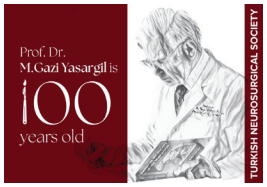
Turk Neurosurg 35(4):603-608, 2025
DOI: 10.5137/1019-5149.JTN.47393-24.2

Original Investigation

Pediatrics

Received: 20.08.2024
Accepted: 16.10.2024
Published Online: 25.06.2025



Epilepsy in Children with Myelomeningocele: A Single-Center Retrospective Cohort Study and Review of the Literature

Esra ULGEN TEMEL[1], Deniz MENDERES[2], Ayse SERDAROGLU[3], Ebru ARHAN[3]

[1]Duzce Atatürk State Hospital, Division of Child Neurology, Duzce, Türkiye
[2]University of Health Sciences, Etlik City Training and Research Hospital, Division of Child Neurology, Ankara, Türkiye
[3]Gazi University Faculty of Medicine, Department of Child Neurology, Ankara, Türkiye

This study has been presented as a poster presention at the 6th Spring Pediatrics Days between 10 and 12 March 2022, Adana, Türkiye

Corresponding author: Ebru ARHAN ✉ petekarhan@yahoo.com.tr

ABSTRACT

AIM: To examine the prevalence of epilepsy and other associated cortical abnormalities in patients with Myelomeningocele (MMC), and to present our findings along with a review of the literature.

MATERIAL and METHODS: A retrospective chart review was conducted with MMC patients followed in our pediatric neurology outpatient clinic between 2015 and 2020.

RESULTS: The study included a total of 23 patients ranging in age from 7 months to 19 years with a median follow-up period of 36 months. The frequency of epilepsy was 43.5% (n=10). Hydrocephalus was present in 20 patients (87%) patients, and 18 patients (78.3%) had concomitant central nervous system anomalies. Epilepsy was diagnosed in 52.6% of the patients with a ventriculoperitoneal shunt but none of those without a shunt.

CONCLUSION: Our study revealed a high incidence of epilepsy among patients with MMC, in contrast to the available literature. As the life expectancy of patients with MMC continues to increase, secondary clinical manifestations such as epilepsy may become more evident. Furthermore, most research on the prevalence of epilepsy and seizures among individuals with MMC was conducted approximately two decades ago. Further studies should examine the changing incidence.

KEYWORDS: Myelomeningocele, Epilepsy, Hydrocephalus, Ventriculoperitoneal shunt, Children

INTRODUCTION

Spinal dysraphism is a term used to describe a wide range of anomalies in which the neural, vertebral, and mesenchymal tissues of the spine fail to close to varying degrees. Myelomeningocele (MMC) and myeloschisis are examples of open spinal dysraphisms not covered by skin (9). The incidence of MMC is approximately 1 in 1000 live births. Although the exact mechanism of their formation is unknown, the etiology is believed to be multifactorial, and most cases are sporadic. Possible risk factors include folate metabolism disorders (maternal folate deficiency, *MTFHR* mutation), certain genetic disorders (trisomy 18, Meckel-Gruber syndrome, Lehman syndrome), maternal diabetes, family history, and certain teratogenic agents (valproic acid, carbamazepine, vitamin A) (9,25).

Approximately 85% of patients with MMC have concomitant hydrocephalus. Hydrocephalus may not always be evident at birth, but a shunt is usually required within the first week of life. The prevalence of shunt placement due to hydrocephalus in patients with MMC was reported to be 81% (24). Many factors are involved in the development of hydrocephalus in these patients. The most important of these is Chiari type II malformation (CM-II), which is present in approximately 80% of children with MMC (3,13). CM-II is characterized by cer-

Esra ULGEN TEMEL : 0000-0002-0841-5935
Deniz MENDERES : 0000-0002-0485-0593
Ayse SERDAROGLU : 0000-0002-2180-0213
Ebru ARHAN : 0000-0001-8950-8588

ebellar vermis and herniation of the fourth ventricle through the foramen magnum, brainstem kinking, tectal beaking, and a small posterior cranial fossa. CM-II may also be accompanied by cerebral abnormalities such as polymicrogyria, cortical heterotopia, corpus callosum dysgenesis, and large massa intermedia (17).

