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Significance of genetic and radiological examinations in diagnosis and therapy of brain glioma in adult patients

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Molecular and imaging studies are applied along with histopathology in diagnosis and differential diagnosis of brain gliomas and they enable personalised clinical management. With knowledge of the patient's clinical condition, a decision whether to observe the patient or proceed to immediate surgical treatment is made based on imaging results. On the other hand, knowledge of molecular predictive markers allows optimisation of chemotherapeutic decisions, e.g., introduction of personalised therapy (application of such drugs as temozolomide, bevacizumab, vemurafenib, dabrafenib and trametinib).

Key words: brain gliomas, personalised medicine, molecular diagnostics, imaging diagnostics, MRI, perfusion MRI, MR spectroscopy, diffusion tensor MRI, fMRI, temozolomide, bevacizumab

Gliomas are among the most common brain tumours (they account for approximately 60% of all tumours in this region), and their clinical course is highly malignant (the average survival time of treated patients is 14–15 months, and for untreated patients 2–4 months). About 3–5 / 100,000 of these neoplasms are diagnosed each year, with a slight predominance of men. Gliomas can develop at any age, but the peak incidence occurs in the fifth and sixth decades of life. Diagnostics is based on the clinical symptoms of the disease, results of imaging studies and histopathological diagnosis [1].

Gliomas are classified by their location (supratentorial and infratentorial), malignancy (from more benign – grade I, to the most malignant ones – grade IV) and the origin of the glial cells [2]. Histopathologically, these tumours are classified based on the cell morphology. With the development of molecular techniques, molecular classification has been introduced, contributing to establishment of an integrated histopathological and molecular classification of brain gliomas.

Histopathological classification of brain gliomas

Histopathologically, gliomas are classified according to the origin of the glial cells into the following categories (tab. I):

- astrocyte tumours (*astrocytomas*),
- tumours of glial ependyma (*ependymomas*),
- oligodendrocyte tumours (*oligodendrogliomas*),
- mixed gliomas (arising simultaneously from different types of cells, but mostly originating from astrocytes or oligodendrocytes) [1, 3].

Currently, according to the 2016 WHO classification, typology of gliomas takes into account not only the histopathologic diagnosis (phenotype), but also molecular alterations of the tumour cells (genotype). The objective is to apply persona-

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lised therapy (individual for a given patient). In rare cases of incompatibility, the genotype of the tumour dominates its phenotype [4].

Molecular classification of brain gliomas

Gliomas are characterised by high genetic heterogeneity, which is observed both within the tumour itself and in brain tumours of the same histopathological diagnosis in different patients. The high molecular diversity of gliomas has substantiated the questioning of clonal theory of development of these tumours (from a single cell) in favour of the multicellular aetiology. Molecular heterogeneity makes both the diagnosis and treatment of gliomas difficult.

Molecular changes in gliomas, as in all neoplasms, can occur at different levels of genome organisation and functioning, that is:

- mutations in genes crucial for neoplastic transformation of gliomas,
- copy number alterations – CNA (the number of copies of genome fragments may change,
- alterations of genes expression (promoter hypermethylation).

Detailed molecular studies of gliomas have shown that among tumours classified by histopathology into the same group, there are subgroups defined by pattern of molecular alterations. This molecular variation is the cause of different clinical course and response to treatment in patients with the same form of tumour, as defined by histology. Therefore, understanding the genetic changes underlying the neoplastic transformation of cells allows for searching for a targeted treatment.

First systemic classification of glioblastoma multiforme (GB) based on molecular alterations has been published in 2008 (The Cancer Genome Atlas [TCGA] Research Network). GBM has been divided into four subtypes with defined dominant genetic changes in each of these subtypes:

- classical – amplification of chromosome 7, deletion of chromosome 10 and amplification of the *EGFR* gene – present in almost 100% of these tumours,
- mesenchymal – deletion or inactivating mutation of the *NF1* gene,
- neural – mutations in the *NEFL, GABR1, SLC12A5, SYT1* genes,
- proneural – mutations in the *IDH1* and *PDGFRA* genes.

