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COEXISTENCE OF MULTIPLE SCLEROSIS AND BRAIN TUMORS: A LITERATURE REWIEW

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Ключевые слова: *рассеянный склероз, опухоль мозга, демиелинизирующие заболевания, глиома, глиобластома, астроцитома, олигодендроглиома*
Key words: *multiple sclerosis, brain tumor, demyelinating diseases, glioma, astrocytoma, glioblastoma, oligodendroglioma*

Abstract. Coexistence of multiple sclerosis and brain tumors: a literature review. Sirko A.H., Dzyak L.A., Chekha E.V. *Concurrent development of primary brain tumors and multiple sclerosis is quite rare. Only a few dozens of such comorbidity have been reported. Nevertheless, given the fact that such pathologies are characterized by similar clinical picture and neuroimaging findings, issues about diagnosis and differential diagnosis of such conditions often arise, which makes the problem relevant. A literature review was conducted using PubMed, by selecting articles on concurrent multiple sclerosis and brain tumors, particularly glial origin tumors, over the past 20 years (1989 to 2019). The search was performed in English, Russian, and Ukrainian using the following key words and terms: comorbidity, concomitance, multiple sclerosis, brain tumor, glioma, astrocytoma, glioblastoma. The analysis included all articles on etiology, pathogenesis, clinical picture, diagnosis, differential diagnosis, neuroimaging, and pathomorphological assessment. After identifying all the articles that met the inclusion criteria and removing duplicate data, 35 literature sources on concurrent primary brain tumors and multiple sclerosis were selected. The conclusion on whether concurrent primary brain tumors and multiple sclerosis develop randomly or have common pathophysiological mechanisms is still under discussion. Potential causes of pathogenesis of both diseases include viral infection, chronic inflammation, neoplastic transformation, and involvement of neurotropic growth factors. The likelihood that two processes, demyelinating and neoplastic, can develop in parallel will never be underestimated. In such cases, strong clinical suspicion arises due to atypical clinical picture characterized by aggressive and rapidly growing neurological symptoms such as aphasia, spastic hemiparesis, epileptic seizures, or signs of intracranial hypertension. In MRI diagnosis, pathological findings such as single lesion of more than 2 cm; mass effect, edema, signal amplification in the form of ring-shaped shadow are the reasons for a more thorough examination and applying additional diagnostic methods: CT, MR spectroscopy, PET, CSF tests to determine oligoclonal antibodies and other markers content, cerebral biopsy. According to the literature, cases of concurrent primary brain tumors and multiple sclerosis are rare though described. Atypical clinical signs, neuroimaging data, and cerebral biopsy which is currently considered as the only method for making accurate diagnosis are helpful in the diagnostic process.*

Реферат. Співіснування розсіяного склерозу та пухлин головного мозку: огляд літератури. Сірко А.Г., Дзяк Л.А., Чеха К.В. *Паралельне виникнення первинних пухлин головного мозку і розсіяного склерозу зустрічається досить рідко. У літературі описано всього декілька десятків випадків подібної коморбідності. Однак, з огляду на той факт, що такі патології характеризуються схожими клінічними проявами і подібними нейровізуалізаційними знахідками, часто виникають питання про діагностику і диференціальну діагностику таких станів, що робить проблему актуальною. Проведено огляд літератури за допомогою бази даних Pubmed, вибрано статті, присвячені поєднанню розсіяного склерозу і пухлин головного мозку, зокрема пухлин гліального походження, за останні 20 років (з 1989 по 2019 рік). Пошук виконувався англійською, російською, українською мовою з використанням таких пошукових слів і термінів: коморбідність, поєднання, розсіяний*