Children with MMC may also develop seizures during follow-up, and accompanying cortical abnormalities are implicated as the etiology of seizures in approximately 20% of these children (9). The reported prevalence of seizures in MMC patients is 15-29% for those with shunts and 2-19.5% among those without shunts. The prevalence of epilepsy is approximately 20% (12,18).

In this study, we aimed to investigate the frequency of epilepsy and other concomitant cortical abnormalities in patients with MMC and present our findings with a review of the literature.

MATERIAL and METHODS

A retrospective chart review of all patients diagnosed with MMC between 2015 and 2020 was conducted in the pediatric neurology outpatient clinic of Gazi University Hospital, a tertiary pediatric referral in Ankara. Data extracted from the hospital records included demographic characteristics, brain imaging results, history of epilepsy, and electroencephalogram (EEG) results. Of 27 patients identified retrospectively, 4 were excluded due to missing data (Figure 1). Statistical analyses were performed using SPSS for Windows, version 23.0 software (IBM SPSS Inc., Chicago, IL). Continuous variables were compared using the Mann-Whitney U test and categorical variables were compared using the chi-square or Fisher's exact test depending on the expected values. Results were considered statistically significant at $p<0.05$. Continuous variables were expressed as mean, standard deviation, and range, and categorical variables as number and percentage. The study was conducted in accordance with the Declaration of Helsinki. Ethics committee approval was obtained from the non-interventional clinical research ethics committee of our center (research code number 2024-541).

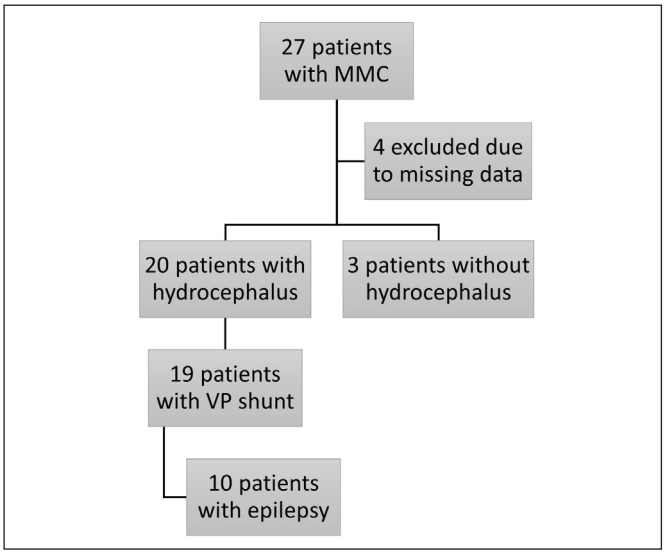


Figure 1: Flowchart of patients with myelomeningocele and epilepsy.

RESULTS

Twenty-three patients ranging in age from 7 months to 19 years (mean, 76.7 ± 71.9 months) met the inclusion criteria. Twelve (52.2%) of these patients were female, and the median follow-up time was 36 months (range, 3-216 months). The prevalence of epilepsy was 43.5% (n=10) overall. Ventriculoperitoneal (VP) shunts were required in all patients with hydrocephalus except one. The patients' data are summarized in Table I.

Central nervous system (CNS) abnormalities other than hydrocephalus included CM-II in 10 patients, corpus callosum agenesis/dysgenesis in 8 patients, periventricular gliosis in 2 patients, and cerebral atrophy in 2 patients. Other concomitant abnormalities were Chiari type I malformation, rhombencephalosynapsis, nodular gray matter heterotopia, interdigitation of the cerebral gyri, frontal encephalomalacia, interhemispheric cyst, and right cerebellar hemisphere hypoplasia.

