Follow-Up of Newborns with Neural Tube Defects: A Single Center Experience

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ABSTRACT
OBJECTIVES: Neural tube defects, defined as the developmental malformations of the central nervous system, are seen in our country at a rate of three per thousand on average. Our study aims to retrospectively evaluate patients with neural tube defects hospitalized in our intensive care unit for the last decade.

STUDY DESIGN: Demographic data, prenatal-maternal characteristics, surgical operation time, intensive care follow-up, and long-term neurological-developmental results of these patients were also evaluated.

RESULTS: Eighty-six percent (n=31) of the patients were diagnosed prenatally. Arnold Chiari type 2 and type 3 malformation was 64% (n=23) and 3% (n=1), respectively. Eighty-nine (n=32) percent of these patients had meningomyelocele, whereas 90% (n=27) of them had defects in the lumbosacral region. The patients were operated on the median postnatal 9th day (4-27). Compared patients who were operated on in the 1st week to the patients operated on following the first week, any difference was not detected in terms of neuromotor and cognitive development, and urinary/stool incontinence frequency. Of 28 patients whose long-term follow-up was questioned, 7 (25%), 25 (89%), and 16 (57%) were able to walk, talk, and go to school along with being compatible with their peers, respectively.

CONCLUSION: We presented our center’s experience to make a significant contribution to the decrease of the neural tube defect frequency, which is commonly seen in our country compared to developed countries.

Keywords: Long-term outcomes, Meningomyelocele, Neural tube defects, Newborn

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Introduction

Neural tube defects (NTD) are defined as the developmental malformations of the central nervous system. More than 10 percent of neonatal deaths are derived from embryological malformation of the nervous system worldwide. The frequency of neural tube defects is approximately 1-11/1000 live births, 3/1000 in our country (1-3). NTD is classified into two groups anatomically depending on the insufficiency of closure of the head or vertebral column. Anencephaly (40%) and meningomyelocele (50%) are the most common types of NTD. Anomalies due to insufficiency of neurulation in the head localization are anencephaly, acrania, craniorachischisis, encephalocele, and iniencephaly. On the other hand, neural tube defects called spinal dysraphism associated with the vertebral column are meningocele, myelomeningocele, and myeloschisis. Additionally, spina bifida occulta, which is asymptomatic in the newborn period or presents with sacral dimples, hair in the sacral region, or curvature in the gluteal...
Data were expressed as mean ± standard deviation, median (minimum-maximum), percentages, and ratio. First of all, distribution analysis was made for the variables through the Shapiro-Wilk test. Mean and standard deviation values were recorded for normally distributed variables whereas median and minimum-maximum values were for non-normally distributed ones. Nonparametric Mann-Whitney U Test was performed to compare the groups. P values less than 0.05 were accepted as statistically significant.

Our study was also registered to the international clinical trials network (ClinicalTrials.gov/ NCT04760509).

Results

Demographic data of the patients included in the study are presented in Table I.

| Maternal and Natal Features |  
|----------------------------|---|
| Maternal age (years) (mean ± SD) | 28.6 ± 5* |
| Risk factors n (%) |  
| Gestational Diabetes | 2 (5.6) |
| Gestational Hypertension | 0 |
| Preeclampsia | 0 |
| Maternal hypothyroidism | 2 (5.6) |
| Planned pregnancy | 0 |
| Preconceptional folic acid use n (%) | 0 |
| Folic acid use during pregnancy n (%) | 34 (94.4) |
| Maternal drug use (Methotrexate) n (%) | 1 (2.8) |
| Female gender, n (%) | 19 (52.8) |
| Cesarean delivery, n (%) | 34 (94.4) |
| Gestational Age (weeks) (mean ± SD) | 38 ± 1.3* |
| Birth weight (grams) (mean ± SD) | 2975 ± 363* |
| Apgar (1st-5th min) (min-max) | 8 (5-9) – 9 (7-10)† |

*Mean ± Standard Deviation, † Median (min-max) yazısı eklenmelidir

Thirty-one (86%) patients were diagnosed with NTD over the antenatal period, while 5 (14%) were diagnosed after delivery. In those patients that were diagnosed during the antenatal period, the mean time of the diagnosis was 21±5 weeks.

