Critical Overview of the Current Status of Organ Donors with Primary Central Nervous System Tumors

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Abstract:

The transmission of donor-related malignancies by organ transplantation is rare event but biological behaviour of malignant tumors developed by the transplanted patients is in general more aggressive than similar ones in non-transplanted population. This paper presents an analysis of our series of cases and a review of the literature to the point of the transmission of cancer from organ donors with primary central nervous system tumors. Patients with primary CNS neoplasms have been accepted for organ donation because these tumors very rarely spread outside the CNS. To our knowledge, after an extensive review of the literature, the CNS tumor transmission risk with transplantation may be estimated between a little more than 0% and 3%. In the light of available data and in accordance with our investigations we consider that patients with CNS tumors can be accepted as donors as long as the risk of dying on the waiting lists is significantly higher than the tumor transferral risk. Organ donors with benign or low-grade CNS tumor should be accepted unreservedly. Donors with high-grade tumors should be consider as "marginal donors" and their assessment can be based on the comparison and the balance between the risk of tumor transmission and the medical condition of the recipient.

Key words: organ donors with CNS tumors; tumor transmission with transplantation; distant metastases

Introduction

The central nervous tumors are a heterogenous group of neoplasms, each with its own biology, behaviour, treatment and prognosis. The term "brain tumor" refers to a collection of histologically and clinically varied neoplasms. Better qualification for these tumors is "intracranial neoplasms", because some do not arise from brain tissue (e.g. meningiomas, lymphomas)(table1)[1]. Notwithstanding, for most intracranial tumors the clinical presentation, diagnostic approach and initial treatment are similar.

The frequency of the CNS tumors occurrance is higher than we expect and realize. The American Cancer Society estimates that 16 800 new intracranial tumor were diagnosed in 1999, more than double number of recognized cases of Hodgkin's disease and over half number of cases of melanoma [2]. The Polish Register of Cancer in 1996 (recently published data in Poland) stated 2664 new recorded brain tumors and 194 new tumors of other parts of nervous system [3].

On account of relatively large group of these patients and an increasing demand for donor organs, efforts are aimed at extending donor pools. Up to date estimations of organ procured from donors with CNS tumors are simply exaggerated and too cautious. Nevertheless it is unacceptable to transplant organ into patients when the possibility of tumor transmission exists.

This article will focus on general presentation of problem related to organ donors with primary central nervous system, estimation of the transmission risk with organ transplantation, the usability of these group of donors and tumor transmission's prevention.

Our present investigation offers analysis of series of primary brain tumors that provided stimulus for our review of this issue, discussion and wide commentary.

Materials and methods

The material comprises the group of analysed medical autopsies carried out in Department of Pathological Anatomy in Wrocław Medical University in the period of last 11 years. From January 1990 to December 2000, 3650 medical autopsies were performed in Department of Pathological Anatomy. We analysed them watch out for diagnosis of central nervous system tumors and their distant metastases.

Results

Central nervous system tumors were diagnosed in 35 cases , what states 0.95% of all autopsies. Recognized cerebral neoplasms included 29 cases of primary CNS tumors and 6 cases of metastatic tumors. Histopatological diagnoses of primary tumors were the following:

*   astrocytoma (n=13):

    astrocytoma pilocyticum
    (grade I) n=1
    astrocytoma gemistocyticum
    (grade II) n=3
    astrocytoma anaplasticum
    (grade III) n=7
    glioblastoma multiforme
    (grade IV) n=2
*   meningioma n=6
*   medulloblastoma n=2
*   craniopharyngioma n=2
*   oligodendroglioma n=1

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Table I. Histological classification of the central nervous system tumors*

Tumors of neuroepithelial tissue
      Astrocytic tumors
            Pilocytic astrocytoma (astrocytomas grade I)
            Diffuse astrocytoma (astrocytoma grade II)
                  - Fibrillary
                  - Protoplasmic
                  - Gemistocytic
            Anaplastic astrocytoma (astrocytoma grade III)
            Glioblastoma multiforme (astrocytoma grade IV)
      Oligodendroglial tumors
      Ependymal tumors
      Mixed gliomas
      Choroid plexus tumors
      Glial tumors of uncertain origin
      Neuronal and neuronal-glial tumors
      Neuroblastic tumors
      Pineal parenchymal tumors
      Embryonal tumors
            Primitive neuroectodermal tumors (PNET)
                  - Medulloblastoma
            Medulloepithelioma
            Neuroblastoma
            Ependymoblastoma