The EEG results of the patients are presented in Table II. Of 10 patients with epilepsy, 40% were using two or more antiseizure drugs and 70% were using valproic acid as an antiseizure drug, either as polytherapy or monotherapy. Four of our patients with epilepsy required multiple shunt replacements. Two of these patients could be managed with more than one antiseizure medication. Epilepsy was not significantly associated with duration of follow-up or age.

When patients with and without VP shunt were compared in terms of the rates of concomitant CNS abnormalities and epilepsy, we noted that among patients with a shunt, 52.6% (n=10) had epilepsy and 89.5% (n=17) had concomitant CNS abnormalities (Figure 2). Of the patients without shunts, 25% had concomitant CNS abnormalities and none had epilepsy.

CNS abnormalities were significantly more common among patients with shunt and hydrocephalus ($p=0.004$ and $p<0.001$, respectively). All patients with epilepsy had VP shunt and concomitant CNS abnormalities (Figure 2).

Table I: Demographic and Clinical Data of the Patients

Characteristic	Value
Age (months) (mean ±SD)	76.7±71.9 (7-228)
Sex (female), n (%)	12 (52.2)
Follow-up period (months) (mean ±SD)	44.7±44.7 (3-216)
Epilepsy, n (%)	10 (43.5)
Hydrocephalus, n (%)	20 (87)
VP shunt, n (%)	19 (82.6)
Additional CNS abnormality, n (%)	18 (78.3)
Total, n (%)	**23 (100.0)**

***VP:** Ventriculoperitoneal, **CNS:** Central nervous system*

Table II: Electroencephalogram (EEG) Findings of the Patients

EEG Findings	n (%)
Normal	5 (38.5)
Multifocal epileptiform discharges	3 (23.1)
Focal epileptiform discharges	4 (30.8)
Cerebral dysfunction	1 (7.7)

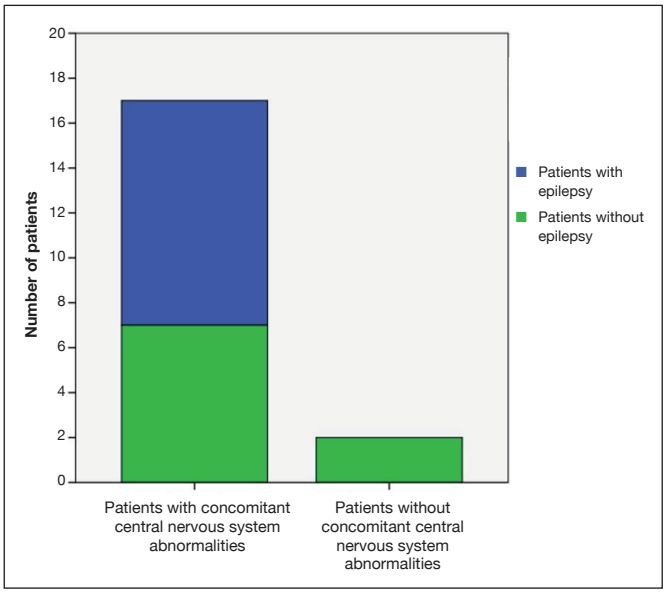


Figure 2: Distribution of shunted patients with and without epilepsy according to the presence of concomitant central nervous system abnormalities.