Thirty-three out of 36 (92%) patients had a defect in the lumbosacral region, 1 (3%) in the thoracic, and 2 (6%) in the cervical regions.

The defect at birth was intact and perforated in 30 (83%) and 6 (17%) patients, respectively. In any patient, meningitis was not observed in the preoperative period. Patients whose bladder was perforated due to the risk of meningitis were managed antibiotic therapy for 7-10 days however any antibiotic therapy was not started for the patients whose bladder was intact.

Hydrocephalus was detected in a total of 25 (69.4%) patients, and they all underwent ventriculoperitoneal (V-P) shunt operations. The day of the operation was determined as the median postnatal 24th day (11-43).
Arnold Chiari type 2 and type 3 malformations were detected in 23 (64%) patients and 1 (3%) patient, respectively. Twenty-one (91%) patients with type 2 malformations were diagnosed in the antenatal period.

Any foot movement was not observed in 26 (72%) patients during the intensive care unit follow-up. Twenty-five (69%) of the patients were detected with urinary incontinence following the observation of “globe vesicle” and 23 (64%) were detected with stool incontinence along with the absence of anal tonus.

Twelve (33%) patients were operated on within the first week whereas the remaining 24 (67%) patients were after the first week. No statistically significant difference was detected between the two groups during the long-term follow-up in terms of foot movement, walking ability, urinary-stool incontinence as well as the duration of hospitalization (p values: 0.195; 0.491; 0.313; 0.226; 0.314, respectively). The day of the operation was the median postnatal 9th day (4-27).

Neural tube defect types and long-term outcomes are shown in Table II.

Thirty-three (92%) patients were discharged, and the other three (8%) patients passed away. Sepsis and pneumonia were the primary reasons behind the mortality in the postoperative period. Meningomyelocele and tonsillar herniation findings were obtained in 3 patients and 1 patient, respectively. The duration of hospitalization was detected as a median of 20 (8-63) days.

The parents of 28 patients were contacted via their phone numbers. The mean age of the patients was 54±19 months (18-89 months). It was stated by the parents of the patients that 7 patients were able to walk. On the other hand, in the cognitive inquiry, 16 (57%) and 25 (89%) patients learned to be compatible with their peers and to be able to talk, respectively. Besides, 19 (73%) of them had clean intermittent catheterization by their families due to neurogenic bladder dysfunction, and 1 (4%) patient received renal replacement (dialysis) therapy for chronic kidney failure were other findings.

### Table II: Neural tube defect types and long-term results (n=36)

| Defect Type          | n (%)                                      |
|----------------------|--------------------------------------------|
| Meningocele (n=3)    |                                            |
| Stool incontinence, neurogenic bladder, unable to walk | 0                                           |
| Neuro-developmental retardation compared to peers | 3 (100)                                    |
| Meningomyelocele (n=32) |                                        |
| Stool incontinence | 22 (69)                                    |
| Neurogenic bladder   | 18 (56)                                    |
| Unable to walk       | 20 (63)                                    |
| Neuro-developmental retardation compared to peers | 11 (34)                                    |
| Encephalocele (n=1)  |                                            |
| Stool incontinence, neurogenic bladder, unable to walk, mental-motor retardation | 1 (100)                                    |

Discussion

The incidence of NTD differs regarding the presence of some factors such as geographical location, the level of development, and the sociocultural status of the family (5).

