neurological deficits in human myelomeningocele arise after secondary destruction of nerve tissue and loss of function during pregnancy [57]. Meuli et al. report findings that secondary neural tissue destruction during pregnancy is primarily responsible for the functional loss and that timely in utero repair of the open spina bifida might rescue neurologic function [58]. Drewek et al. dealt with the toxic effects of human amniotic fluid on organotypic cultures of rat spinal cord. Using a lactate dehydrogenase outflow test to evaluate toxicity, amniotic fluid was found to become toxic at approximately 34 weeks of gestation. This toxic effect of amniotic fluid occurs relatively suddenly. Surgical closure of a myelomeningocele defect prior to the onset of amniotic fluid toxicity has the potential to prevent injury to sensitive myelodysplastic spinal cord tissue [59].

4.1 Genetic factors

The number of mouse mutants and strains with neural tube defects at present exceeds 240, including 205 representing specific genes, 30 for unidentified genes, and 9 multifactorial strains. Some mutations in isolation do not cause neural tube disorders, but are caused by di-genic, tri-genic, and oligo-genic combinations. This fact corresponds to the nature of the genetic etiology of human neural tube defects. Experimental mouse mutants that have only exencephaly are 4-fold more frequent than those that have spina bifida aperta with or without exencephaly. Many diverse cellular functions and biochemical pathways are involved; the mutants with neural tube defect draw new attention to chromatin modification, the protease-activated receptor cascade, and the ciliopathies. Few mutants directly involve folate metabolism. The research of many mutants is the basis for a complete understanding of the processes of elevation and fusion of nerve folds along mechanically distinct cranial-caudal segments of the neural tube [60]. Neural tube closure is affected by many cellular biological functions, with cytoskeletal, cell cycle, and molecular regulation of cell viability present in mutant mice. Neural tube closure is also affected by transcriptional regulators and proteins that affect chromatin structure. Folic acid supplementation is one of the most effective methods of primary prevention of some neural tube disorders in humans, although the mechanism of action of folate is unclear. In cases where folic acid has no preventive effect, it is possible to reduce the risk of mouse mutants by administering inositol. This finding may determine the strategy for preventing neural tube defects in the future [61]. Exencephaly, the developmental precursor of anencephaly, is most commonly encountered after gene mutation in mice, but spina bifida aperta is also observed in more than 40 mutant strains. Rare putative mutations in the planar cell polarity genes *Vangl2* (Vang-like protein 2), *Scrib* (Scribble planar cell polarity protein), *Dact1* (Disheveled binding antagonist of β -catenin 1), and *Celsr1* (Cadherin EGF LAG seven-pass G-type receptor 1) cumulatively contribute to over 20% of cases with craniorachischisis, a rare defect; no contributing variants were found for *Prickle1* (Prickle planar cell polarity protein 1) or *Ptk7* (Protein tyrosine kinase 7). Planar cell polarity rare putative mutations have a weaker role in myelomeningocele, being found in approximately 6% of cases and cumulated across *Celsr1*, *Fuz* (Fuzzy planar cell polarity protein), *Fzd6* (Frizzled class receptor 6), *Prickle1*, *Vangl1* (Vang-like protein 1), and *Vangl2*. These results demonstrate that planar cell polarity - gene alterations contribute to the etiology of human neural tube defects [60, 62]. Opposite to unaffected individuals, patients with neural tube defects display though rare, but present missense gene mutations were confirmed by sequencing of the coding regions of human orthologues of these genes. Substantial part of neural tube defects is associated with variants in genes of the planar cell polarity and a