склероз, пухлина головного мозку, гліома, астроцитома, гліобластома. В аналіз були включені всі статті з інформацією про етіологію, патогенез, клініку, діагностику, диференціальну діагностику, нейровізуалізаційну і патоморфологічну оцінку. Після ідентифікації всіх статей, які задовольняли критеріям включення і видалення повторюваних даних було відібрано 35 джерел літератури, що стосуються поєднання первинних пухлин головного мозку і розсіяного склерозу. Тривають дискусії з приводу того, чи є поєднання первинних пухлин головного мозку і розсіяного склерозу випадковим або має спільні патофізіологічні механізми. Факторами, залученими в патогенез обох захворювань, можуть бути вірусна інфекція, хронічне запалення, неопластична трансформація і участь нейротропних факторів судинних та клітинних факторів росту. Ніколи не слід недооцінювати ймовірність того, що два процеси, демієлінізуючий і пухлинний, можуть розвиватися паралельно. У подібних випадках атипова клінічна картина у вигляді агресивної і швидко наростаючої неврологічної симптоматики, такої, як афазія, спастичний геміпарез, епілептичні напади, ознаки внутрішньочерепної гіпертензії зумовлюють високий рівень клінічної настороженості. При МРТ-діагностиці виявлення нетипових даних у вигляді одиночного вогнища, площею понад 2 см; мас-ефекту, наявність набряку, посилення сигналу у вигляді «кільцеподібної тіні» також є приводами для більш ретельного обстеження і підключення інших методів діагностики: КТ, МР-спектроскопії, ПЕТ, дослідження ліквору на наявність олігоклональних антитіл й інших маркерів, а також церебральної біопсії. За даними літератури, поєднання первинних пухлин головного мозку і розсіяного склерозу є рідкісною, але описаною патологією. Допомогою для точної діагностики в такому випадку є атипові клінічні прояви, нейровізуалізаційні дані, а також церебральна біопсія, яка на цей момент є єдиним методом для встановлення точного діагнозу.

Multiple sclerosis (MS) is a chronic autoimmune inflammatory, neurodegenerative (primarily demyelinating) multifactorial nervous system disease [23]. MS is one of the primary causes of non-injury disability in young and middle-aged people [32]. According to different estimates, 2 to 3 million people worldwide have MS [11]. MS incidence in a population varies widely: from high in Europe and North America (over 100 per 100,000 inhabitants) to low in Africa, Japan, and other Asian countries (2 per 100,000) [34], however even such figures may be not reliable due to incomplete data on over populated countries such as China and India [2].

Primary CNS tumors are diverse in terms of biology and genetics [16]. According to the WHO classification, there are about 100 subtypes of 29 histological variants of primary CNS tumors [33]. Cerebral tumors account for approximately 3% of all cancer cases [21]. Mortality in cerebral tumors remains high [24]. Brain cancer prognosis depends on patient's age and tumor histology. Most cerebral neoplasms develop from glial cells [6].

MATERIALS AND METHODS OF RESEARCH

A literature review was conducted using PubMed, by selecting articles on concurrent multiple sclerosis and brain tumors, particularly glial origin tumors, over the past 20 years (1989 to 2019). The search was performed in English, Russian, and Ukrainian using the following key words and terms: comorbidity, concomitance, multiple sclerosis, brain tumor, demyelinating diseases, glioma, astrocytoma, glioblastoma. The analysis included all articles on etiology, pathogenesis, clinical picture, diagnosis, differential diagnosis, neuroimaging, and pathomorphological assessment. After identifying all the articles that met the inclusion criteria and removing duplicate data, 35 literature sources on concurrent primary brain tumors and multiple sclerosis were selected.

RESULTS AND DISCUSSION

Gliomas make up to 70% of all cerebral neoplasms and glioblastomas are the most common and malignant histological subtype among them [7]. According to literature, including CBTRUS, 61.5% of all gliomas are glioblastomas, 18.8% – non-glioblastoma astrocytomas, 10.7% – oligodendrogliomas, 3.6% – ependymomas, and 5.4% – other gliomas [31]. A to glioma occurrence growth tendency is reported in industrial developed countries. Higher incidence is in Caucasians vs. Africans and Asians. Except for pilocytic astrocytomas (WHO Class I), glioma patients have a poor prognosis. According to some reports, a 5-year survival in glioblastoma patients is less than 3%.

In general, global risk of cancer development in multiple sclerosis (MS) patients is important. This is due to the fact that such patients undergo immunomodulatory therapy, which may potentially have an impact on the risk of cancer in any location [21]. However, the data on cancer occurrence in MS patients is contradictory. Some sources report that this cohort of patients generally has lower risk of developing cancer [28], including gastrointestinal tract, prostate, and ovarian cancer [34], or Non-Hodgkin's Lymphoma [3]. At the same time, there is an increased risk of urinary tract and nasopharyngeal cancer. Other sources report higher incidence of cancer, including breast cancer in MS patients [8].