For a decade a total of 43 infants were diagnosed with NTD and received inpatient treatment in the NICU. The number of births in our hospital was 22,510 during this period however the frequency of NTD in live births was approximately 1.9 per thousand. In other studies, which have been conducted in our country, it was indicated that the frequency of NTD was between 3 and 5.8 per thousand live births (5,6). Similarly, a study conducted by Celik et al. from our hospital revealed that the rate of NTD was detected to be 2.26 per thousand (5). We consider that the reason behind why the frequency of NTD decreased was the fact that some of the patients with the prenatal diagnosis were referred to other centers due to the increase in the number of centers with perinatology-neonatology in our country, rather than a real decrease.

NTDs are a group of malformations, which present themselves through multifactorial etiology, notably both genetic and environmental factors, including nutrition. The deficiency of folic acid at the time of conception and in the period following the formation of organs is indicated as the environmental factor, which is considered to be responsible for the malformation (6-9). The study conducted by Celik et al. between the years 1995 and 2009 indicated that the rate of folic acid use before and during pregnancy was 11.1% whereas this rate increased up to 94% solely during the period of pregnancy in our study (5). This result reveals that the rate of folic acid use during pregnancy in our country increases; however, the rate of planned pregnancy and preconception folic acid use is still low.

Folic acid functions in single-carbon transfer reactions, and it exists in a variety of chemical forms. Folate coenzymes (dihydro and tetrahydrofolate) are involved in not only DNA but also purine syntheses, and amino acid conversions. Conversion of homocysteine to methionine provides methionine for the synthesis of S-adenosyl methionine. It is a well-
known fact that mutations in genes encoding enzymes in homocysteine metabolism play a role in the pathogenesis of NTD (10,11). One of the reviews had said that a role in preventing NTDs with exogenous folic acid. Exogenous folic acid probably prevents many NTDs by regulating epigenetic modifications (methylation) and/or cell proliferation (synthesis of purines). On the other hand, spontaneous elimination of defective embryos, through exacerbation of embryonal NTDs and excess miscarriages, is a more controversial hypothesis of the action of folic acid supplementation (12). Methotrexate, a dihydrofolate reductase inhibitor, is likely to cause NTD by antagonizing folic acid when used perpetually throughout pregnancy, particularly during embryogenesis and organogenesis. One patient’s mother had methotrexate use. Therefore, high-dose folic acid supplementation is recommended for mothers who need to use methotrexate constantly (13). We considered that the use of methotrexate may have led to NTD in this patient.

It was proven that hyperglycemia raises the levels of free radicals, which are known as both “highly reactive” oxygen and nitrogen types. Therefore, the emerging embryopathy leads to NTD damage throughout the neurulation stage in the central nervous system, thereby increasing the risk of NTD (14). The mothers of two patients in our study were diagnosed with uncontrolled gestational diabetes, and as a result, we considered that these patients may have developed embryopathy due to hyperglycemia and NTD.

Evaluating the fetal cranium and spinal cord via detailed ultrasonography in patients who had suspected findings as a consequence of the screening test helps make the definitive prenatal diagnosis. Eighty-six percent of our patients were diagnosed through detailed ultrasonography in the antenatal period, at an average of 21 weeks.

Fetuses diagnosed before 26 weeks had meningomyelocele repair in the antenatal period in a large-scale MOMS study abroad, including 200 patients. This study revealed that both motor and mental development in the postnatal 30th week were found to be better, but maternal and fetal risks of antenatal surgery were reported. So, more studies are required (15,16). The findings of both studies, which are the follow-up of this study in question support the data (17,18). In the second analysis of the MOMS study (MOMS2), which was evaluated almost at the 30th months, the physical functionality benefits of antenatal repair for myelomeningocele reported at 30 months continued into school ages between 5 and 10, and that antenatal repair was beneficial were detected in. These findings demonstrate how antenatal repair of myelomeningocele is beneficial for school-aged children (19). In our hospital and, to the best of our knowledge, in our country, there is not any experience regarding the NTD repair in the fetal period. For this reason, the operations of the patients with NTD should be performed in the early postnatal period.