non-canonical Wnt signaling pathways [62]. This is particularly significant, since planar cell polarity-gene mutations are potent causes of mouse neural tube defects, generating several phenotypes particularly the severe defect craniorachischisis. Initiation of neural tube closure is disrupted in homozygous mice due to the presence of mutations in planar cell polarity genes. This fact provides a strong association between neural tube defects and planar cell polarity signaling. Missense gene sequence variants detected in humans with neural tube defects are heterozygous and have a wider range of phenotypes than in mouse mutants. It is the interactions between mutations in several heterozygous genes that may be responsible for neural tube defects in humans [63]. Genes of folate one-carbon metabolism are another group of genes linked to neural tube defects. Methylene tetrahydrofolate reductase is an enzyme essential for conversion of homocysteine to methionine generating 5-methyltetrahydrofolate. Variant of this gene 677C > T results in the conversion of valine to alanine at codon 222. This variant causes reduced activity of this enzyme. The homozygous 677TT genotype, in either mother or fetus, particularly in connection with folate deficiency could be a risk factor for neural tube defects. The examination of non-Latin European studies revealed that the association of homozygous dominant genotype with neural tube defect has only been proven for Irish populations, both by case-control studies, and by family-based tests, such as the allele transmission disequilibrium test [64]. Pickell et al. refer that biological evidence linking maternal methylene-tetrahydrofolate reductase and folate deficiencies to adverse pregnancy outcomes in mice mutants. It underscores the importance of folate in reducing the incidence of early embryonic defects and in the prevention of the development of placental abnormalities that may increase susceptibility to other defects [65]. The glycine cleavage system is a multi-enzyme component of mitochondrial folate metabolism, and glycine cleavage system-encoding genes therefore represent candidates for involvement in neural tube defects. Mutations in genes of the glycine cleavage system, which reduce the activity of two mitochondrial enzymes of folate-mediated one-carbon metabolism (glycine-decarboxylase and amino-methyltransferase), are also found among patients with neural tube defects and in this case loss of function of the mouse orthologues produces neural tube defects [66]. Glycine decarboxylase in the glycine cleavage system acts to transfer one carbon unit to the folate metabolism of one carbon. Mutations in glycine decarboxylase cause a rare recessive disease - non-ketotic hyperglycemia. However, these mutations have also been identified in patients with neural tube disorders. Nevertheless, the relationship between non-ketotic hyperglycemia and neural tube disorders remains unclear. Formate supplementation normalizes the folate profile, restores embryonic growth and prevents neural tube defects, suggesting that glycine decarboxylase-deficiency causes neural tube defects through limiting supply of one-carbon units from mitochondrial folate metabolism [67]. Mitochondrial enzyme activity supplies 70% of the cell's one-carbon units for metabolism, as formate molecules, and it seems possible that genetic variants in this pathway may prove to be important risk factors for neural tube defects [3].

4.2 Non-genetic factors

A variety of environmental factors have been linked with neural tube defects (**Table 1**). Folic acid seems to play crucial role in the pathophysiology of neural tube disorders. It is inevitable in the synthesis of deoxyribonucleic acid and ribonucleic acid precursors. Dihydrofolate reductases convert folic acid into tetrahydrofolate. Essential step is methylation of the folic acid that is responsible for its functionality. Supplementation of folic acid is linked with decreased incidence of neural tube defects by 71% [68]. Animal studies have not provided enough information

to establish metabolic and genomic mechanism underlying human folic acid responsiveness in neural tube defects [69]. 5-methyl-tetrahydrofolate is the active co-factor of enzymes involving one-carbon transfer reactions forming purine and pyrimidine. Folate receptors take up MTHF into the cell, glutamates and carrier protein can be added to form polyglutamate folates that cannot cross cell membranes. Folic acid is directly associated with cell proliferation as for in neurulation. Neural folds express the folate receptors. The absence of folic acid halts neural tissue proliferation and migration during neurulation leading to neural tube disorders. In the last decades there has been significant worldwide decrease in overall incidence of neural tube defects due to the periconceptual supplementation of folic acid. Folate food fortification became priority in many countries. However, despite indisputable benefits of folic acid supplementation neural tube defects continue to be a substantial part of perinatal morbidity and mortality worldwide. Recent studies demonstrating novel roles and interactions between innate immune factors such as the complement cascade, neurulation, and folate metabolism are explored [70]. Despite the great effect of the folate food fortification programs, there are still cases of neural tube defects also after periconceptual supplementation. This might be due to defects in folate metabolism, receptors or transport proteins that put these women into higher susceptibility. Genetic alterations leading to impaired structure or function of receptor proteins, particularly α - and β -folate-receptors, which have function in neural cells, can lead to failure in neurulation [8, 71]. The C677T polymorphism in the methylenetetrahydrofolate reductase gene has been reported to play a critical role in the pathogenesis of neural tube defects. This association has been widely demonstrated, but the results are inconclusive. Meta-analysis performed to rule out the relation between C677T polymorphism in the methylenetetrahydrofolate reductase gene and neural tube defects demonstrated that this mutation decreases the activity of enzymes required for folate metabolism, thus reducing the serum folate concentration. Yang et al. found no association between any of the fathers' genotypes and neural tube defects, whereas a significant correlation between C677T polymorphism in the methylene-tetrahydrofolate reductase gene and neural tube defect-risk was found in patients with neural tube defect and in their mother [8, 72]. Folate antagonists such as phenytoin, valproic acid, and carbamazepine have a direct effect on neural tube defects due to inhibiting the activity of folate [73]. Apoptosis and proliferation play important roles in embryonic development and are required for neural tube closure. The antifolate drug methotrexate induces folate dysmetabolism by inhibition of dihydrofolate reductase and causes abnormal apoptosis and proliferation. Methotrexate causes a folate and folate-associated dysmetabolism, and further induced abnormal apoptosis and proliferation, which may play a critical role in the occurrence of neural tube defects caused by folate deficiency [74]. Mutation in homeobox genes and fibroblast growth factor dysfunction has some roles in the pathogenesis of neural tube defects [8]. The important role of vitamin B12 in development of nervous system is known. It is necessary in folate metabolism in converting homocysteine from this metabolic pathway into methionine. Along with methionine synthase it reduces the toxicity of homocysteine. Under circumstances of vitamin B12 deficiency homocysteine serum levels increase. The high homocysteine level can cause posttranslational modification of folate receptors that can after modification represent an autoantigen. Production of antibodies against these autoantigens leads to decrease of folate activity [8, 70]. Valproic acid is widely used to treat epilepsy and bipolar disorder and is also a potent teratogen, but its mechanisms of action in any of these settings are unknown. This anticonvulsant increases risk of neural tube defects by 10-fold when taken during the first trimester of pregnancy [67]. Potent histone deacetylase inhibitory activity of valproic acid may disturb the balance of protein acetylation