Particular GBM subtypes are associated with specific prognosis and treatment response [5, 6]. As demonstrated by Verhak et al., comprehensive treatment with chemotherapy and radiotherapy, or with more than three cycles of chemotherapy, gave positive results in patients with classical, mesenchymal and neural glioblastoma multiforme [7].

Development of molecular testing techniques deepened the knowledge of genetic changes in brain tumour cells, leading to publication in 2016 of the WHO classification of brain gliomas based on integrated histopathologic and molecular assessment [8, 9]. In this approach, gliomas – classified histopathologically as astrocytomas, oligodendrogliomas and oligoastrocytomas are divided depending on the present genetic changes into the group of tumours with *IDH* mutation and:

- with *ATRX* and *P53* mutation (diffuse astrocytomas with *IDH* mutation),
- 1p / 19q codeletion (oligodendrogliomas with the *IDH* mutation and 1 / 19q codeletion),
- without *IDH* mutation (diffuse astrocytomas without *IDH* mutation, oligodendrogliomas without *IDH* mutation),
- undefined in other groups (not otherwise specified – NOS).

The presence of the *IDH1 / IDH2* gene mutation is of key importance in the classification of diffuse brain gliomas. Diversity of molecular alterations observed in the said types of gliomas indicates that these are molecularly separate sub-groups.

GBMs without *IDH* mutation are clinically classified as *de novo* tumours. They occur in almost 90% of patients over 55 years of age and display a more aggressive clinical course than gliomas with *IDH* mutation. They are also characterised by frequent (30–50% of cases) hypermethylation of the promoter of *MGMT* gene, which is associated with a better response to treatment with alkylating agents such as temozolomide.

GBMs with *IDH* mutation are usually tumours derived from diffuse poorly differentiated gliomas and are most often diagnosed in younger patients. The NOS group includes tumours in which the mutational status of *IDH* could not be identified. In such cases, in order to rule out the rare *IDH* mutations, sequencing of these genes is highly recommended [8].

Table I. Classification of gliomas by the type of cells they originate from and by malignancy [1, 3]

Cell type	Examples of gliomas	WHO grade
astrocytomas	pilocytic astrocytoma diffuse astrocytoma anaplastic astrocytoma glioblastoma multiforme	grade I grade II grade III grade IV
ependymomas	ependymoma subependymoma ependymoma anaplastic ependymoma	grade I grade I grade II grade III
oligodendrogliomas	oligodendroglioma anaplastic oligodendroglioma	grade II grade III
mixed gliomas	oligoastrocytoma	grade II/III

Tumours with *IDH* gene mutation are divided, depending on the molecular changes, into two subgroups:

- with codeletion of short arm of chromosome 1 (1p) / long arm of chromosome 19 (19q) and mutation of the promoter of *TERT* gene,
- with mutation of *ATRX* and *P53* genes.

With these mutations, it is possible to determine which group of glial cells (astrocytes or oligodendrocytes) is the origin of the lesion, and 1p / 19q deletion is the differentiating feature for oligodendrocytes regardless of the histopathologic image of the lesion.

In GBMs with the *IDH* mutation derived from poorly differentiated astrocytomas (identifiable by presence of *ATRX* and *TP53* mutations), hypermethylation of the *MGMT* promoter is also common. It involves better prognosis for patients treated with alkylating agents [10].

Radiological diagnosis of gliomas

The imaging method of choice in diagnosing gliomas is magnetic resonance imaging (MRI) [11, 12]. Computed tomography (CT) may be helpful in detecting calcifications, which are quite common in oligodendrogliomas and ependymomas. Moreover, as a method more easily available than MRI, CT is often used as a preliminary examination in cases of unclear neurological symptoms. Positron emission tomography (*PET*) combined with CT (PET / CT) is a complementary method that allows assessment of malignancy of gliomas by determining the degree of uptake of fluorodeoxyglucose (FDG) or other radiometabolites [13, 14]. There is hope for future developments with combination of PET and MRI (PET/MRI) in which functional advantages of PET in defining malignancy of gliomas are added to precise morphological assessment with MRI [15].