Tumors of the meninges
      Tumors of meningothelial cells
      Mesenchymal non-meningothelial tumors
      Primary melanocytic lesions
      Tumors of uncertain histogenesis

Tumors of peripheral nerves
      Schwannoma
      Neurofibroma
      Perineuroma
      Malignant peripheral nerve sheat tumor (MPNST)

Lymphomas and hematopoietic neoplasms
      Malignant lymphomas
      Plasmacytoma
      Granulocytic sarcoma

Germ cell tumors
      Germinoma
      Embryonal carcioma
      Yolk sac tumor (Endodermal sinus tumor)
      Choriocarcinoma
      Teratoma
      Mixed germ cell tumor

Tumor of the sellar region
      Craniopharyngeoma
      Pituitary adenoma
      Pituitary carcinoma
      Granular cell tumor

Metastatic tumors

* This table has been abridged and modified from the World Health Organisation classification [1,2].

ependymoma n=1
* hemangioblastoma n=1
* pineocytoma n=1
* gliosarcoma n=1
* cholesteatoma n=1

Metastatic brain tumors were results of malignant dissemination from:
* carcinoma of lungs n=4
* adenocarcinoma sigmatis n=1
* carcinoma embryonale testis n=1.

On autopsies and histological evaluation of the liver, kidneys, lungs in cases of primary CNS tumors, no metastases or other neoplastic lesions were detected.

Contrary to expectation there were any distant of primary CNS tumor within our relatively abounding in cases material. But there is no evidence to support and suggest that the hypothesis about unusual rarity of distant metastases' occurrence in brain tumors is correct and confirmed.

Our results are not accurate and entirely adequate because of the following obstacles.

1. Lack of informations about examined patients with CNS tumors makes generalization hardly possible. A detailed, accurate and scrupulous past medical history, especially refers to oncological disease and familial history of neoplasms, is often not available to pathologists and physicians. Interpretation is difficult due to the shortage of data on the moment of making diagnosis of tumor, types of treatment, time interval between treatment and death.

2. We have not enough satisfactory answers for question whether the death of patients was from the neoplasm per se. The majority of examined patients died of postoperative complications during the period of few months after surgery. The longest survival after tumor's resection was 4 month. Causes of death included in our cases respectively:
* intracranial bleeding (mainly in site of tumor removal) n=12
* massive bilateral bronchopneumonia n=10
* generalized neoplastic process n=3
* meningitis, meningoencephalitis n=2
* pulmonary embolism n=2
* circulatory and respiratory insufficiency n=1
* recent myocardial infarction n=1
* colliquative brain necrosis n=1

On account of early deaths, we have not standard time of observation and following-up of respective patients with CNS tumors. It is not known whether malignant dissemination and systemic metastases would develop in these group of patients.

3. Not all analysed autopsies including histopathological estimation of organs which can be site of metastases: liver, lungs, kidneys, adrenals, lymph nodes, thyroid. There was no examination and sampling of peritoneal fluid which can comprise malignant cells, especially when shunting procedure in patients were performed. But even when the peritoneal fluid is negative for tumor's cells, we haven't sure about safely excluding of metastases.

4. Brain histology is difficult and time consuming. Histopathological estimation of tumor is very intricate.

In the same tumor areas of different grades may be diagnosed and it brings problem with classification of such a tumor. Diagnosis mistakes can occur either. An enlargement of the scope of our knowledge about tumors with the detailed analysis of their histological, genetical and chromosomal determinants have not improved the facilitation of diagnosis.

Despite deficient and scanty data, a thorough analysis led us to the conclusion the risk of unintentional and inadvertent transmission of tumors from donors to recipients must be regarded.

Discussion

It seemed reasonable to reevaluate opinions and views which are the results of recent fast progress in basic sciences related to neurooncology and confront them with commonly well known issues escaped many times our notice in course of diagnosis, treatment and potential organs' procurement in cases of CNS neoplastic disorders.