and deacetylation, leading to neurulation failure [75]. Valproic acid activates transcription from diverse exogenous and endogenous promoters and have teratogenic effects in vertebrate embryos, while non-teratogenic analogues of valproic acid do not inhibit histone deacetylase and do not activate transcription [76]. Production of neural tube defects due to fumonisin (group of mycotoxins derived from *Fusarium* and their *Liseola* section) exposure in rodent embryos has identified sphingosine phosphate metabolism as a key target of the toxin, potentially compromising folate utilization [3]. Neural tube defects are among the most common of the malformations associated with diabetic embryopathy. Pax3 (paired box 3) is an important developmental control gene, the expression of which is impaired in the embryos of diabetic mice, and therefore neural tube apoptosis occurs [77].

4.3 Pathogenesis of open spinal dysraphism

Two phases of neural tube formation occur in higher vertebrates: closure and canalization. Primary neurulation is initiated at the boundary between future hindbrain and cervical spine on day 22 after fertilization (**Figure 3**). At the rostral extremity of the forebrain begins closure and backwards continues zipping to meet forward closure from the hindbrain. On the 24th postconceptional day rostral neuropore closure is completed, spinal closure lasts longer till the 26th day, progressively forming lower parts of the neuroaxis. Meningomyelocele is an open defect of neural tube as a result of closure failure of the neural folds in the dorsal midline. It can be consequence of failure of any part of neurulation process. Craniorachischisis is the most severe neural tube defect with almost completely dorsally opened brain and spine. This defect is a result of closure failure on 22nd day. Analysis of mice with mutations of *Vangl2* gene has revealed a defect of late gastrulation. The process of convergent extension involves the intercalation of cells in the midline to lengthen and narrow the body axis [3]. Planar cell polarity signaling is necessary for initiation of neural tube closure in higher vertebrates. In mice with planar cell polarity gene mutations, a broad embryonic midline prevents the onset of neurulation through wide spacing of the neural folds. Cellular autonomic error of convergent spread requiring planar cell polarity signaling via Rho-associated protein kinase plays a role in development of neural tube defects [78]. Anencephaly is a defect of neural tube closure where initial closure is successful but cranial neurulation fails. Open spina bifida defects are results of failure in subsequent spinal neurulation. These lesions can be of various levels and sizes depending on the stage at which the 'zipping' process fails [3]. The molecular mechanism based on the antagonism of *Bmp2* (Bone morphogenetic protein 2) signaling is the basis for the regulation of the formation of dorsolateral hinge points during mouse neural tube closure. Spinal closure in the curly tail (Grainy head like transcription factor 3) mutant fails later, due to enhanced curvature of the body axis, producing a spina bifida confined to the lumbar and sacral region [79]. *Zic2*-mutant (*Zic* family member 2) mice fail early in spinal neurulation, owing to lack of dorsolateral neural plate bending, and display a large spina bifida from thoracic level downwards [78].