DISCUSSION

The most common conditions associated with MMC are CM-II and hydrocephalus (13). In previous studies, the frequency of seizures was found to be 17-48.5% in patients with hydrocephalus, regardless of the etiology (15,19). In our study, epilepsy was observed at a rate of 50% in the group with hydrocephalus. The frequency of seizures is higher in conditions associated with structural causes and cases of hydrocephalus that develop as a sequel of bacterial meningitis compared to hydrocephalus associated with MMC (15). The mere existence of a shunt raises the likelihood of seizures in individuals with MMC. This is believed to be related to minor cortical damage caused during the shunt procedures. Seizures may also be triggered by shunt infection or malfunction. Although provoked seizures are more frequently linked to shunt-related disorders, there have been reports suggesting shunt presence may be linked to the development of epilepsy (8,14,15). According to classical knowledge, a seizure provoked by a transient factor that temporarily lowers the seizure threshold in a normal brain does not contribute to a diagnosis of epilepsy (10). However, in a brain exhibiting invasive and structural changes, differentiating a provoked seizure is often challenging. In a recent study, the association of shunt-related provoking factors and epilepsy development was noted, given that preventing shunt malfunctions and infections may result in an improved long-term prognosis for seizure prevention (14).

Compared to the literature, the prevalence of epilepsy in shunted patients (52.6%) and in all patients with MMC (43.5%) was higher in our study. This may be related to the fact that seizures can now be detected more easily and in a shorter time with advances in technology and increased accessibility. Another reason may be that our center is a tertiary referral center and thus receives more complicated cases. Population studies on this subject will help determine more accurate rates. In addition, most studies on the incidence of epilepsy and seizures in patients with MMC were conducted with data collected 2-3 decades ago. Over time, patients with more severe malformations are likely to experience secondary clinical manifestations such as epilepsy more frequently as care improves and life expectancy increases.

The incidence of seizures is low in patients with MMC without VP shunt, whereas seizures and epilepsy are more common in patients with VP shunt (8). In our study, none of the patients without VP shunt were diagnosed with epilepsy. The higher frequency of epilepsy in shunted patients may be the result of adverse effects of the drainage system, such as brain damage created during the procedure, CNS infections, and increased intracranial pressure due to dysfunction (14,21). Four of our patients who were diagnosed with epilepsy required several shunt replacements. In a study conducted on patients with MMC, the overall prevalence of epilepsy was found to be 31%. This rate was 10% in patients who did not require any shunt revision and increased to 58% after one revision and 67% after two or more revisions (21). Studies in the literature (indexed in PubMed) examining the coexistence of MMC with seizures and/or epilepsy are summarized in Table III.

It is believed that in MMC patients with epilepsy, the VP shunt could not be the sole causative factor, and concomitant CNS abnormalities are also involved in epileptogenesis (14,27,30). In our study, 9 of 10 patients with epilepsy underwent cranial imaging (CT/MRI). Of those, 7 had CM-II, 3 had corpus callosum agenesis/dysgenesis, 2 had encephalomalacia/gliosis, and cerebral atrophy, interhemispheric cyst, and rhombencephalosynapsis were each detected in 1 patient. As seen in our study, not all CNS defects in MMC patients are epilepsy-related. It is clear that epilepsy in these children has a multifactorial etiology, with no single cause.

Current studies showing that the incidence of MMC has decreased over time (7,20). This may be largely due to greater awareness of modifiable causes, which resulted in increased use of folic acid during pregnancy and careful antenatal follow-up of mothers using antiseizure drugs. In addition, the life expectancy of these patients is longer due to early intervention and good care. In one study comparing MMC patients born in the periods of 1971-1981 and 1996-2006, the incidence of MMC was found to be 2.5 in 10,000 births vs. 1.1 in 10,000 births, respectively. However, one of the most striking findings reported in the study was the mortality rates, which were found to be 18% and 0%, respectively. No differenc-

Table III: Studies Evaluating the Coexistence of Epilepsy and/or Seizures in Patients with Myelomeningocele

