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SEMIOLOGY OF PATHOLOGICAL CONDITIONS IN PATIENTS INDICATED FOR STEREOTACTIC BIOPSY

SEMIOLOGIJA KOD PACIJENATA INDIKOVANIH ZA STEREOTAKSIČNU BIOPSIJU

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Summary

Introduction. Brain tumors produce symptoms and signs which are often non-specific, and therefore they may occur for more than a few months prior to diagnosis. The aim of this study was to determine the frequency of referent signs and symptoms among patients referred for stereotactic brain biopsy. **Material and Methods.** In this study, we retrospectively analyzed medical history of 65 patients (67.7% males and 32.3% females) between the ages of 16 and 81 years. The following symptoms and signs were included in the analysis: organic brain syndrome, lateralization of crossed pyramidal tract, cranial nerve dysfunction, speech disorders, cerebellar-vestibular syndrome, nausea, vomiting, headache, the occurrence of at least one epileptic seizure and respondents' physical weakness. **Results.** Physical weakness was the most frequent symptom to be recognized (76.9%), whereas pyramidal neurological lateralization was the most commonly recognized sign (58.5%). There was a significant correlation between the course of disease and physical weakness (rho = -0.34, p = 0.005), as well as the course of disease and lateralization of the pyramidal tract (rho = 0.65, p = 0.00). No significant correlation was found between other clinical signs and symptoms. **Conclusion.** An accurate diagnosis and early recognition of signs and symptoms may be useful in determining indications for stereotactic brain biopsy.

Key words: Image-Guided Biopsy; Stereotaxic Techniques; Brain Neoplasms; Signs and Symptoms; Early Detection of Cancer

Sažetak

Uvod. Tumori mozga izazivaju nespecifične simptome i znakove koji se mogu ispoljiti i više od nekoliko meseci pre postavljanja dijagnoze. Cilj ovog istraživanja bio je utvrđivanje učestalosti referentnih znakova i simptoma kod pacijenata indikovanih za stereotaksičnu biopsiju mozga. **Materijal i metode.** Istraživanje je sprovedeno kao retrospektivna studija. Analizirana je medicinska dokumentacija 65 bolesnika (67,7% muškaraca i 32,3% žena) starosti od 16 do 81 godinu. Analizirani su sledeći simptomi i znaci: organski moždani sindrom, piramidna lateralizacija, disfunkcija kranijalnih živaca, poremećaji govora, cerebralno-vestibularni sindrom, mučnina, povraćanje, glavobolja, pojava barem jednog epileptičkog napada ili fizičke slabosti. **Rezultati.** Fizička slabost je najčešće prepoznat simptom (76,9%), dok je piramidna lateralizacija najprepoznatljiviji znak (58,5%). Pokazana je značajna korelacija između trajanja bolesti i telesne slabosti (rho = -0,34, p = 0,005), kao i toka bolesti i lateralizacije piramidnog trakta (rho = 0,65, p = 0,00). Nema signifikantne korelacije između ostalih kliničkih znakova i simptoma. **Zaključak.** Tačna dijagnoza i rano prepoznavanje znakova i simptoma mogu biti korisni za određivanje indikacije za stereotaktičnu biopsiju mozga.

Ključne reči: biopsija vođena slikom; stereotaksične tehnike; tumori mozga; znaci i simptomi; rana detekcija kancera

Introduction

Brain tumors account for less than 2% of all tumors. Nearly 20,000 people in the United States are diagnosed with malignant brain tumors each year, and approximately two-thirds of them have fatal outcome [1, 2]. In Europe, the incidence rate of brain tumors ranges from 4.5 to 11.2 cases per 100,000 men and from 1.6 to 8.5 per 100,000 women [3]. According to the data of Central Serbia Cancer Registry for the same incidence rate there were 11.7 cases per men and 9.2 per women [4]. Despite the relatively low survival rate as compared to the overall tumor rate (2.3%), brain tumors may become fatal because they may disrupt the function of unaffected brain structures, most frequently due to compression of tumor adjacent regions [3, 5]. Although many advances have been made in the field of early detection of brain tumors, presentation with symptoms and clinical signs of tumor may

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still last for more than a few months before the tumor is diagnosed [6]. The most frequent clinical presentations develop as a result of compression and invasion of surrounding brain structure either through vascular compression or elevated intracranial pressure, and therefore brain tumor symptoms tend to present with combination of generalized and focal neurologic deficits [7]. Previous studies related to clinical presentations of tumors in children and adults were dependent on tumor location, its size and growth rate [7–9].