Brain cancer occurrence in MS patients is typically higher than in the general population and makes up 1.44 (1.21-1.72) [14]. The same can be said about detectability of primary CNS tumors in

MS patients. This is probably due to the alertness of MS patients regarding relapses and regular neuroimaging screening [10]. According to some authors, systematic analysis of the data did not show increased or decreased risk of glioma in MS patients, while an increased risk was found for meningiomas [32]. It is also reported that some autoimmune diseases, including MS, may adversely affect the survival in gliomas and meningiomas.

The combination of MS and glial origin cerebral tumors is rarely found in scientific literature [4, 6]. This comorbidity was first described in 1912 by Bosch. Since 1960, several dozen cases of combined MS and cerebral neoplasm have been described in the literature [13].

MS is considered to be a basic pathology with subsequent development of brain gliomas, most often of astrocytic origin [15]. MS association with other histological subtypes of cerebral tumors, including astrocyte, oligodendrogliomas, and glioblastomas, has been also described [23, 30]. Nevertheless, it is rather difficult to assess true brain tumors occurrence in MS patients.

We cannot exclude common etiopathogenetic factors of brain cancer and multiple sclerosis. This applies to ethnic factors and race — both gliomas and MS are more common in Caucasians [12]. Influence of infections, viruses, and allergens — JC polyomavirus (JCV) [19], or Epstein-Barr infection (EBV) carrier increases the risk of development of both MS and CNS lymphoma, but not glial tumors [27]. There were no significant correlations with such etiological factors as age: brain tumors are more common in children and elderly persons; MS, in young and middle-aged people. Sex: cerebral neoplasms develop more frequently in men, while MS is more common in women. There is no evidence to confirm possible association between MS and ionizing radiation, intoxication, electromagnetic radiation, which are identified brain cancer risk factors [10].

Discussions are continuing as to whether immunomodulatory treatment in MS patients can contribute to cancerogenesis. According to a recent study, it was found that MS patients who take immunosuppressants generally have a higher risk of cancer; some sources mention the risk of 2.26% (2.02% in women, 2.7% in men) [28, 30] and the authors point out the need for further study.

Currently, the diagnosis of both brain tumors and multiple sclerosis is based on clinical and neuroimaging data [17, 11].

In 2016, MS criteria were updated to become the “gold standard” of diagnosis. The first criteria developed by MAGNIMS in 2010 are known as the McDonald criteria. Since the beginning of 2011, as new information was obtained from the studies conducted, among other methods, with high (3.0 T and 7.0 T) magnetic field strength MR scanners, the need to revise some of 2010 McDonald criteria arose. This resulted in creation of a new, 2016, version of the MAGNIMS criteria, last amended in 2017. The two most significant changes included in the 2017 amendment are the following [6, 11]:

- MS can be diagnosed early in patients with a clinically isolated syndrome given that a patient has dissemination in space, oligoclonal antibodies in CSF, while such diagnosis does not require dissemination in time;
- symptomatic and/or asymptomatic MR lesions, except for optic tract lesions, can be assessed in terms of dissemination in space and time.

Nevertheless, similar clinical signs of multiple sclerosis (MS) and cerebral neoplasms raise a question on the need of differential diagnosis of such conditions. Of all cerebral tumors, multiple sclerosis is most often masked by primary CNS lymphomas which have similar neuroimaging parameters [8, 12].

Despite the availability of various neuroimaging methods [28], clinical cases remain difficult to verify. The literature describes neuroimaging parameters which are atypical for MS, such as:

- single lesion with area of > 2 cm,
- mass effect,
- edema,
- signal amplification in the form of a ring-shaped shadow [25].

To describe such brain lesions in MS, the terms demyelinating pseudotumor, tumor-like demyelinating lesions, and giant plaques are used. Clinically, they are associated with aggressive and rapidly growing neurological symptoms, such as aphasia, spastic hemiparesis, and epileptic seizures, and intracranial hypertension signs [5]. Therefore, it is exactly these signs of MS that often mimic brain tumors and vice versa. In such cases, other diagnostic methods, such as CT, MR spectroscopy, PET, CSF tests to determine oligoclonal antibodies and other markers content, cerebral biopsy [20], are considered helpful.