Article Author, year	MMC (n)	Hydrocephalus (n)	VP shunt (n)	CNS malformations or disorders (n)	Seizures (n)	Epilepsy (n)
Noetzel and Blake, 1991 (18)	140	109	109	6	24 (5 with CNS malformation, 18 shunted)	N/A
Danzer et al., 2010 (8)	48	N/A	24	N/A	8 (6 shunted)	3 (shunted)
Amaral et al., 2019 (1)	15	N/A	13	N/A	6	N/A
Klepper et al., 1998 (16)	44	44	N/A	N/A	N/A	4
Spazzapan and Velnar, 2021(26)	20	N/A	13	N/A	4	N/A
Bartoshesky et al., 1985 (2)	111	106	98	14 (shunted)	25 (24 shunted)	N/A
Talwar et al., 1995 (27)	81	66	66	63	17	14 (12 with CNS pathology)
Okurowska-Zawada et al., 2007 (21)	86	70	49	N/A	N/A	27
Bowman et al., 2001 (4)	71	N/A	61	N/A	16 (all shunted)	N/A
Brown et al., 2008 (5)	35	N/A	31	18	31	N/A
Wasserman and Holmbeck, 2016 (29)	95	N/A	79	N/A	13	N/A
Chadduck and Adametz, 1988 (6)	190	N/A	144	N/A	33 (32 shunted)	N/A
Hack et al., 1990 (11)	346	346	346	N/A	51	N/A
Karakas et al., 2022 (14)	122	108	98	57 (cerebellar malformation)	24	15
Yoshida et al., 2006 (30)	6	N/A	N/A	5	N/A	0
Tully et al., 2016 (28)	78	78	67	78	N/A	5
Persson et al., 2005 (23)	84	84	N/A	N/A	N/A	8
Persson et al., 2006 (22)	44	44	N/A	N/A	N/A	5

MMC: *Myelomeningocele,* ***CNS:*** *Central nervous system,* ***N/A:*** *Not available*

es were observed in terms of hydrocephalus or CM-II (20). In our study of patients from the years 2015-2020, the proportions of patients with hydrocephalus, CNS malformations, and VP shunt were similar to those in the literature (87%, 78.3%, and 82.6%, respectively). However, the prevalence of epilepsy was higher in our patients than the literature. We attribute this to the above-mentioned fact that data on the incidence of epilepsy are generally 2-3 decades old, and the decrease in mortality is associated with an increase in the incidence of controllable morbidities such as epilepsy. Early intervention reduces early complications. Furthermore, longer life expectancy in these patients may increase complications such as VP shunt dysfunction and infections, which subsequently trigger the development of seizures and epilepsy. One of the most recent studies examining seizures in MMC included patients between 1975 and 2013. In that study, seizures were observed in 19.7% of the patients (14). However, the study covered a period of approximately 40 years, without grouping by decade. New studies examining the relationship between MMC and epilepsy according to current data are needed.

Our study has several limitations. The first is that as a single-center study, it may not reflect the actual numbers in the population. Secondly, as our center is a tertiary hospital, patients with mild findings are less likely to present. Thirdly, studies in which MRI imaging and EEG traces are available and can be evaluated together for all patients may have provided clearer results. As patients have easier access to pediatric neurologists in recent years, conducting a comprehensive study that includes MRI and EEG results as well as provoked seizures and epilepsy subgroups will yield more accurate data on this subject.

CONCLUSION

Epilepsy is less common in patients with MMC compared to other causes of hydrocephalus. Morbidity rates in these patients are likely increasing due to prolonged life expectancy resulting from medical advances. Epilepsy is one of these morbidities, and we hypothesize that the incidence of the disorder may rise as a result of potential complications caused by VP shunts. While our findings are consistent with this hypothesis, more precise results can be obtained from population-based research.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: EA, EUT

Data collection: EUT, DM

Analysis and interpretation of results: DM, EUT

Draft manuscript preparation: EUT, EA

Critical revision of the article: EA, AS

Other (study supervision, fundings, materials, etc...): AS, EA

All authors (EUT, DM, AS, EA) reviewed the results and approved the final version of the manuscript.