The most common presenting clinical signs and symptoms among patients with brain tumors were headache in 30-50% of cases, focal neurological deficits in 40-60% of cases [7], seizures occurred in about 30% -50% of cases [6, 7], as well as non-specific clinical presentations such as physical weakness and psycho-organic changes. However, these clinical presentations may also occur in other brain lesions such as brain abscess or non-cancerous changes [10, 11], and therefore there is a delay in diagnosis and treatment in many patients whose first presenting symptoms are not correctly diagnosed until other clinical symptoms and signs develop. Stereotactic biopsy for brain tumors and tumor-like lesions is indicated for such patients. The aim of this study was to determine the frequency of referent clinical signs and symptoms in the patients with stereotactic biopsy-proved lesions according to the type and location of the lesion, as well as the course of the disease and respondents' age.

Material and Methods

We performed a retrospective analysis of the data obtained from medical history, surgical protocol and pathohistological examination of the biopted tissue in the patients who were treated at Clinical Center of Vojvodina, Clinic for Neurosurgery in the period from 1/1/2009 to 30/7/2009. Informed consent was obtained prior to participation in the research by Clinic for Neurosurgery, Clinical Center of Vojvodina, as well as by the Ethics Committee of the Clinical Center of Vojvodina for the implementation of this research. We analyzed the initial signs and symptoms, diagnosis, age, gender, pathohistological examination of the biopted tissue and location of lesions using medical history of 65 patients. The following symptoms and clinical signs were included in the analysis: organic brain syndrome, lateralization of crossed pyramidal tract, cranial nerve dysfunction, cerebellar-vestibular syndrome, nausea, vomiting, headache, the occurrence of at least one epileptic seizure, as well as physical weakness of respondents. The order in which symptoms and clinical signs develop was not specified in the available documentation and accordingly, this information could not be included in the analysis. In terms of location, lesions were classified into two groups: a group of cerebral cortical lesions and a group of structural lesions in deep brain structures. Based on the type of lesion, brain tumors were classified whether they belonged to a group of primary brain tumors, whether they were benign or malignant tumors, and whether they belonged to the group of gliomas. The respondents were divided into three age groups: 1–54 years, 55–66 years and over 67 years.

Out of 65 respondents included in this retrospective study, 41 were men (67.7%) and 21 were women (32.3%), their age ranging from 16 to 81 years, the mean age being 59.1 years (Mean = 62 years, SD = 12.91). The sample included only those respondents whose records were available, and who were indicated for computed tomography-guided stereotacic biopsy of intracranial lesions that required pathohistological and microbiological diagnosis. The following indications were included: deep positioned lesions (deep-seated lesion) localized in a surgically inaccessible locations, the patients at higher risk for invasive open surgical biopsy, cystic abscess with suspected lesions or granulomatous infection, multifocal lesions, lesions which appear to have better clinical outcomes if minimally invasive procedures were done after a diagnosis of lymphoma or teratoma, as well as the patients who are often not referred for invasive surgical approach and longer sedation due to their age and comorbidity.

The retrospective analysis of available documentation showed that 61 out of 65 respondents referred for stereotactic intervention had tumor-like lesions and they underwent tissue biopsy, while the other four patients underwent biopsies without findings in the diagnosis of tumor changes.

In this study, measures of descriptive statistics were used arithmetic mean, standard deviation, attributive frequency features (n) and percentage (%). Nonparametric measures, such as Spearman's correlation coefficient, were also used to determine the correlation between the ordinal and numerical variables. In addition, nonparametric χ^2 square test was used to measure differences in frequency distributions of attributive features. In all analyses, differences were interpreted as statistically significant if the p value was less than 0.05 ($p < 0.05$).