4.4 Pathogenesis of closed spinal dysraphism

Secondary neurulation is responsible for forming of the neural tube in the low sacro-coccygeal regions, following the closure of the caudal neuropore. The end of the embryo comprises the tail bud whose mesenchymal cell core progressively reorganizes into longitudinal cell condensations. The most dorsal of these condensations undergoes canalization, converting the solid neural precursor into epithelial

secondary neural tube [77, 80]. Closed spinal dysraphisms are covered with skin and they are not in contact with surrounding environment as they are consequence of failure of secondary neurulation. Occult spina bifida is outcome of inappropriate separation and differentiation of neural and mesenchymal tissues. Research helped to identify a bipotential neuro-mesodermal precursor cell lineage within the tail bud. Differentiation and separation of these precursor cells are essential for proper development and existence of these cells explains incomplete separation of these layers in case of its malfunction. The histological and ultrastructural properties of secondary neurulation in C57BL/6 mouse embryos were examined as a first step to analyze the cause of the presence of this process in mammalian embryos. Secondary neurulation in mouse embryos consists of two phases - platelet formation and cavitation. These two events occur simultaneously. The medullary rosette consists of elongated tail bud cells, radially arranged around a central lumen formed by cavitation. The secondary portion of the neural tube forms in 10-day embryos by progressive enlargement of the central lumen and addition of tail bud cells to the rosette. The medullary plate also consists of elongated tail bud cells. These cells expand ventrally from the basal aspect of the dorsal superficial ectoderm into the slit-like cavity formed by cavitation. The formation of the secondary neural tube occurs in 11- to 12-day-old embryos in the process of forming additional lateral and ventral tail cells into the medullary plate. Free cells and cell debris that do not show signs of necrosis often occur in the forming lumen of the secondary neural tube. Small intercellular junctions form at the juxta-luminal ends of the tail bud cells during the formation of the medullary rosette or plate, and cavitation occurs. Cavitation per se during secondary neurulation is a relatively passive phenomenon, which results principally from neighboring cells becoming polarized apicobasal and incorporated into a primitive neuroepithelium. The latter constitutes the walls of the forming secondary neural tube [3, 81]. The clinical observation that the distal spinal cord is often tethered to surrounding tissues, in spina bifida occulta, can therefore be recognized as a disorder of secondary neurulation. The frequent and striking association of closed spinal dysraphism with intradural lipoma is not well explained. The progressive generation of axial tissues (spinal cord, skeleton and musculature) of the body has long been proposed to depend on the activity of multipotent stem cells. The data strongly support their existence, there is little definitive information about their multipotency or extent of contribution to the axis [3, 82]. Spinal lipomas are the most common form of occult spinal dysraphism. Lipomas represent a wide spectrum of diseases in regard to pathological anatomy, symptomatology, and treatment options. These lesions are united by a similar embryology and pathophysiology. The treatment of these lesions is controversial. Some physicians advocating surgical treatment for all patients regardless of clinical symptoms and others proposing that surgery in cases of the clinical manifestation [83].

4.5 Postnatal pathogenesis of the spina bifida

The spina bifida is associated with another brain malformations and development of the hydrocephalus. Brain defects involve the spectrum of anomalies related to the Chiari II malformation in about 90% of cases [83]. Chiari II malformation is associated with herniation of normal-sized cerebellum caudally through the foramen magnum [84]. Insufficient distribution of the embryonic ventricular system can be considered to be the cause of Chiari II malformation in children with myelomeningocele. Defective occlusion and an open neural tube secrete fluid accumulation, which affects the normal development of the brain. These mechanisms result in small posterior fossa and disorganization of the brain [85]. Volume reduction of the cerebellum is more associated with thoracic level spinal lesions than lumbar or

