Death caused by undiagnosed primary intracranial neoplasmas - an autopsy study

Ljiljana Bogdanovic1*, Slobodan Savic2, Gordana Basta-Jovanovic1, Sanja Radojevic-Skodrić1, Jelena Bogdanovic3

Abstract: Aim. The purpose of this study was to find the incidence of death caused by undiagnosed intracranial tumors.

Methods. Autopsy material of the Institute of Forensic Medicine in Belgrade, from 1990 to 2004, was analyzed. The cases in which the cause of death is undiagnosed brain tumor have been extracted.

Results. Brain tumors have caused death in 10 cases, of that 7 persons had benign tumors and three malignant and that was 3.9% of 259 indistinct natural deaths caused by pathological disorders of the brain. Of those three cases of malignant neoplasmas of the brain, one has been proven by pathohistological analysis to be an astrocytome of third grade malignity while the second case was a glioblastome. The histological type of tumor in the third case could not be determined because of big necrotic changes in the histological preparation. In the group of benign tumors leading to death, five cases were menigothel tumors (meningiomas), and two cases were indistinct histogenesis (hemangioglioblastomas).

Conclusion. The incidence of sudden death caused by undiagnosed primary intracranial tumors is extremely low. In every case with a suspicion to intracranial pathology a multidisciplinary approach that includes a total autopsy with thorough documentation and neuropathological tests is necessary.

Key Words: brain tumors, sudden death, forensic medicine

Primary tumors of the brain are, by current world statistics, represented in less than 2% in relation to malignant tumors of other localizations [1]. It is estimated that glial tumors represent 50-60% of primary tumors of the brain, meningeomas approximately 25%, schwannomas about 10%, and the rest are other tumors of the CNS [1, 2]. Since the patients with intracranial tumors have early appearance of the symptoms, because of the increase of the intracranial pressure, sudden death caused by them is an extremely rare event in the practice of Forensic Medicine. Increased accessibility of modern and extremely sensitive radiological technology (MRI) offers the possibility of early discovering primary intracranial tumors, resulting in a considerably lower percentage of the cases of sudden death caused by these tumors in medicolegal material. However, despite developed neurological diagnostics, some cases of primary intracranial tumors stay unrecognized during the patient’s lifetime. There are cases of tumors of the brain that developed without clearly expressed clinical manifestations, and they were discovered for the first time at autopsy.

The purpose of this study was to find the incidence of deaths caused by undiagnosed intracranial tumors.

1) Institute of Pathology, School of Medicine, Belgrade, Serbia. * Corresponding author: Ljiljana Bogdanovic, Institute of Pathology, School of Medicine, Belgrade, Serbia, e-mail: jbogdanovic@ptt.rs
2) Institute of Forensic Medicine, School of Medicine, Belgrade, Serbia
3) Emergency Center, Clinical centre of Serbia
Material and Methods
A detailed analysis of reports of legal medicine autopsies in a fifteen-year-period (1990-2004) of the Institute of Forensic Medicine in Belgrade has been done. The cases in which the death was caused by undiagnosed primary intracranial tumor have been extracted.

Results
In the analyzed fifteen-year-period, since 1990 to 2004 year, in the Institute of Forensic Medicine in Belgrade, 16,018 autopsies were done. All cases of natural death were thoroughly examined and their percentage in overall number in that period was 19.2% (3067 cases).

Among the cases of pathological disorders of the brain and brain blood vessels the most frequently diagnosed as causes of indistinct natural death were intracerebral hemorrhages-104 cases (40.1%), subarachnoidal hemorrhage-75 cases (28.9%), ischemic brain infarction-41 cases (15.8%), epileptic attack-17 cases (6.6%), meningitis-12 cases (4.2%). Brain tumors caused death in 10 cases, 7 of them were benign and three were malignant, they represented 3.9% of 259 indistinct natural deaths caused by pathological brain disorders.

In six of the found 10 cases of intracranial tumors histological preparations were available. Of the three cases of malignant neoplasmas of the brain, one case was proven, by pathohistological analysis, to be an anaplastic astrocytoma (astrocytoma of the third grade of malignancy), while the other one was a glioblastoma. The histological type of tumor in the third case was not possible to determine because of big necrotic changes that were visible in the histological preparation, but this case was included in the research based on data from the autopsy report in which we found that the tumor was malignant. In a total of 7 cases of benign tumors, histological preparations were available in three cases. In the other four cases which did not have available histological preparations, information about the histological type of the tumors was obtained during a previous pathohistological examination. The tumors were meningeal tumors, in 5 cases – meningeothelial tumors (meningeomas), and two cases were tumors of indistinct histogenesis (hemangioblastomas).