Results

Based on the pathohistological findings, the structure of the respondents was as follows: 29 patients were diagnosed with glioblastoma multiforme, which was the most prevalent diagnosis in this respondent group with 44.6%. In our study malignancy-associated lesions were found in 45 patients (69.2%), while benign lesions were found in 16 (24.6%) and non-cancerous lesions occurred in 4 patients (6.2%). In relation to the primary and secondary brain tumors, the total of 56 cases (86.2%) was diagnosed with a primary tumor, 5 with a secondary tumor (7.7%) and 4 with non-cancerous lesions (6.2%). The highest percentage of respondents was diagnosed with glioma (76.9%) (glioblastoma multiforme in 44.6%, anaplastic astrocytoma in 16.9%, astrocytoma grade II in 10.8%, astrocytoma grade I in 1.5%, ependymoma grade II in 1.5% and oligodendroglioma

in 1.5%), while the percentage of other lesions was 23.1%.

Based on the location of biopted lesion, the brain lesion was located on the surface of the brain in most cases. Out of 50 patients (76.9%) who had superficial lesions of the brain, 15 patients had the right hemisphere lesions (23.1%), 29 patients had the left hemisphere lesions (44.6%), 6 patients had lesions on both sides (9.2%), whereas 15 patients had lesions of the deep structures of the brain (23.1%).

As for the symptoms, the most frequent ones were weakness (76.9%), organic brain syndrome (47.7%), headache (43.1%) and/or nausea (13.8%).

The most common presenting clinical signs are pyramidal neurological lateralization (58.5%), speech disorders (40%), cranial nerve dysfunction (35.4%), cerebellar-vestibular syndrome (20.0%) incidence of epileptic seizure (13.8%), vomiting (12.3%).

The frequency of referent symptoms and clinical signs among patients with stereotactic biopsy-proved lesions was evaluated according to the lesion location. Although one symptom and/or clinical sign cannot be solely attributed to one location or the type of change, nausea and vomiting are more frequently observed in the patients whose surface structures of the brain were affected, while other symptoms and signs showed no significant difference **(Table 1).**

In relation to the type of lesion, the frequency of clinical signs and symptoms was highest among the patients with primary tumors, whereas the absence of nausea, vomiting, cerebellar syndrome was observed in the patients with secondary tumors, and only one patient was recorded with organic brain syndrome, headache, seizure and speech disorders. Physical weakness and pyramidal neurological lateralization were observed in most respondents who had primary and secondary tumors **(Table 2)**.

Spearman's rank correlation coefficient was used to evaluate whether there was a correlation between the course of acute, subacute, or chronic manifestations of the disease that may become indicated for stereotactic brain biopsy, and the occurrence of the first disease-related events. A statistically significant correlation was obtained between the course of the disease and pyramidal neurological lateralization, where the strong, positive correlation rho = 0.65, p = 0:00 was found, and between the course of disease and physical weakness, where the moderately strong, negative correlation rho = -0.34, p = 0.005 was obtained. Other variables were not significantly correlated. Using $\chi 2$ test, we assessed the course of disease (acute, subacute and chronic). Further, there was a statistically significant difference ($\chi 2 = 4.63$, p = 0.03) among the respondents with the pyramidal neurological lateralization in relation to the disease course of the respondents with this clinical sign. The comparison of grouped frequency distributions showed that the highest percentage of respondents with the acute course of disease had pyramidal neurological lateralization (77.3%), followed by the respondents in subacute phase (51.7%) and chronic phase (42.9%). Furthermore, $\chi 2$ test showed a statistically significant difference in physical weakness compared to the course of disease ($\chi 2 = 7.67$, p = 0.02). In addition, the highest percentage of respondents with self-reported physical weakness was in the group of those who were in the acute course of the disease (95.5%), followed by the respondents in the subacute course of disease (72.4%) and chronic disease (57.1%).