REFERENCES

1. Amaral C, Nardeli CS, Saito IC, Valerio JS, Filho M, Straioto FG: Myelomeningocele: Medical considerations and stomatologic aspects in the dental treatment. J Craniofac Surg 30:2517-2519, 2019. https://doi.org/10.1097/SCS.0000000000005973
2. Bartoshesky LE, Haller J, Scott RM, Wojick C: Seizures in children with meningomyelocele. Am J Dis Child 139:400-402, 1985. https://doi.org/10.1001/archpedi.1985.02140060082035
3. Beuriat PA, Szathmari A, Rousselle C, Sabatier I, Di Rocco F, Mottolese C: Complete reversibility of the chiari type II malformation after postnatal repair of myelomeningocele. World Neurosurg 108:62-68, 2017. https://doi.org/10.1016/j.wneu.2017.08.152
4. Bowman RM, McLone DG, Grant JA, Tomita T, Ito JA: Spina bifida outcome: A 25-year prospective. Pediatr Neurosurg 34:114-120, 2001. https://doi.org/10.1159/000056005
5. Brown TM, Ris MD, Beebe D, Ammerman RT, Oppenheimer SG, Yeates KO, Enrile BG: Factors of biological risk and reserve associated with executive behaviors in children and adolescents with spina bifida myelomeningocele. Child Neuropsychol 14:118-134, 2008. https://doi.org/10.1080/09297040601147605
6. Chadduck W, Adametz J: Incidence of seizures in patients with myelomeningocele: A multifactorial analysis. Surg Neurol 30:281-285, 1988. https://doi.org/10.1016/0090-3019(88)90300-x
7. Clemmensen D, Thygesen M, Rasmussen MM, Fenger-Gron M, Petersen OB, Mosdal C: Decreased incidence of myelomeningocele at birth: Effect of folic acid recommendations or prenatal diagnostics? Childs Nerv Syst 27:1951-1955, 2011. https://doi.org/10.1007/s00381-011-1473-2
8. Danzer E, Finkel R, Gerdes M, Schwartz EM, Rintoul NN, Adzick NS, Johnson MP: The relationship of seizure activity and chronic epilepsy in early infancy and short-term neurodevelopmental outcome following fetal myelomeningocele closure. Neuropediatrics 41:140-143, 2010. https://doi.org/10.1055/s-0030-1263164
9. Du Plessis AJ, Johnston MV: Fetal and neonatal neurology. In: Arzimanoglou A, O'Hare A, Johnston MV, Ouvrier R, (eds), Clinics in Developmental Medicine Aicardi's Diseases of the Nervous System in Childhood, 4th ed, Mac Keith Press 2018:8-9. https://doi.org/10.1111/dmcn.14344
10. Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, Engel J Jr, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshe SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S: ILAE official report: A practical clinical definition of epilepsy. Epilepsia 55:475-482, 2014. https://doi.org/ 10.1111/epi.12550
11. Hack CH, Enrile BG, Donat JF, Kosnik E: Seizures in relation to shunt dysfunction in children with meningomyelocele. J Pediatr 116:57-60, 1990. https://doi.org/10.1016/s0022-3476(05)81645-2
12. Isik U: Seizures in children with myelomeningocele. In: Ozek MM, Cinalli G, Maixner WJ, (eds), The Spina Bifida: Management and Outcome. Springer Milan Milano, 2008:297-301. https://doi.org/10.1007/978-88-470-0651-5_25
13. Januschek E, Rohrig A, Kunze S, Fremerey C, Wiebe B, Messing-Junger M: Myelomeningocele - a single institute analysis of the years 2007 to 2015. Childs Nerv Syst 32:1281-1287, 2016. https://doi.org/10.1007/s00381-016-3079-1
14. Karakas C, Fidan E, Arya K, Webber T, Cracco JB: Frequency, predictors, and outcome of seizures in patients with myelomeningocele: Single-center retrospective cohort study. J Child Neurol 37:80-88, 2022. https://doi.org/10.1177/08830738211053132
15. Keene DL, Ventureyra EC: Hydrocephalus and epileptic seizures. Childs Nerv Syst 15:158-162, 1999. https://doi.org/10.1007/s003810050359
16. Klepper J, Busse M, Strassburg HM, Sorensen N: Epilepsy in shunt-treated hydrocephalus. Dev Med Child Neurol 40:731-736, 1998. https://doi.org/10.1111/j.1469-8749.1998.tb12340.x
17. McLone DG, Dias MS: The Chiari II malformation: Cause and impact. Childs Nerv Syst 19:540-550, 2003. https://doi.org/10.1007/s00381-003-0792-3
18. Noetzel MJ, Blake JN: Prognosis for seizure control and remission in children with myelomeningocele. Dev Med Child Neurol 33:803-810, 1991. https://doi.org/10.1111/j.1469-8749.1991.tb14964.x
19. Noetzel MJ, Blake JN: Seizures in children with congenital hydrocephalus: Long-term outcome. Neurology 42:1277-1281, 1992. https://doi.org/10.1212/wnl.42.7.1277