Primary intracranial tumors were found in sexes, six female persons and four persons of male sex, ages between 30 and 80 years.

In 4 of the 10 cases of undiagnosed intracranial tumors, the patients did not have characteristic symptoms that would indicate the presence of the tumors. The other 6 deceased patients had characteristic symptoms caused by intracranial neoplasmas.

Only four subject who had symptoms that could indicate the presence of the tumor had seen a doctor. In most cases (7 - 70% of overall 10) natural death caused by undiagnosed intracranial tumors had signs of suspicions natural death, rarely registered as unknown death (2 or 20%), and only one case was a sudden natural death.

Discussion
In the analyzed fifteen-year-period (from 1990 to 2004), in the Institute of Forensic Medicine in Belgrade 16,018 autopsies were done, of that, in 12,882 cases, the cause of death was determined. The percentage of natural deaths in the overall number of autopsies in that period was 19.2% (3067 cases).

Among pathological disorders of the brain and brain blood vessels that were causes of natural deaths the most frequently diagnosed was intracerebral hemorrhage (40.1%). Brain tumors caused death in 10 cases, which is 3.9% of the overall number of undetermined natural deaths caused by pathological brain disorders.

Primary intracranial neoplasmas are relatively rare. It is estimated that the annual incidence of these tumors in the USA is 14 in 100,000 reported cases [3]. In persons between 20 and 30 years of age, the mortality of these neoplasms is extremely high, and they have been the third most common cause of death in that age group in the last two decades [4]. Intracranial tumors, as well as other organ tumors, are divided into benign and malignant tumors. The pathohistological nature of the tumors influences clinical features and the prognosis of the diseases, but the localization of intracranial tumors is far more important. The tumor can be benign, but if it is localized in unapproachable parts of the brain, such as the brain stem and the fourth brain chamber, the prognosis is not favorable and is not different than that of a malignant tumor [5].

These neoplasmas, because of a sudden increase of the intracranial pressure, cause symptoms such as: headaches, nonspecific changes of personality and focal neurological failures, that influence them to come to see the doctor early on [6], and because of this the cases of sudden death caused by undiagnosed malignancies of the brain in medicolegal practice are very rare. However, the practice in autopsies has proven that in some cases the brain tumors had reached a considerable size, and their clinical manifestations were inconspicuous, so the tumors
were first diagnosed at autopsies. This happens with tumors that grow very slowly and in such a location in the brain that they cause no significant compressive effects.

In numerous researches cases of death caused by primary intracranial neoplasms in medicolegal material were analyzed, but the findings were not valid because that research included hospital cases, i.e. the cases that are not the subject of legal-medicine researches. Eberhart et al. [4] found during a twenty-year-long analyzed period, from year 1980 to 1999, eleven cases of undiagnosed brain tumors that were the cause of death in a total of 54,873 autopsies. Gezelius and Eriksson found 11 cases of primary intracranial neoplasms that caused death, which was 0.16% of a total of 7020 autopsies. They had found only one case of astrocytoma. The same authors feature the results of several other research studies that had found more cases of this tumor type. For example, Huntington found three cases of astrocytoma out of six cases of sudden death caused by malignancies in this localization. Wood et al. found 9 cases of astrocytoma a total of 19 brain tumors, and Keiding et al – 9 of 20.

In other cases in all these research studies the tumors were benign, i.e. meningeomas [7]. DiMaio et al. [8] found 19 cases of undiagnosed intracranial neoplasms that were the cause of death in 10,995 autopsies. In their research they found 9 tumors from the astrocytoma category – glioblastomas, four cases of oligodendro gliomas and one case of medulloblastoma, microglioma, meningioma, teratoma, colloid cysts and chomophobic adenoma. Vougioklakis, Mitselou and Agnantis [9] describe two cases of sudden death caused by primary intracranial neoplasms from a total of 1,985 cases of autopsies performed in the Institute for Legal Medicine in Greece in the period from 1998 to 2005. They described one case of astrocytoma and one case of glioblastoma. Many authors [10, 11] described cases of sudden death caused by undiagnosed intracranial tumors, mostly glioblastomas. Among these research studies is a case of sudden death caused by undiagnosed glioblastoma in a patient who was treated for schizophrenia for many years [12]. Matschke and Tsokos [13] had found only three cases of sudden death caused by undiagnosed glioblastoma, out of 14,442 cases of autopsies performed in the Institute for Legal Medicine in Hamburg in the period from year 1991 to 2003.