Moreover, by examining the correlation between the respondents' age and presentation of clinical signs and symptoms we found that there was a medium strong positive correlation between the respondent's age and epileptic seizure (rho = 0.34, p

Table 1. Frequency of referent clinical signs and symptoms based on location of lesion
Tabela 1. *Učestalost kliničkih simptoma i znakova u odnosu na lokalizaciju lezije*

Clinical signs and symptoms *Klinički znaci i simptomi*	Group of cerebral cortical lesions *Kortikalne moždane lezije* *N = 50*		Group of structural lesions in deep brain structures/*Lezije u dubokim moždanim strukturama* N = 15	
	N	%	N	%
Organic brain syndrome/*Moždani sindrom*	26	52%	5	33.33%
Pyramidal neurological lateralization *Piramidna neurološka lateralizacija*	30	60%	8	53.33%
Cranial nerve dysfunction *Lezija kranijalnih nerava*	17	34%	6	40%
Cerebellar syndrome *Cerebelarna simptomatologija*	10	20%	3	20%
Headache/*Glavobolja*	21	41%	7	46.67%
Nausea/*Mučnina*	8	16%	1	6.67%
Vomiting/*Povraćanje*	8	16%	0	0%
Speech problems *Problemi sa govorom*	21	42%	5	33.33%
Epileptic seizure/*Epileptični napad*	7	14%	2	13.33%
Physical weakness/*Fizička slabost*	38	76%	12	80%

= 0.00), as well as a weak negative correlation with acute or chronic brain syndrome (rho = -0.29, p = 0.01).

By means of the χ^2 test, we assessed the differences among the patients regarding the age (divided into three groups of 16 to 54 years, 55 to 66 and 67 to 88 years), and the occurrence of symptoms and clinical signs. Among the observed respondent groups, a statistically significant difference (χ^2 = 8:45, p <0.01) was obtained only in the patients who had an epileptic seizure, while for those with organic brain syndrome the threshold value of 0.05 was obtained. According to the grouped frequency distributions, epileptic seizure was most frequent in the patients under 55 years of age (31.6%), and the organic brain syndrome in the patients over 67 years of age (61.9%), while for those between the ages of 56 and 66 years, the percentage was 48%. No statistically significant difference was found for other symptoms and clinical signs.

Discussion

Tumor that grows intracranially may lead to brain compression or infiltration. Meningiomas are the most common benign brain tumors in people over 45 years of age and biopsies are often not necessary due to the very nature of the tumor [1]. Glial tumors are the most common brain tumors and account for 77% of all primary brain tumors [12]. Glioblastomas represent about 30% of all brain tumors [13], and in the sample studied, the most malignant glioblastoma multiforme occurred in 45% of patients. If we take into account the age of our respondents, their mean age being 62 years, then the frequency of this type of tumor can be also associated with a higher incidence of its occurrence in elderly respondents [12, 14, 15].

A lot of the clinical signs and symptoms a patient may experience depend on the tumor location. The majority of tumors in the elderly are in the cerebral hemispheres [16]. Jennings and his associates stated that 76% of most commonly affected brain structures involve cortex lesions [17]. Similar data based on Vates research (2003) show that lesions which occur most frequently affect the superficial cortex [18]. In the present study, we found that brain lesions occuring most frequently affected superficial cerebral structures (77%), whereas the lesions affected the deep brain structure in 23% of cases. In more than 60% of cases, biopted lesions involved superficial structures in the left brain hemisphere. According to our findings, the clinical signs and symptoms were correlated to tumor location [14, 19]; however, they were often nonspecific initially. Headaches are typically associated with brain tumors. Prevalence of headache ranges from 48% to 71% in unselected series [20], while the same author has found that nausea and vomiting occur in 46% – 60%, as well as that these symptoms are rarely presented with children and older adults. Stark et al. [21] reviewed the presence of clinical signs and symptoms among 478 patients, with the mean age of 60.42 years, who most commonly had symptoms of hemiparesis 41.3%, then neuropsychological changes 37.0%, while headache (nausea) vomiting occurred in slightly more than 30% of patients, and seizures in 23.0%. Babu et al. [22] also found that the occurrence of headache and nausea was most frequent, and unlike them, Jung et al. [13] reported seizures to be the initial presenting sign in 45.3% of patients; headache in 32.6% of patients, and other neurological symptoms such as hemiparesis in 19.8% of patients. The occurrence of nonspecific symptoms such as physical weakness, headache, vomiting, and epileptic seizures were also reported in children [10].