The close of the defect within the postnatal 48-72 hours is recommended in the studies regarding this matter (20-25). However, in our study, the median operation days of the patients were postnatal 9th days (minimum 4th and maximum 27th days). When evaluating the patients by classifying them into two groups, in the postnatal first week and after the first week, about their operation time, no statistical difference was detected in terms of foot movement, walking ability, urinary/stool incontinence as well as hospitalization duration. Meticulous patient care in the preoperative period in our intensive care unit along with undeformed sac and differences of the location of the defect and also the deficiency of the number of the patients as well as the development of neural tissue loss of the patients as from the antenatal period may have contributed to this result. According to the studies conducted in developed countries, operation in the postnatal first 48-72 hours is recommended to reduce the risks that patients with meningomyelocele may particularly face, such as neural tissue loss, infection, and neurological-developmental issues (15,16). We could not evaluate whether the early operation affected prognosis since there was no patient operated on in the first 48-72 hours in our study.

V-P shunt was inserted in 84% and 86% of the patients with NTD in the studies conducted by Oakeshott and Bowman et al., respectively (26,27). However, in our study, 69.4% of the patients were diagnosed with hydrocephalus and a V-P shunt was inserted. All patients that were inserted V-P shunt due to hydrocephalus were meningomyelocele patients. The reason why the rate in our study was found to be low may have derived from the sac size differences in patients with NTD. These results can vary based on the anatomic features of the patients along with patient selection criteria.

Arnold Chiari type 2 and type 3 malformations were detected in 23 (64%) patients and 1 (3%) patient, respectively. Arnold Chiari type 3 malformation, detected and operated on merely in one of the patients, is a very rare condition and can be fatal if left untreated (28).

Even though Arnold Chiari type 2 malformation accompanies most meningomyelocele cases, it may be diagnosed as of the antenatal period (29-31), and it is also characterized by the collapsed appearance of bilateral frontal bone on ultrasonography (lemon sign), posterior cranial fossa smaller than its normal volume, compressed cerebellum (banana sign), and obliteration of the 4th ventricle and the "cisterna magna" (32).

The whole pregnant women whose babies are detected to have an anomaly prenatally in our hospital have been discussed in the multidisciplinary perinatology council and therapeutic abortion option is offered to these pregnant women with a high risk of severe prognosis like a high level of mental-motor retardation, which is incompatible with life. Some patients involved in our study and diagnosed during the antenatal period were referred in the later stages of pregnancy. All
patients that were referred within the first two or three months of pregnancy and that had severe defects were offered to terminate their pregnancy. Besides, detailed information regarding the possible prognosis expectation was given after the multidisciplinary perinatology-neonatology council gathering, however, the rate of the people who decided to terminate their pregnancy was found to be quite lower.

Fourteen percent of the patients were diagnosed in the postnatal period whereas the remaining 86% of the patients were diagnosed in the antenatal period. However, pregnant women were determined not to terminate their pregnancy. It is no doubt that there are many reasons why pregnant women did not accept the offer of the termination of pregnancy (therapeutic abortion) in which sociocultural educational levels of the families or religious background can be involved. On the other hand, it is also probable to come across such a kind of circumstance in developed countries to a lesser extent. If gynecologists, neurosurgeons, and pediatric neurologists explain possible risks and prognosis expectations regarding severe neuro-motor and developmental issues that can be come across in the long-term follow-up of the patients with NTD may have a positive impact on the decisions of the families and therefore a decrease in the natality of the babies with NTD may be observed.

Twenty-eight out of 36 patients in our study were asked about their developmental stages on the phone, and it was learned that merely 7 (25%) patients were able to walk and 19 (68%) were performed clean intermittent catheterization due to urinary incontinence. Lumbosacral defect in particular manifests itself with the loss of motor function in the advanced period, urinary/anal sphincter dysfunction, and neurogenic bladder, and our patients presented similar results (26). Two separate studies conducted in the years of 2003 and 2011 revealed that 90-95% of the patients followed due to the presence of NTD had neurogenic bladder during their long-term follow-up (26,29). Nevertheless, in our study, we detected 19 (68%) patients with a neurogenic bladder.