Cancer in organ recipients

The higher risk of developing malignant tumors in transplanted patients is a fact widely acknowledged over last two decades. Transplant recipients evince an increased risk of cancer [4]. Posttransplantation malignancies may be encountered in three areas:
* de novo arising tumor occuring after transplantation;
* cancer that was present in the recipient prior to organ transplantation;
* neoplasm misdiagnosed in the organ donor and inadvertenly transmitted to the recipient within the graft [4,5].

The first group of posttransplantation neoplasms makes most problems. Patients with tumors arising de novo can developed them in all types of solid organ [5]. What is interesting, neoplasms commonly seen in general population , like carcinomas of the bronchi, breast, colorectum, prostate and the uterine cervix were not very common in transplanted patients. Rather mostly unusual tumors were observed [5]. Two of the most common types of neoplasms are skin cancers and lymphomas – posttransplant lymphoproliferative disease (PTLD) [5]. There are no central nervous system tumors among wide spectrum of neoplasms arising de novo in organ allograft recipients [5]. Searching the causes of possibility de novo occuring malignancies was aimed at bringing to mind multiple factors, including:
* direct carcinogenic effects of the immunosuppressive agents;
* general immunosuppressed state;
* oncogenic viruses;
* synergistic effects of other carcinogenic agents (sunlight, hormonal factors, viral infections);
* cancerigenic influence of chemo- and radiotherapy applied to some recipients prior to transplantation (bone marrow) [5].

The main issue we want to acquaint readers with is cancer transferal with the graft occured in recipients. Experiments have demonstrated that cancer can be successfully transmitted into immunosuppressed animals and humans [6]. For that reason patients with a

history of malignancy are now rejected for organ donation. The only exceptions to the current rule precluding organ procurement in cases of donor malignancies are made for:
* low-grade skin cancer (basal cell and squamous cell carcinomas);
* carcinoma in situ (CIS) of the uterine cervix;
* primary central nervous system tumors [4,6,7].

The brain tumors have been warranted by the fact that these neoplasms very rarely spread outside the CNS [4-7]. This group is considered suitable for organ donation since a transdural spread beyond cerebral borders is believed to be unlikely unless a potential donor had undergone cranial surgery, ventriculosystemic shunting or irradiation therapy [7].

The first reports about transmission of cancer from ogran donors evidenced in the 1960's [6]. Since that time Cincinnati Transplant Tumor Registry (CTTR) has been collecting data on such cases. Up to 1997 the CTTR has collected 270 patients with transplanted organs from donors with malignancies [4,6]. 117 patients (43%) received organs transmitted or containing neoplasms [6]. The CTTR reported 5 donors whose CNS tumor was transmitted to 9 recipients [6]. 6 recipients revealed signs of distant metastases that caused death in 5 of them. Unsuspected distant metastases occured from the tumors of 4 donors with glioblastoma multiforme, 1 with medulloblastoma and 1 with unspecified brain tumors.These data from the CTTR are comprised in comprehensive, attainable data from the literature. In accordance with our knowledge and aforesaid the literature statement, 13 cases of CNS tumor transferral with solid organ transplantation nave been reported [4]. In the recipients who developed cancers they were usually histologically identical to those in the organ donors [4]. Jonas and collegues [7] collected data on 342 donor hepatectomies with subsequent transplantation. Primary cerebral neoplasia was cause of 13 donors' death (3.8%) and included: glioblastoma (n=4), meningioma (n=3), astrocytoma (n=2), neurocytoma (n=1) and ependymoma (n=1). There were 46 recipients of organs from these 13 donors. Reccurent malignancy was observed once, in a liver graft recipient, 4 months after transplantation of liver from donor with glioblastoma multiforme. They added to the literature the next case of a liver graft-transmitted brain tumor metastasis.

The transmission risk with organ transplantation
Problem of estimation of the transmission risk with organ transplantation is at present unsettled. There has been no published prospective study on these theme and rate can be only estimated from retrospective studies [4].