As compared to these studies, our data show that the majority of respondents reported the occurrence of physical weakness, and pyramidal neurological lateralization was identified in more than half of the respondents, there was also a manifestation of spee-

Table 2. Frequency of referent clinical signs and symptoms based on the type of lesion
Tabela 2. *Učestalost kliničkih simptoma i znakova u odnosu na tip lezije*

Clinical signs and symptoms *Klinički znaci i simptomi*	Primary tumors N = 56 *Primarni moždani tumori N = 56*		Secondary tumors N = 5 *Sekundarni moždani tumori N = 5*		Other N = 4 *Drugo* N = 4	
	N	%	N	%	N	%
Organic brain syndrome/*Moždani sindrom*	28	50%	1	20%	2	50%
Pyramidal neurological lateralization *Piramidna neurološka lateralizacija*	34	60.71%	3	60%	1	25%
Cranial nerve dysfunction/*Lezija kranijalnih nerava*	21	37.50%	2	40%	0	0%
Cerebellar syndrome/*Cerebelarna simptomatologija*	13	23.21%	0	0%	0	0%
Headache/*Glavobolja*	26	46.42%	1	20%	1	25%
Nausea/*Mučnina*	8	14.28%	0	0%	1	25%
Vomiting/*Povraćanje*	8	14.28%	0	0%	0	0%
Speech problems/*Problemi sa govorom*	24	42.85%	1	20%	1	25%
Epileptic seizure/*Epileptični napad*	8	14.28%	1	20%	0	0%
Physical weakness/*Fizička slabost*	44	78.57%	4	80%	2	50%

ch disorders in 40% of the sample, which would correspond to the results of the previous studies [12, 13, 22]. A slightly lower frequency in comparison to previous research was found in the presentation of epileptic seizures (13.8%). A review of literature shows that seizures, based on tumor location, may occur in 30–60% of patients [7, 23]. In addition, seizures occur in 20% of patients with supratentorial brain tumors, and in 70% of patients with primary parenchymal tumors, whereas 40% of the patients with metastatic brain tumors will have a seizure in the course of disease [6]. There was no statistically significant correlation between the type of change, location of lesion and presentation of symptoms i.e. clinical signs. This means that most brain lesions include symptoms and clinical signs that are frequently not attributable to one specific clinical sign and symptom, but rather constitute a group of signs and symptoms that together indicate the nature of the disease. The clinical picture of brain lesions is the result of their mass, surrounding edema, as well as infiltration and destruction of brain tissue. Regardless of the histology of the lesion, the diagnosis most often indicates physical weakness, neurological signs, headache, and partial or generalized seizures. Another explanation is that different parts of the brain control different functions and thus symptoms depend on which part of the brain is affected. The diagnosis of tumor can be suspected if the symptoms develop over a short period of time (i.e. less than 6 months) [20, 21]. Although there is no exact pattern which clearly connects the course of disease with the diagnosis, the largest number of the respondents in this study was in the subacute phase of the disease. It was found that the highest percentage of respondents with a pyramidal neurological lateralization and physical weakness was in the group of those who were in the acute course of the disease. Physical weakness and pyramidal neurological lateralization showed the strongest correlation with the course of the disease, because it is usually an indication for computed tomography scanning of endocranium, after which working diagnosis is determined. Among the most common symptoms were motor and sensory deficits [19] and there were various reports on the patients who underwent brain biopsy because the initial diagnosis of central nervous system tumor depended on brain magnetic resonance imaging combined with stereotactic brain biopsy [19, 24, 25]. Initial symptoms of incidental presentation and seizures had a longer overall survival than did headache or other neurological symptoms [22].