sacral lesions. Few volumetric MRI studies of the entire cerebellum have been published. Even less quantitative information is available in patients with hindbrain malformations, including the Chiari II malformation which is ubiquitous in patients with meningocele. Children with thoracic level lesions have smaller cerebellar volumes relative to those with lumbo-sacral lesions, who had smaller volumes compared to children without the pathological development. The reduction in cerebellar volume in children with meningocele represents a reconfiguration involving anterior lobe enlargement and posterior lobe reduction [86]. Most of patients with open spinal defect display abnormal MRI finding. Distortion of the midbrain where colliculi fuse into a single beak pointing posteriorly and invaginate into cerebellum are present in about 65% of cases [3]. About 70% of patients have elongated medulla with kinking at the spino-medullary junction [83]. The basal ganglia and subcortical structures usually have normal appearance on MRI. Meningocele differentially disrupts brain regions whereby some structures are volumetrically normal whereas others are reduced or enlarged. In hippocampus, volumetric reduction coupled with increased mean diffusivity may imply reduce cellular density and aberrant organization. The increased volume and markedly reduced mean diffusivity of putamen indicate increased density. The hippocampus, but not the amygdala, is reduced in volume, and the putamen is enlarged [3, 87]. Almost half of the children with meningocele have hypogenesis of the corpus callosum involving either the splenium and posterior body or the rostrum [83]. The results of the Treble-Barna et al. study contribute to emerging evidence of memory impairment in adults with meningocele and provide quantitative evidence of impaired hippocampal macrostructure as a neural correlate of memory impairment in this population. These anomalies suggest that the disruption of neural migration associated with meningocele is prolonged into the second trimester, since the corpus callosum develops from 8 to 20 weeks prenatally [88]. Anomalies of the corpus callosum are an important indicator of additional brain anomalies. Quantitative studies show marked volume and integrity differences, especially posteriorly in cases with hypogenesis or severe hypoplasia [89]. The hypoplastic corpus callosum is not macro- or microstructurally intact in cases of the spina bifida, even when it appears radiologically intact. Both volume and integrity of posterior regions are related to reductions in intelligence quotient and to interhemispheric processing. Reduced integrity of the corpus callosum has been shown also in the genu, but not in commissura anterior [90]. Anomalies of the corpus callosum are associated with reduced interhemispheric communication and general difficulties integrating information in language, reading, and social domains [3]. Abnormalities of the corpus callosum are known to occur in the majority of patients with Chiari II malformation, and also callosal defects can be associated with spinal closed dysraphism. Chiari II malformation is associated with eye movement difficulties as well as problems with the precision and timing of motor movements and rhythmicity. When the neuroaxis emerges as a whole, the structures of embryological ectodermal origin and cranial and spinal structures are not independent regions from each other and thus, asymptomatic closed spinal dysraphisms have been demonstrated to accompany dysgenesis of the corpus callosum [91]. Secondary consequences of the spina bifida include hydrocephalus which results primarily from obstruction of cerebrospinal fluid flow at the IV. ventricle level, with other factors including aqueductal stenosis, venous hemodynamics and ependymal denudation. Cortical reorganization occurs around the area of ventricular dilatation [3]. Frontal regions are enlarged and there is a reduction in the volume of posterior cortical regions [92]. The reduction of cortex thickness and also white matter is associated with the mechanical effects of hydrocephalus. Overall reduction in white matter and increased neocortical thickness in the frontal lobes suggest that the spina bifida