It was reported in a study that 75% of patients with meningomyelocele and 60% of these patients with VP shunts had normal intelligence (IQ>80) (13). We made a phone call with our patients’ families due to the pandemic, and the developmental stages and school success of the patients and whether they received special education or not were questioned, we learned that 57% of the patients were able to go to school without any need for special education. We concluded that slightly more than half of the patients had intelligence compatible with their peers. The reason why the children that need special education have mental-motor retardation is mostly hydrocephalus and severe malformation of the central nervous system. As the child grows, the isolation from society and the lack of stimuli due to the inability to walk or urinary-stool incontinence can lead to negative results in terms of the development of the children.

Considering the limitations of our study, the first one was the retrospective design of our study. Moreover, we could not able to invite our patients to the hospital, and therefore their current neurological examinations and age-appropriate developmental screening tests could not be performed. For this reason, we had to ask only about their developmental stages and school success on the phone. The second limitation was, on the other hand, the deficiency in the number of patients, and therefore we could not be able to receive information from all the patients regarding their situations. If we reached all parents, there might be some differences in the long-term outcomes.

Conclusion

Neural tube defects are central nervous system malformations that can occur depending upon some genetic and environmental factors, the etiology of which has not been still clearly understood yet, that can be diagnosed easily in the antenatal follow-up, and that can vary in severity from mild to severe. Planned pregnancies, regular follow-up of the pregnancy, questioning the additional diseases of the mother during the follow-up period and keeping them under control, evaluating the impacts of the drugs on the fetus used by the mother before and throughout pregnancy, increasing the folic acid intake from the food, and receiving supplemental folic acid as of the preconception period are going to increase the frequency of this malformation.

Termination of pregnancy in severe cases diagnosed in the prenatal period is the most rational approach to prevent these individuals from leading a difficult life with their severe disabilities and to prevent the burden they impose on their families and society. For this reason, it is essential to provide the most precise diagnosis and prognosis in the prenatal period. Starting fetal surgical intervention in our country, which can be made in the prenatal period, and the referral of the patients to the centers in which there are experienced perinatology, neonatology, neurosurgery, and pediatric neurology specialists following prenatal diagnosis along with early surgical repair in the postnatal period are going to contribute to reducing neurological-developmental risks, which may be come across in the long-term period. We presented our center’s experience to make a significant contribution to the decrease of the neural tube defect frequency, which is commonly seen in our country compared to developed countries.

Ethics approval and consent to participate: We have a statement about consent for using data. The study was reviewed and approved by the ethics committee of Hacettepe University Non-Interventional Ethics Committee. Ethics approval reference number: 2020/20- 89 All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request. / The datasets and code used and/or analyzed
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References

1. Au KS, Ashley-Koch A, Northrup H. Epidemiologic and genetic aspects of spina bifida and other neural tube defects. Dev Disabil Res Rev. 2010;16(1):6-15. Doi: 10.1002/ddrr.93. PMID: 20419766, PMCID: PMC3053142.

2. Boulet SL, Yang Q, Mai C, Kirby RS, Collins JS, Robbins JM, et al. National Birth Defects Prevention Network. Trends in the postfortification prevalence of spina bifida and anencephaly in the United States. Birth Defects Res A Clin Mol Teratol. 2008;82(7):527-32. Doi:10.1002/ brda. 20468. PMID: 18481813.

3. Tuncbilek E. Türkiye’deki yüksek nöral tüp defektleri ve önleme ile yapılabilecekler. Çocuk Sağlığı ve Hast Derg. 2004;47:79-84.

4. Tuite GF, Thompson DNP, Austin PF, Bauer SB. Evaluation and management of tethered cord syndrome in occult spinal dysraphism: Recommendations from the international children's continence society. Neurolour Urodyn. 2018;37(3):890-903. Doi: 10.1002/nau.23382. PMID: 28792087.