With such comorbidity, the signs of perifocal edema typical of a tumor resolve after standard glucocorticosteroid therapy, which makes differential diagnosis difficult [9]. Also, according to the literature [33], the spectroscopic picture in case of inflammatory changes in cerebral tissues includes: decreased N-acetyl aspartate spectra and increased choline spectrum, accompanied by cell destruction. This data may have no informative value for

differential diagnosis of demyelinating lesions and highly malignant gliomas [31].

Therefore, in most cases, cerebral biopsy is the only diagnostic method in case of atypical clinical and radiological characteristics [17]. On the other hand, the likelihood that two processes, demyelinating and neoplastic can develop in parallel will never be underestimated [33].

According to current concepts about pathophysiological MS development mechanisms, treatment approaches are as follows: control of disease exacerbations (so-called relapse) using high doses of steroid hormones — a "pulse therapy" and disease-modifying treatment aimed at preventing and reducing exacerbations incidence and preventing disease progression, and symptomatic therapy which involves the use of different drug groups: immunomodulators, interferon preparations, monoclonal antibodies, amino acids, and cytostatics. Treatment will be selected individually and regulated by international clinical recommendations implemented in many countries, including Ukraine.

Cerebral neoplasms treatment approaches depend on tumor histological subtype and are also regulated by international standards [9]. High grade gliomas treatment usually involves cytodestructive therapy followed by radiotherapy and/or chemotherapy [15, 32].

Brain gliomas and multiple sclerosis comorbidity is rare but this pathology is described in the literature. It is not completely clear whether their occurrence is accidental or consequential to pathophysiological mechanisms that are similar to carcinogenesis, such as autoimmune processes, immunosuppression, chronic inflammation, or certain genes expression [31].

Recently, data on possibly common genetic determinants of multiple sclerosis, cancer, and neurodegenerative diseases are released to the public [26, 30].

There are several assumptions that indicate possible relationship between MS and cerebral neoplasms. On the one hand, this can be explained by chronic inflammation that causes destruction of myelin sheaths of nerve fibers and hyperproliferation of cells involved in remyelination: firstly, oligodendrocytes during active phases of a disease and, secondly, astrocytes involved in old plaques [5].

This theory is supported by occasional studies based on morphological changes in brain tissues in MS, when cells with signs of dysplasia and intermediate characteristics between reactive glial cells and tumor cells were detected [29]. This fact is also confirmed by the data on nerve growth factors (neurotropic growth factors), which not only stimulate the recovery of oligodendrocytes and remyelination in multiple sclerosis, but also may contribute to neoplastic transformation of nerve glial cells [23].

In addition, MS patients have a higher incidence of multifocal gliomas, which can be explained by the so-called Willis theory (a two-stage hypothesis). According to the theory, neoplastic transformation occurs in 2 stages: the first stage is associated with changes in brain parenchyma due to multiple sclerosis; the second is due to the influence of external stimuli such as virus infection [19, 23], biochemical and hormonal factors that stimulate neoplastic transformation.

During histopathological examination, signs of persistent DNA-viral infection in a biopsy specimen cells were verified, which can indirectly confirm the above theories of tumor and multiple sclerosis pathogenesis [7].

It is also evidenced that adding drugs for multiple sclerosis treatment (teriflunomide) to gliomas treatment improved clinical outcomes and survival in mice in experimental environment. Such data also suggest possible common pathogenetic mechanisms of both diseases [31].

CONCLUSION

1. There is still insufficient data to understand whether MS affects tumor growth intensity. Complexity of diagnosis and errors in neuroimaging are noteworthy as, for example, pseudotumor form of MS can mask gliomas or early-stage gliomas can resemble MS. On the other hand, new symptoms may indicate clinical MS progression rather than tumor growth and vice versa.
2. Patient's clinical evaluation plays the leading role in differential diagnosis of gliomas and relapse of multiple sclerosis. Clinical suspicion of wrong diagnosis will arise if a patient has steady progression of neurological deficiency for 4 weeks or more.
3. Additionally, symptoms that are not typical of multiple sclerosis, e.g. disorders of consciousness, convulsive seizures, will cause more detailed examination with application of additional diagnostic techniques: cerebrospinal fluid study, contrast enhanced MRI, spectroscopy, positron emission tomography, and, ultimately, brain biopsy, which currently remains an indispensable diagnostic method in controversial cases.

Conflict of interests. The authors declare no conflict of interest

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