In our research 10 cases of undetermined natural deaths caused by primary intracranial neoplasmas were recorded, 7 cases were benign tumors, and three were malignant. Out of three cases of malignant tumors of the brain, in one case pathohistological analysis proved anaplastic astrocytoma, i.e. astrocytoma of third grade malignancy, while the other case was a glioblastoma. The histological type of the tumor in the third case could not be determined because of necrotic changes in the histological preparation, but we included this case in the research based on information from the autopsy report where the tumor was pronounced to be a malignant one. In the cases in which the pathohistological analysis had proven benign tumors, they were meningeomas (5 cases) and hemangiomas (2 cases). Considering the previously mentioned fact that clinical features of any intracranial tumor depend more on the localization of the tumor than on its histological type, the bibliographic data that as many as two thirds of cases of undetermined natural deaths are caused by benignant primary intracranial neoplasmas is no surprise [13]. It is well known that the glioblastoma is the most malignant astrocytic tumor that responds to gradus IV by the WHO criteria, and makes 12% to 20% of all intracranial tumors and 50 to 60% of all astrocytic tumors.

These are tumors found in adults mostly between 45 and 75 years-of-age, though they can be found in children, as well. There are two types of glioblastomas. The primary (de novo) glioblastoma begins without a noticeable precancerous lesion, is usually found in persons older than 55 years of age and is characterized by excessive expression of epidermal growth factor receptors (EGFR) which is included in cell proliferation control. Opposed to this form is in secondary glioblastoma that may begin by malignant alteration of diffuse (grade II) or anaplastic (grade III) astrocytoma. Secondary glioblastoma is found in younger persons, about 45 years of age, and often contains mutations in the p53 tumor suppressor gene [13, 1].

In patients with these tumors death can be caused by the destruction of vital centers in lower parts of the brain stem, caused by the infiltration of the tumor. Matschke and Tsokos quote opinions of other authors who think that the main mechanism of dying in the cases of sudden death caused by undiagnosed intracranial tumors is an increase of the intracranial pressure because of the local effect of the tumor mass and a disturbance of cerebrospinal liquor flow [13-15]. It is known that the increase of the intracranial pressure is the main of all pathophysiological processes in brain tumors. The increase of the intracranial pressure is commensurately the speed of growth of the expansive process [5]. In patients with undiagnosed tumors of the brain sudden death can be caused by an acute hemorrhage into the tumor tissue. Hemorrhage is sometimes massive and clinically similar to the brain stroke.

This mechanism of dying is especially characteristic for all tumor types that are prone to hemorrhage, such
as the case with glioblastoma multiforme ("glioblastoma appoplectiforme") [1, 13]. Hemorrhage begins because of the lesion of the blood vessels caused by the infiltrative nature of the tumor. Numerous research studies have shown that a certain number of primary intracranial tumors grow asymptotically. Gezelius and Eriksson quote in their research that 6 of 11 cases of intracranial tumors discovered in autopsy had grown without obvious symptoms. They also quote other authors’ data that 5 out of 19 and 8 out of 32 cases of intracranial neoplasmas were asymptomatic before death of the patient [7]. In the analyzed sample, in four cases of death caused by undiagnosed tumors of the brain, according to given heteroanamnestic information, patients had no symptoms.

Most patients in the analyzed group who had symptoms that could have indicated the presence of intracranial neoplasmas (4 of 6) had contact with doctors during their life time, and diagnostic procedures were performed in order to discover the cause of the symptoms, but the diagnosis was not reached. Similarly to the results of this research, the bibliographic data also indicate that the patients who had characteristic symptoms caused by intracranial neoplasmas did seek doctor’s help, but the accurate diagnosis was not reached [7, 10, 12, and 13].

These cases are the subject of legal-medical attention because of the presence of suspicion of trauma, intoxication, alcoholism etc. In some cases, the suspicious circumstances of the cases (such as problematic relations in the family, existence of the last will and testament written by the diseased who had intracranial tumor, existence of a life-long support contract, especially if the death came soon after such a contract had been signed etc.) and clinical changes caused by undiagnosed intracranial process in correlation to one another had given the cases the labels of suspicious death. Of a total of 10 cases of death caused by undiagnosed intracranial tumors, 7 cases had characteristics of suspicious natural death.

In conclusion, the incidence of sudden death caused by undiagnosed primary intracranial tumors is extremely low. In most cases death caused by undiagnosed intracranial tumors was caused by benignant tumors (meningiomas). Among malignant tumors, astrocytoma of the third grade of malignancy and glioblastoma multiform were found. In all cases that are suspected to have intracranial pathology, a multidisciplinary approach that includes a complete autopsy with thorough documentation and neuropathological tests is necessary.

References