The CTTR based on data on 55 donors reported 18% risk of transmission (10 of 55 recipients developed evidence of transmitted malignancy) [4,6]. But it should be taken into account that most of patients who remained well weren't reported to the Registry. Afore-mentioned Jonas et al. [7] based on data on 46 recipients estimated the transmission risk as 2%. Colquhoun et al. [8] reviewed data on 84 recipients from 34 donors and estimated risk as 3%. Due to a small number of analyzed

recipients after the sporadic transmission, this estimation can be admitted as statistical bias [4]. Other retrospective data presented at the Second Meeting of the French Speaking Transplantation Society (Brugge, Belgium, December 1998), 9th Congress of the European Society for Organ Transplantation (Oslo, Norway, June 1999), data from Eurotransplant Foundation database, data from the Australian and New Zealand Transplant Registry and the United Network for Organ Sharing (UNOS) confirm that the risk of transmission with grafts from donor with primary CNS tumor may be evaluated between 0% and 3% [4].

Penn et al. [9] calls in question afore-mentioned sources of data. Many of them provide inadequate information because of including benign tumors, not precisely stated time interval between treatment of malignancy and donation, and uncertainty about complete cure in patients with cancer-free intervals of 5 yearsor more time. Besides there are no data regarding scrupulous treatment of many malignancies. As it is known brain tumors rarely spread outside the CNS spontaneously [9].

If a potential donor has not received any treatment as ventriculosystemic shunts, extensive craniotomies, radiotherapy or chemotherapy, the danger of spontaneous malignant dissemination outside the CNS is extremly small [6].

Distant metastases of the CNS tumors
Albeit at first it was considered that primary brain tumors never metastasize outside the CNS, according to the contemporary knowledge of the neoplastic disease it is unquestionable that metastases occasionally occur [4-6,9].

The incidence of brain tumor metastases has been estimated between 0.4% and 2.3% [10]. The sites of predilection for remote dissemination are (in decreasing rate): lungs, pleura, lymph nodes, bone, liver, heart, adrenal glands, kidney, mediastinum, pancreas, thyroid and peritoneum [11].

There are many theories explaining the low rate of CNS tumors metastases of which some recently have been challanged. Hypothetical factors appointing it are:
* the absence of true lymphatic vessels in brain;
* the true impassable dura;
* the specific metabolic requirements of brain cells;
* the unique extracellular matrix of the brain;
* the tough basement membrane surrounding intracerebral blood vessels;
* the soft walled cerebral veins which present the early occlusion and collapsing by the advancing tumor [4].

Risk factors for extraneural spread of brain tumors are determined. The most important are neurosurgical procedures: craniotomy or ventriculosystemic shunting [4,12]. A major craniotomy opens up direct, vascular and/or lymphatic pathways for extracranial spread and has an immense impact on favoring distant metastases [7,9]. Ventriculoatrial and ventriculoperitoneal shunting provides a route for metastases. Medulloblastoma is reported to be the type of tumor most likely to metastasize via ventricular shunts [13]. Even so, more than 10 % of all reported cases have shown distant metastases

without any previous surgical manipulation [14]. The next factor connecting with widespread neoplastic lesions is high-grade tumor histology, especially glial tumors and medulloblastoma [4,7]. Tumors of glioblastoma group have spread access to the systemic circulation and can implant and grow in lungs, liver and other tissue. The cancerous potential of others primary cerebral neoplasia is less explicit [7]. Previous tumor radiation therapy is also well recognized as risk factor for extraneural seeding of brain tumors [4,12].Another issue is an aggressive multimodality therapy composed of chemotherapy and prolonged use of corticosteroids which may depress the immune system and allow the spread and growth in extraneural location [9].

It must be admitted that precise histological diagnosis of tumor may not be available at the time of organ retrieval and transplantation.With redard to the localization of metastatic tumors it is significant that the liver has tenfold risk of becoming a prime target for metastatic growth of neural malignancies compared to the kidneys [14].To our knowledge only one case of malignancy transmission was connected with heart [15]. Donor suffered from medulloblastoma and underwent a ventriculoatrial shunting.

For all these reasons in cases of grafts from donor with CNS tumor, zero risk of transmission is not achievable [4].