reflects a long-term disruption of brain development that extends far beyond the neural tube defect [93]. Hydrocephalus associated with the spina bifida is caused by an obstruction of the cerebrospinal fluid flow from IV. ventricular or malformation of the cerebral aqueduct. Ventriculomegaly causes systematic destruction of white matter periventricular axons. Motor, sensory, visual as well as memory systems can be disrupted by stiffening of periventricular structures, including the corpus callosum and the fimbria-fornix pathway. Secondary changes occur in neuronal cell bodies and synapses, with neurons not undergoing apoptosis. The clinical syndrome of hydrocephalic brain dysfunction is caused by subcortical detachment. Some of the brain dysfunctions are reversible due to the restoration of blood flow through the brain and the normalization of the extracellular environment [94]. Diffusion tensor tractography revealed diffusion tensor characteristics of myelination impairment and pathological development as well as abnormalities in intrinsic axonal characteristics and extra-axonal space in the association pathways of children with the development of the spina bifida. The differences in the diffusion metrics are suggestive of the pathological white matter development and persistent degeneration with increased age [95]. Hydrocephalus exerts primarily a linear effect on cognitive and motor outcomes. Deviations from normative standards for volumes of frontal versus posterior regions are associated with reductions in intelligence quotient and fine motor dexterity [3]. With the exception of fine motor skills and small differences in memory and spatial domains, children with spina bifida and arrested or shunt-dependent hydrocephalus have similar neuropsychological profiles [96]. Patients with the spina bifida have extensive motor deficits in the trunk, upper limbs, eyes, and speech articulators that correspond to disorders characteristic for cerebellar lesions. The structure and function of the brain correlates with a number of motor dysfunctions. Motor learning is maintained in the spina bifida. Pathological are motor functions that require predictive signals and accurate calibration of motion time signs. This creates a deficit in the coordination of smooth movement and the cerebellar triad - ataxia, dysmetria, and dysarthria. Said motor function in individuals with the spina bifida is impaired phenotypically very similarly to cerebellar lesions. The age-based cerebellar motor plasticity is limited in individuals with this neurodevelopmental disorder [97]. Attention deficit reflecting problems with posterior attention systems involving orienting and arousal mediated by the mid-brain, with tectal anomalies directly correlated with the severity of difficulties with stimulus control. Procedural learning and attention functions involving sustained attention and persistence are relatively preserved, possibly reflecting less impairment in frontal-striatal regions and basal ganglia [3, 98]. Impairments in attentional disengagement in the spina bifida are not attributable to the general effects of hydrocephalus but are instead associated with specific midbrain anomalies that are part of the Chiari II malformation [99]. Development of individuals with severe forms of spina bifida throughout the lifetime is strongly affected by neurocognitive and movement disorders. Neurocognitive difficulties cause problems in keeping attention, learning, language comprehension and pragmatics as well as in assimilation of information. Procedural learning, word reading, vocabulary and social activation are usually not affected. Infants with spina bifida do not learn motor contingencies as easily or at the same rate as infants with typical development and are more likely to decrease motor responses when sensory feedback is absent. Intellectual disability is relatively infrequent, affecting perhaps 20–25% of people with the spina bifida and often after complications associated with the hydrocephalus. Status of cognitive functions in spina bifida patients is very variable as well as intelligence quotient scores. Impairment of intelligence and cognitive skills is mostly associated with presence of possible complications, such as hydrocephalus. Treatment of hydrocephalus is burdened with eventual complications as shunt

obstruction, malfunction or infections. Repeated shunt complications can have impact on intellectual performance. Environmental and socio-economic factors also influence achieved abilities. Motor and cognitive outcomes are directly related to level and extent of spinal lesion, what reflects the association of more severe brain pathology with higher level and bigger extent of defect [3, 100]. Executive function impairments potentially have a detrimental effect on the individual's emotional health and coping. Goal management training is a cognitive rehabilitation method for improving executive function. Compensatory intervention to manage executive dysfunction, effective and lasting benefits can be achieved in regard to aspects of perceived emotional health and coping [101].

5. Conclusion

The spina bifida involves congenital problems that result in abnormal bone formation in the spine and spinal cord. Closed spinal dysraphism is the mildest form of the neural tube defects which involves a hidden vertebral defect and minimal neural involvement. Open spinal dysraphism refers to a defect in which neural tissues communicate with the external environment such as meningocele and myelomeningocele. The incidence of neural tube defects has different rates among different ethnicity, geography, gender, and also countries. Various nutritional, maternal and environmental factors play a role in the etiology and pathogenesis of the spina bifida. However, the impact of these factors is ambiguous and further research is needed in this area.

Conflict of interest

The authors declare no conflict of interest.

Appendices and Nomenclature

T – thoracic vertebra.

L – lumbar vertebra.

WHO – World Health Organization.

EUROCAT – European network of population-based registries for the epidemiological surveillance of congenital anomalies.

C677T – variant of methylenetetrahydrofolate reductase.

Vangl1 – Vang-like protein 1.

Vangl2 – Vang-like protein 2.

Scrib – Scribble planar cell polarity protein.

Dact1 – Disheveled binding antagonist of β -catenin 1.

Celsr1 – Cadherin EGF LAG seven-pass G-type receptor 1.

Prickle1 – Prickle planar cell polarity protein 1.

Ptk7 – Protein tyrosine kinase 7.

Fuz – Fuzzy planar cell polarity protein.

Fzd6 – Frizzled class receptor 7.

Pax3 – Paired box 3.

Bmp2 – Bone morphogenetic protein 2.

Zic2 – Zic family member 2.

C57BL/6 – inbred strain of laboratory mouse.

MRI – magnetic resonance imaging.

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