The incidence of primary brain tumors among all tumors increases with age so in patients between the ages of 75 and 85 years, it ranges from 7 to 23.4% [16]. The highest incidence of glioblastomas and astrocytomas is among individuals aged 65–74 [12]. Evidence observation also includes the presentation of age-related clinical signs and symptoms. The first recording supports seizure presentations as the main clinical sign in the patients from the youngest age group, which occurs in one third of the cases presenting in this age group. An increased risk of brain tumors appears to be more related to a history of epileptic seizures, but it is difficult to determine whether these seizures are the result of the early development of tumors or tumor caused by many years of epileptic seizures [12]. Different authors suggest that seizures may occur in brain tumor patients of median age [26]. In addition, some researchers suggest that overlapping or dual pathology is possible in tumor-like lesions of the brain, such as glial tumors and focal cortical dysplasia, thus reflecting neurobiological source of epileptic seizures [27]. Unlike previous research, we obtained data on the presentation of organic brain syndrome in respondents over 67 years of age, which was also shown in the previous studies, in which physical weakness, depression and psycho organic changes in respondents over 67 years of age were recognized as the main symptoms of brain tumors [28].

Conclusion

In this study, we showed clinical signs and symptoms in the patients referred for stereotacic brain biopsy as compared to the location of lesion, the course of disease, and the age of patients. The study also showed that the most commonly seen symptom in the study group was physical weakness, while the most common clinical sign was pyramidal neurological lateralization. Moreover, there was a statistically significant correlation between disease progression and physical weakness, as well as disease progression and pyramidal neurological lateralization. Results did, however, show that there was no statistically significant correlation between other clinical signs and symptoms. The analysis of the age–related differences across the respondent age groups showed the largest number of seizures in the youngest group of respondents (up to 54 years of age), and the largest number of acute or chronic brain syndrome in the oldest group of respondents (67 years and over). There was a statistically significant difference among the respondent groups in terms of the time elapsed between the onset of clinical signs and symptoms of physical weakness, with the largest number of these symptoms present in the group who developed symptoms during the acute phase (1–21 days). Limitations of this study refer to the fact that the sequence of symptoms and clinical signs was not viewed in their exact chronological order so it can be useful to conduct a further research which should include these issues. Thus, accurate and timely assessment of symptoms and clinical signs may help in determining the indications for stereotacic brain biopsy.

References

1. CBTRUS Statistical Report: Primary Brain and Central Nervous System Tumors Diagnosed in the United States in 2004-2008 (March 23, 2012 Revision). Hinsdale, IL: Central Brain Tumor Registry of the United States; 2012.

2. Davis FG, McCarthy BJ. Epidemiology of brain tumors. Curr Opin Neurol. 2000;13:635-40.

3. Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. GLOBOCAN 2008: Cancer Incidence and Mortality Worldwide. IARC Cancer Base No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. [cited 2014 Aug 11]. Available from: http://globocan.iarc.fr

4. Registar za rak. Statistički izveštaj: Incidenca raka i mortaliteta u Centranoj Srbiji. Izveštaj broj 11. Beograd: Institut za javno zdravlje "Dr Milan Jovanović Batut"; 2011.

5. American Cancer Society. Cancer Facts and Figures 2012. Atlanta: American Cancer Society; 2012.

6. Cloughesy T, Selch MT, Liau L. Brain. In: Haskell CM, editor. Cancer Treatment. 5th ed. Philadelphia, Pa: WB Saunders Co; 2001. p. 1106-42.

7. Lepić T. Novine u terapiji primarnih tumora mozga. U: Tončev G, Stojanović M, urednici. Novine u terapiji neuroloških oboljenja. Kragujevac: Prizma Klinički centar Kragujevac, Klinika za Neurologiju, Društvo neurologa Srbije; 2012. s. 163-71.

8. Wilne S, Collier J, Kennedy C, Koller K, Grundy R, Walker D. Presentation of childhood CNS tumors: a systematic review andmeta-analysis. Lancet Oncol. 2007;8:685-95.