The usability, avails and disposal of organ donors with CNS tumors

Although the number of patients being considered for transplantation has increased steadily, unfortunately the number of donors has remained relatively stagnant. Because the increasing number of potential organ recipients outpaces organ donation, the key issue is to utilize all useful donors and at the same time avoid organs that may bring unexpected hindrances.

Less than 2% of all people who die fulfill the criteria for organ donation [16]. The criteria used to decide whether to use organ are reasonably well established, but they are often weighed differently by different surgeons. Contraindications to cadaveric donation are divided into absolute and relative. When relative contraindications exist, the donor is described as marginal. One of the most important absolute contraindications is presence of malignant tumor – except primary brain tumors [16].

Donors with CNS tumors account for 1% to 4% of the organ donor pool [4,8]. In 1997 the Council of Europe published a document entitled "International Consensus Document" including guiding rules and directions on prevention of tumor transmission from donors to recipients [17]. The panel of experts, basing on pre-cited in this article the CTTR data [6], proposed and adviced guidelines relating to donors with primary CNS tumors. In compliance with the instruction of Council of Europe Consensus Document, CNS tumors watch out for their use for organ donation was divided into three categories:
- CNS tumors that can be considered for organ donation:
  * benign meningiomas

  * pilocytic astrocytomas (grade I)
  * oligodendrocytomas
  * ependymomas
  * schwannomas
  * ganglicytomas
  * gangliogliomas
  * epidermoid cysts
  * colloid cysts of third ventricle
  * choroid-plexus papillomas
  * pineocytomas
  * hemangioblastomas (irrelevant to von Hippel-Lindau disease)
  * well-differentiated teratoma
  * craniopharyngiomas
  * pituitary adenomas
- CNS tumors that can be considered for organ donation depending on special characteristics:
  * low-grade astrocytoma (grade II)
  * gliomatosis cerebri
- CNS tumors that should not be considered for organ donation – unequivocally excluding:
  * anaplastic astrocytoma (grade III)
  * glioblastoma multiforme
  * medulloblastoma
  * anaplastic oligodendrogliomas
  * malignant ependymomas
  * anaplastic malignant meningiomas
  * pineoblastomas
  * chordomas
  * intracranial sarcomas
  * germ-cell teratoma
  * lymphomas [4,17].

Detry et al. [4] point out that only 50%-60% of central nervous system tumors are malignant. That is why a tissue diagnosis plays a crucial role in advance of donor's evaluation and qualification. Biopsy-proven benign intracranial neoplasms don't make problems and contraindications to donation [9,16]. Primary cerebral neoplasia include a variety of diverse neural lesions, which may be indistinguishable by noninvasive diagnostic examination. Therefore histopatologic features are indispensable for the proper diagnosis.Autopsies performed after organ procurement have demonstrated that cerebral metastases of occult primary neoplasms are able to mimic primary brain cancer [6,12]. Thus conviction respecting the origin of brain tumors is essential.

Organ donors with CNS tumors represent only a small portion of donor pool but about 70% of them had undergone surgical intervention prior to braindeath what is one the most important factor for types of neural tumors [7]. Nevertheless the exlusion of these donors will increase the number of deaths on the waiting lists.

In conformity with International Consensus Document [17] donors with high-grade malignant CNS tumors, especially astrocytomas and glioblastomas [7] should be rejected and donors with low-grade malignant brain tumors should be used in special circumstances [17].

Primary tumors of CNS show some different features which give significant meaning for prognosis and treatment.