5. Çelik HT, Meliboyev M, Nizamov İ, Yurdakök M. Meningomyelocele ve Arnold-Chiari malformasyonu: 45 vakânın değerlendirilmesi. Çocuk Sağlığı ve Hastalıklar Dergisi. 2010;53(1):10-6.

6. Czeizel AE, Dudás I, Vereczkey A, Bănhidy F. Folate deficiency and folic acid supplementation: the prevention of neural-tube defects and congenital heart defects. Nutrients. 2013;5(11):4760-75. Doi: 10.3390/nu5114760. PMID: 24284617, PMCID: PMC3847759.

7. Liu J, Xie J, Li Z, Greene NDE, Ren A. Sex differences in the prevalence of neural tube defects and preventive effects of folic acid (FA) supplementation among five counties in northern China: results from a population-based birth defect surveillance programme. BMJ Open. 2018; 8(11):e022565. Doi: 10.1136/bmjopen-2018-022565. PMID: 30413501, PMCID: PMC6231556.

8. Lee S, Gleeson JG. Closing in on mechanisms of open neural tube defects. Trends Neurosci. 2020;43 (7): 519-32. Doi: 10.1016/j.tins.2020.04.009. PMID: 32423763, PMCID: PMC7321880.

9. Avagliano L, Massa V, George TM, Qureshy S, Bulfiambante GP, Finnell RH. Overview on neural tube defects: From development to physical characteristics. Birth Defects Res. 2019;111(19):1455-67. Doi: 10.1002/bdr2. 1380. PMID: 30421543, PMCID: PMC6511489.

10. Bailey LB, Rampersaud GC, Kauwell GP. Folic acid supplements and fortification affect the risk for neural tube defects, vascular disease and cancer: evolving science. J Nutr. 2003;133(6):1961S-1968S. Doi: 10.1093/jn/133.6. 1961S. PMID: 12771346.

11. Imbard A, Benoist JF, Blom HJ. Neural tube defects, folic acid and methylation. Int J Environ Res Public Health. 2013;10(9):4352-89. Doi: 10.3390/ijerph10094352. PMID: 24048206, PMCID: PMC3799525.

12. van Gool JD, Hirche H, Lax H, De Schaepprijver L. Folic acid and primary prevention of neural tube defects: A review. Reprod Toxicol. 2018;80:73-84. Doi: 10.1016/j.reprotox.2018.05.004. PMID: 29777755.

13. Duru S, Türkoğlu E. Miyelomeningosel. Türk Nöroşirürji Dergisi. 2013;23:226-32.

14. Turhan E, Varol FG, Gurkan H, Sayin CN. Complex nature of neural tube defects: a regional experience. Gynecol Obstet Reprod Med. 2018;24(3):119-23. Doi: 10.21613/ GORM.2017.769.

15. Adzick NS, Thom EA, Spong CY, Brock JW 3rd, Burrows PK, Johnson MP, et al; MOMS Investigators. A randomized trial of prenatal versus postnatal repair of myelomeningocele. N Engl J Med. 2011;364(11):993-1004. Doi: 10.1056/NEJMoa1014379. PMID: 21306277, PMCID: PMC3770179.

16. Elbabaa SK, Gildehaus AM, Pierson MJ, Albers JA, Vlastos EJ. First 60 fetal in-utero myelomeningocele repairs at Saint Louis Fetal Care Institute in the post-MOMS trial era: hydrocephalus treatment outcomes (endoscopic third ventriculostomy versus ventriculo-peritoneal shunt). Childs Nerv Syst. 2017;33(7):1157-68. Doi: 10.1007/ s00381-017-3428-8. PMID: 28470384.

17. Reece EA. Obesity, diabetes, and links to congenital defects: a review of the evidence and recommendations for intervention. J Matern Fetal Neonatal Med. 2008;21(3):173-80. Doi: 10.1080/14767050801929885. PMID: 18297572.