9. The Childhood Brain Tumor Consortium. The epidemiology of headache among children with brain tumor. Headache in children with brain tumors. J Neurooncol. 1991;10:31–6.

10. Hayashi N, Kidokoro H, Miyajima Y, Fukazawa T, Natsume J, Kubota T, Kojima S. How do the clinical features of brain tumours in childhood progress before diagnosis? Brain Dev. 2010;32(8):636-41.

11. Hutter A, Schwetye KE, Bierhals AJ, McKinstry RC. Brain neoplasms: epidemiology, diagnosis, and prospects for cost-effective imaging. Neuroimaging Clin N Am. 2003;13 (2):237-50.

12. Živković N, Mihailović G, Marković M, Berisavac I, Spaić M. Epidemiological features of brain tumors. Srp Arh Celok Lek. 2014;141(11-12):823-9.

13. Jung TY, Jung S, Moon JH, Kim IY, Moon KS, Jang WY. Early prognostic factors related to progression and malignant transformation of low-grade gliomas. Clin Neurol Neurosurg. 2011;113(9):752-7.

14. Kim JE, Kim DG, Paek SH, Jung HW, Lobato RD, Ostertag C. Stereotactic biopsy for intracranial lesions: reliability and its impact on the planning of treatment. Acta Neurochir (Wien). 2003;145(7):547-55.

15. Kondziolka D, Lunsford LD. The role of stereotactic biopsy in the management of gliomas. J Neurooncol. 1999;42 (3):205-13.

16. Flowers A. Brain tumors in the older person. Cancer Control. 2000;7(6):523-38.

17. Jennings MT, Frenchman M, Shehab T, Johnson MD, Creasy J, LaPorte K, et al. Gliomatosis cerebri presenting as intractable epilepsy during early childhood. J Child Neurol. 1995;10(1):37-45.

18. Vates GE, Chang S, Lamborn KR, Prados M, Berger MS, Schramm J. Gliomatosis cerebri: a review of 22 cases. Neurosurgery. 2003;53(2):261-71.

19. Kilic AK, Kurne AT, Oguz KK, Soylemezoglu F, Karabudak R. Mass lesions in the brain: tumor or multiple sclerosis? Clinical and imaging characteristics and course from a single reference center. Turkish Neurosurg. 2013;23(6):728-35.

20. Kirby S, Purdy RA. Headache and brain tumors. Curr Neurol Neurosci Rep. 2007;7(2):110-6.

21. Stark AM, Van De Bergh J, Hedderich J, Mehdorn HM, Nabavi A. Glioblastoma: clinical characteristics, prognostic factors and survival in 492 patients. Clin Neurol Neurosurg. 2012;114(7):840-5.

22. Babu R, Kranz PG, Karikari IO, Friedman AH, Adamson C. Clinical characteristics and treatment of malignant brainstem gliomas in elderly patients. J Clin Neurosci. 2013;20(10):1382-6.

23. Mehta M, Vogelbaum MA, Chang S, Patel N. Neoplasms of the central nervous system. In: DeVita VT Jr, Lawrence TS, Rosenberg SA, editors. Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins; 2011. p. 1700-49.

24. Fallah A, Banglawala S, Ebrahim S, Paulseth JE, Jha NK. Tumefactive demyelinating lesions: a diagnostic challenge. Can J Surg. 2010;53(1):69-70.

25. Grujičić M, Vučković N, Vuleković P. Osnovne morfološke karakteristike meningeoma. Med Pregl. 2010;63(3-4):237-40.

26. Faguer R, Tanguy J, Rousseau A, Clavreul A, Menei P. Early presentation of primary glioblastoma. Neurochirurgie. 2014;60(4):188-93.

27. Blümcke I, Wiestler OD. Gangliogliomas: an intriguing tumor entity associated with focal epilepsies. J Neuropathol Exp Neurol. 2002;61(7):575-84.

28. Norden DM, Bicer S, Clark Y, Jing R, Henry CJ, Wold LE, et al. Tumor growth increases neuroinflammation, fatigue and depressive-like behavior prior to alterations in muscle function. Brain Behav Immun. 2015;43:76-85.

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