The relation of the tumor to its surroundings is crucial aspect decided of possibilities of an early diagnosis and totality of removal [18]. The evaluation of the totality of removal depends on the possibility of distinguishing the tumor from the surrounding noninfiltrated tissue. There is a lot of difficulties in differentiation between tumor and its surrounding. Morphological similarities of the tumor and ground tissue where tumor is developing appear very often. It makes the proper diagnosis of the borderline between the tumor and infiltrated surrounding impossible. There are two reasons of such condition: inaccessibility to the subject of examination and morphology of the alteration. The morphological differences between tumor and ground because of demonstration of two different types of texture, are well enough delineated e.g. in carcinoma of the uterine collum, ventricle [18]. This permits to recognize more precisely the various tissue components and the border-line can be established. With regard to primary CNS tumor, e.g. glial tumors, the difficulties in differentiation between the tumor and surrounding are rapidly increasing especially when glial tumors are recognized as highly differentiation [18] and diffuse type of growth. There is no doubt that lack of significant differences between tumor and normal cells of the ground tissue besed on macroscopical and microscopical evaluation makes the distinguishing limited and even impossible. Neither histologic and histochemical nor immunocytochemical methods are safe and dependable to permit the distinction. Usually the recognition of border-line, as neoplastic from non-neoplastic cell, is based on morphological criteria but the most important factor in this diagnostic procedure is expirience of neurosurgeon and neuropathologist [18]. They both play decisive role in the procedure of diagnosis and effectiveness of treatment depending on tumors' removal.

The second valid factor determining totality of removal is localization of tumor. In central nervous system total removal is possible only in limited number of cases. It should be taken into account that enlargement of the surgical defect may give cripplehood as the consequence. In several cases surgery is aiming at decompressing the mass effect ("debulking") and limits to minimize damage and dysfunction of the brain. The surgical procedure are connected with technical difficulties: approaching the various region of the brain, the depth of infiltration. All these factors indicate that lack of differences of tumor texture in relation to ground tissue, lack or uncertainty of morphological criteria in differentiation between neoplastic and non-neoplastic cells in high-grade glioms are the most significant objections in the evaluation of total tumors removal within CNS. On that account we have not sure if the totaly removal was performed and there are no tumor's remnants which can became seeds of recurrent neoplasm. It constitutes unequivocal argument against accounting these patients to be completely cure. CNS tumors have tendency to growing again but with higher grade of malignancy [18,19].

The next point we must pay attention is the discrepancy between morphology and biological behavior of tumors [18]. Recent studies in molecular biology (Watanabe et al. 1998 [20]) confirmed observations that the dissociation between morphology and biological behavior is connected with the following phenomenon: tumors consisting of cells with signs of low activity may behave like highly aggressive one and can condition unfavourable prognosis [37]. The abovementioned authors based upon molecular investigations in the gemistocytic phenotype of astrocytoma state that in spite of proved small proliferative activity (determined with titrated thymidine, bromoxyuridine or with use of the monoclonal antybody Ki-67/MIB 1) [18], prognosis in this type of tumors in unfavorable. Tumor cells evaluated as cells of low proliferative activity are involved in the transformation of gemistocytic astrocytoma in a tumor of higher malignancy. Notwithstanding, this group of tumors is not the only one which display such behavior. In the light of data analogous abnormative aggressiveness was observed in meningiomas [21]. These observations speak in favor of the opinion that tumors with low anaplasia morphologically for unknown reason behave like anaplastic aggressive tumors showing high invasive activity [18,21]. It can be expected that other molecular markers indicating to malignancies with higher accuracy and specificity will bring us closer to the solution of problem with divergence observed between known morphology and biology. Up to now molecular markers as a tool in the biological characterization of brain tumors have not contributed in decisive manner to the effectiveness of treatment, even so they may be associated with clinical parameters as age, and histological as grade.

Another phenomenon closely connected with aforesaid issue is an unexpected enhanced aggressiveness of the CNS tumors despite their morphology. Tumors estimated in accordance with their morphology as low-grade malignant for unknown as yet reason show high proliferative activity [18]. This status most frequently is observed in: astrocytomas of cerebellum, brain stem and optic nerve, oligodendrogliomas, meningiomas and neurinomas [18].

Further factor assigning different biological behaviour of CNS tumors deserves special mention. Age is one of the most important agents in the diagnostic procedure especially in astrocytomas, glioblastomas, oligodendrogliomas and ependymomas [18]. Tumors typically occured in childhood can have completely different behavior than the same type in adults. E.g. astrocytomas predominant infratentorial in childhood and in the majority of cases are benign tumors with good prognosis. Supratentorially localization in adults shows less beneficial prognosis because of their malignancy. Medulloblastomas are predominantly tumors of childhood. Only seldom such primitive and anaplastic texture is found in adults [18,22,23]. On the contrary glioblastoma is tumor of advanced age.