20. North T, Cheong A, Steinbok P, Radic JA: Trends in incidence and long-term outcomes of myelomeningocele in British Columbia. Childs Nerv Syst 34:717-724, 2018. https://doi.org/10.1007/s00381-017-3685-6
21. Okurowska-Zawada B, Sobaniec W, Kulak W, Smigielska-Kuzia J, Paszko-Patej G, Sienkiewicz D, Sendrowski K: Clinical-electroencephalographic analysis of brain bioelectrical activity in children with myelomeningocele and internal hydrocephalus. Adv Med Sci 52 Suppl 1:200-203, 2007.
22. Persson EK, Hagberg G, Uvebrant P: Disabilities in children with hydrocephalus--a population-based study of children aged between four and twelve years. Neuropediatrics 37:330-336, 2006. https://doi.org/10.1055/s-2007-964868
23. Persson EK, Hagberg G, Uvebrant P: Hydrocephalus prevalence and outcome in a population-based cohort of children born in 1989-1998. Acta Paediatr 94:726-732, 2005. https://doi.org/10.1111/j.1651-2227.2005.tb01972.x
24. Rintoul NE, Sutton LN, Hubbard AM, Cohen B, Melchionni J, Pasquariello PS, Adzick NS: A new look at myelomeningoceles: Functional level, vertebral level, shunting, and the implications for fetal intervention. Pediatrics 109:409-413, 2002. https://doi.org/10.1542/peds.109.3.409
25. Shaer CM, Chescheir N, Schulkin J: Myelomeningocele: A review of the epidemiology, genetics, risk factors for conception, prenatal diagnosis, and prognosis for affected individuals. Obstet Gynecol Surv 62:471-479, 2007. https://doi.org/10.1097/01.ogx.0000268628.82123.90
26. Spazzapan P, Velnar T: Myelomeningocele in Slovenia: Results of a 10-year follow-up. J Neurosurg Sci 65:369-376, 2021. https://doi.org/10.23736/S0390-5616.18.04481-8
27. Talwar D, Baldwin MA, Horbatt CI: Epilepsy in children with meningomyelocele. Pediatr Neurol 13:29-32, 1995. https://doi.org/10.1016/0887-8994(95)00088-w
28. Tully HM, Ishak GE, Rue TC, Dempsey JC, Browd SR, Millen KJ, Doherty D, Dobyns WB: Two hundred thirty-six children with developmental hydrocephalus: Causes and clinical consequences. J Child Neurol 31:309-320, 2016. https://doi.org/10.1177/0883073815592222
29. Wasserman RM, Holmbeck GN: Profiles of neuropsychological functioning in children and adolescents with spina bifida: Associations with biopsychosocial predictors and functional outcomes. J Int Neuropsychol Soc 22:804-815, 2016. https://doi.org/10.1017/S1355617716000680
30. Yoshida F, Morioka T, Hashiguchi K, Kawamura T, Miyagi Y, Nagata S, Mihara F, Ohshio M, Sasaki T: Epilepsy in patients with spina bifida in the lumbosacral region. Neurosurg Rev 29:327-332; discussion 332, 2006. https://doi.org/10.1007/s10143-006-0035-7