18. Moldenauer JS, Yang Q, Mai C, Kirby RS, Collins JS, Robbins JM, et al. National Birth Defects Prevention Network. Trends in the postfortification prevalence of spina bifida and anencephaly in the United States. Birth Defects Res A Clin Mol Teratol. 2008;82(7):527-32. Doi:10.1002/ brda. 20468. PMID: 18481813.

19. Houtrow AJ, MacPherson C, Jackson-Coty J, Rivera M, Flynn L, Burrows PK, et al. Prenatal repair and physical functioning among children with myelomeningocele: a secondary analysis of a randomized clinical trial. JAMA Pediatr. 2021;175(4):e205674. Doi: 10.1001/jamapediatrics.2020.5674. PMID: 33555337, PMCID: PMC7871205.
20. Gaskill SJ. Primary closure of open myelomeningocele. Neurosurg Focus. 2004;16(2):E3. Doi: 10.3171/foc.2004.16.2.4. PMID: 15209486.

21. Biggio JR Jr, Wenstrom KD, Owen J. Fetal open spina bifida: a natural history of disease progression in utero. Prenat Diagn. 2004;24(4):287-9. Doi: 10.1002/pd.853. PMID: 15065103.

22. Burke R, Liptak GS; Council on Children with Disabilities. Providing a primary care medical home for children and youth with spina bifida. Pediatrics. 2011;128(6):e1645-657. Doi: 10.1542/peds.2011-2219. PMID: 22123894.

23. Cavalheiro S, da Costa MDS, Moron AF, Leonard J. Comparison of prenatal and postnatal management of patients with myelomeningocele. Neurosurg Clin N Am. 2017;28(3):439-48. Doi: 10.1016/j.nec.2017.02.005. PMID: 28600017.

24. Copp AJ, Stanier P, Greene ND. Neural tube defects: recent advances, unsolved questions, and controversies. Lancet Neurol. 2013;12(8):799-810. Doi: 10.1016/S1474-4422(13)70110-8. PMID: 23790957, PMCID: PMC4023229.

25. Blount JP, George TM, Koueik J, Iskandar BJ. Concepts in the neurosurgical care of patients with spinal neural tube defects: An embryologic approach. Birth Defects Res. 2019;111(19):1564-76. Doi: 10.1002/bdr2.1588. PMID: 31576681.

26. Oakeshott P, Hunt GM. Long-term outcome in open spina bifida. Br J Gen Pract. 2003;53(493):632-6. PMID: 14601340.

27. Okurowska-Zawada B, Kułak W, Otapowicz D, Sienkiewicz D, Paszko-Patej G, Wojtkowski J. Quality of life in children and adolescents with cerebral palsy and myelomeningocele. Pediatr Neurol. 2011;45(3):163-8. Doi: 10.1016/j.pediatrneurol.2011.04.006. PMID:21824563.

28. Ivashchuk G, Loukas M, Blount JP, Tubbs RS, Oakes WJ. Chiari III malformation: a comprehensive review of this enigmatic anomaly. Childs Nerv Syst. 2015;31(11):2035-40. Doi: 10.1007/s00381-015-2853-9. PMID: 26255148.

29. Bowman RM, McLone DG, Grant JA, Tomita T, Ito JA. Spina bifida outcome: a 25-year prospective. Pediatr Neurosurg. 2001;34(3):114-20. Doi: 10.1159/000056005. PMID: 11359098.

30. Greene ND, Copp AJ. Neural tube defects. Annu Rev Neurosci. 2014;37:221-42. Doi: 10.1146/annurev-neuro-062012-170354. PMID: 25032496, PMCID:PMC 4486472.

31. McLone DG, Dias MS. The Chiari II malformation: cause and impact. Childs Nerv Syst. 2003;19(7-8):540-50. Doi: 10.1007/s00381-003-0792-3. PMID: 12920543.

32. Bulas D. Fetal evaluation of spine dysraphism. Pediatr Radiol. 2010;40(6):1029-37. Doi: 10.1007/s00247-010-1583-0. PMID: 20432022.