Cytogenetic alterations in the CNS tumors have an important impact on behavior and prognosis of illness. Primary chromosomal changes are associated with initiation or early stages evolution of the tumor [19]. On these changes overlap secondary alterations, which are results of the clonal progression cells subpopulations [19]. Occuring of these deviations can be prognostic

marker of disease. The most characteristic feature for brain tumors, especially for astrocytomas, is various cytogenetic and molecular progression, as well the accumulation of genetic changes during their evolution towards malignant tumor. Predominatingly occuring numerical deviations are:

- accessory chromosome 7 (70-80% of tumors);
- loss of chromosomes: 10 (50-60% of tumors), 22 (15-20%), gonosomes;
- presence of accessory *double bodies* (dmin – double minutes).
  The most common structural deviations are:
- deletions and translocation 9p (35% of tumors);
- abnormalities 19q [19].

Chromosome 7 trisomy is accepted as marker of neoplastic transformation, what is confirmed and documented by Kimmel et al. [24]. Acquirement of accessory chromosome 7 is the mean of genom instability not only in malignant cells but in normal cells. This condition is connected with increased predisposition to acquisition and accumulation chromosomal aberration [25]. PNET-s are generally characterized by diploid karyotype with single structural chromosome aberration, the most common of which are:

- isochromosome 17q (loss of short arm with supressor gene responsible for evolution of medulloblastoma);
- loss of chromosome 22 (deletion often described in desmoplastic medulloblastoma) [19].

Biological and clinical signification of these deviations is not known up to now [22]. The same structural anomaly occures in 60% of meningiomas. Complete or partial deletion of chromosome 22 results from fracture in area q11.2-q12. Loss of heterozygosity (LOH) phenomenon in meningiomas suggest presence of suppressor gene within region 22q12.3 – qter which inactivation is causally connected with initiation and clonal evolution of meningiomas. This type of deletion – described also in other neuroectodermal tumors, e.g. medulloblastoma, glioma and astrocytoma is accompanied unfavourable evolution and progression of these tumors [19,25]. Intensification of numerical and structural chromosomal deviations reveals positive correlation with grade of tumor's cellular atypy and its aggressivity, expressed in recurrence and malignant transformation [19]. Tendency to growing again and cytogenetic alterations in PBT cause that in the vast majority of patients even proper and precisely diagnozed, it is impossible to predict biologic course of disease and its influence upon prognosis and treatment.

Most of neuroepithelial tumors are sporadic, but they can occasionally complicate genetic syndromes. They can be component of complex syndromes associated with developing of various organs' malignancies such as neurofibromatosis type 1, type 2, Li-Fraumeni Syndrome and Turcot's Syndrome [26]. Neuroectodermal tumors can be constituent of phacomatoses-neuroectomesodermal dysplasias (*viscerocystic retinoangiomatosis syndrome*). One of them is von Hippel-Lindau disease (VHL), disorder predisposing affected individuals to central nervous system and retinal hemangioblastoma, renal carcinoma, phechromocytoma, pancreatic islet cell tumors and endolymphatic sac tumors [27]. This autosomal dominant disorder is caused by a mutation of VHL suppressor gene localized on chromosome 3p25 [27].

Over 150 germline mutation have been described and some genotype-phenotype correlation have been characterized. On the basis of this correlation two types of VHL disease were distinguished:

A. Type 1 – with renal cell carcinoma without pheochromocytoma;

B. Type 2 , subdivided into three categories:
  * 2A – with pheochromocytoma but no renal cancer;
  * 2B - with both: pheochromocytoma and renal cell cancer;
  * 2C - with pheochromocytoma only [27].

The CNS tumors and retinal angioma are observed in VHL types 1, 2A and 2B [27]. Hemangioblastoma is the most characteristic and most common presenting manifestation of disease, observed in 44% to 72% of affected individuals. The site of predilection is posterior fossa (80% patients) and spinal cord (20% patient) [27], typically cerebellum (70% of all cases) [28]. Although hemangioblastoma is histologically benign, the dynamics of growth is varied [27,29] and it remains the main cause of morbidity and mortality in VHL disease. Cerebellar hemangioblastoma can be isolated tumor without other manifestation of von Hippel-Lindau disease (known as Lindau's tumor) [28]. However because of fact that the tumor can be symptom of syndrome, in each case apart from fundamental management, it require wider diagnostics [29]. Presence of hemangioblastoma indicates the other neoplasm: renal cell carcinoma, pheochromocytoma, retinal changes or pancreatic tumor. Risk of diagnosis VHL disease in case of hemangioblastoma is approximately 20%. Reccurence of tumors after treatment is registered in 8% of cases [29]. For that reason at the moment of diagnosis we don't know whether there are seeds of tumor in kidneys, adrenals, pancrea, liver, which will be revealed through natural way in 3rd decade of life or under the influence of immunosupression after transplantation.

PNET-s in the majority of cases are sporadic tumors, notwithstanding there are reports about familial predisposition [30]. It is demonstrated that we can observe genetically determined clinical syndromes in which neoplasms of varied but characteristic organic localization appear with high rate in families. There is well-known category of familial diseases: syndrome of inherited predisposition to tumors, comprising as well the CNS tumor. Three of them deserve special remarks on account of their comparatively frequent occurrance and connections with brain tumors: Li-Fraumeni Syndrome (LFS), Turcot's Syndrome and Syndrome of familial predisposition to brain tumors [26,27]. Li-Fraumeni syndrome, describe in 1969, is a rarely diagnosed syndrome of inherited tendency to tumors caused in most cases by inactivation of p53 gene on 17 chromosome [31,32]. Tumors occuring in families the most frequently are sarcomas (rhabdomyosarcoma), breast cancer, leukemias, cancer of the suprarenal glands and brain tumors. The most common are gliomas, than PNET-s [31,32]. Approximately 50% families with LFS show mutation within chromosome 17, gene p53 [31]. Tumors

in patients suffer from LFS present aggressive course. Mean age in the moment of diagnosis in these individuals is 25 years [32]. Turcot's syndrome we define as familial intestinal polyposis associated with primary brain tumors of type glioblastoma multiforme or PNET [30]. There are also examples of familial brain tumors in the absence of any known genetic syndrome [2]. Multiple meningiomas are found in patients with neurofibromatosis type 2. Moreover, all meningiomas are characterized by the loss of chromosome 22q, which is also the molecular marker of neurofibromatosis type 2 [33]. Patients with breast cancer have an increased frequency of meningiomas, which need to be distinguished from metastases to brain [34].

The present focus of research on cancer let us progressively understand a specific cancer's behavior at the molecular level and exploit the genetic aberrations of the malignant cell to devising of highly specific and effective therapy. But the heterogenity of tumors, their unforeseeable arising, the delivery of therapy cause that former regimen and procedires in patient are ineffective. The first step to including these group of potential donors into donors pool is improving the diagnosis and care of patients with CNS tumors. Brain tumors show different proliferative activity and their biological behavior many times disagree with our pathological and clinical experiences.

Conclusions

The aim of this review was to present the literature and own experience on pathways of malignant dissemination in cases of primary CNS tumors and organ donors

with these tumors. We shall conclude by saying that our considerations and reflections are aimed at helping transplant physicians in the decision process to refuse or accept organ harvested from this pool of donors.

No wonder that, as other aforementioned authors, we are looking for an answer to the questions about the use of donors with CNS malignancies.

Many factors contribute to an insufficient number of organ donors. General distrust of the health care system, religious myths, ethical dilemmas and misperceptions regarding consent to donation are alas common among people.

However some issuances [7] do not recommend the use of donors suffering from primary CNS tumors for organ, especially liver, transplantation, the authors, like others [6,8], consider that patients with CNS tumors should be accepted as donors as long as the risk of dying on the waiting list is much higher than risk of tumor transmission from donor to the recipient. Exclusion of these potential donors would lead to a decrease in the donor pool and would unnecessarily waste valuable organs.

Organ transplantation is a lifesaving procedure that brings other numerous known complications, difficulties and liabilities. Watch out for that issue donor's tumor transferal is very rare and may occure even using organ from donor with no history of malignancies [4].

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