However, the currently recommended primary MRI protocol for imaging brain tumours includes the following sequences: 3D T_1-weighted imaging, T_2 / FLAIR, DWI, SWI, contrast-enhanced 3D T_1-weighted imaging performed with a MR unit with a magnetic field strength of at least 1.5 tesla [16]. In everyday clinical practice, thin-section (1 mm) 3D T_1 sequence with contrast enhancement is applied. It is used to develop a 3D plan of neurosurgery, referred to as neuronavigation [17, 18].

Objectives of MRI in diagnosing gliomas

Confirmation of a proliferative process

Gliomas are easily detected by MRI. Most of them are hypointense in T_1-weighted images, and hyperintense in T_2-weighted images and the FLAIR sequence. They are usually surrounded by a zone of finger-like vasogenic oedema and cause a mass effect of compression of the ventricular system, extracerebral fluid spaces and other intracranial structures. Upon contrast administration, malignant gliomas (HGG, WHO 3 and 4) display regular contrast enhancement, while highly differentiated gliomas (LGG, WHO 1 and 2) usually enhance minimally or do not enhance at all [19, 20].

Differentiation with non-neoplasmatic processes, such as ischaemic changes

Some non-neoplasmatic processes may mimic gliomas. For example, ischaemic changes in the subacute period may have similar signal characteristics and display partial contrast enhancement [21]. Differentiation is based on history, additional MRI sequences (restriction of diffusion in diffusion-weighted imaging in the first 7–15 days after ischaemic stroke; decreased perfusion in perfusion MRI) and the dynamics of the MRI image in follow-up studies (evolution of ischaemic infarction). Also, brain abscesses and other inflammatory processes can mimic the appearance of gliomas, especially highly differentiated ones. Patient history, microbiological tests and the MRI pattern itself are helpful in diagnosis [22, 23].

Differentiation of gliomas from other proliferative processes e.g., lymphomas, metastases

MRI appearance in non-glioma intracranial tumours may be similar to those of gliomas, but their detailed analysis often allows for proper diagnosis. For example, lymphomas, as hypercellular tumours, show diffusion restriction and at the same time have low perfusion [24]. Metastases are typically located on the interface of the white and grey matter, and have a disproportionately large zone of oedema compared to the size of the tumour itself [25]. Meningiomas and neuromas are located extraaxially and usually provide strong and uniform enhancement [26].

Grading of gliomas

Standard MRI has limited potential of assessing the grade of tumour malignancy. The main symptom in this regard is the contrast enhancement. Low-grade gliomas (highly differentiated) most often do not enhance or their enhancement is slight, while high-grade, undifferentiated gliomas generally display strong, although heterogeneous, contrast enhancement. Further, malignant gliomas frequently contain hypointense necrotic zones and are surrounded by a more extensive oedema zone than low-grade gliomas [27, 28]. Advanced MRI techniques are also useful in assessing the malignancy of the tumour.

Attempt at differentiating particular forms of gliomas

The possibilities of suggesting a specific histopathological type of cerebral glioma based on a standard MRI examination are limited. Glioblastoma multiforme usually displays a characteristic pattern of a multifocal tumour, frequently affecting both cerebral hemispheres (butterfly glioma) with irregular contrast enhancement and areas of necrosis [29]. Calcifications are a characteristic feature of oligodendrogliomas [30], while ependymomas are distinguished by a characteristic intraventricular location [31].

Importance of radiological studies in the prognosis and treatment planning of brain gliomas

Correct diagnosis of glioma, and especially determination of its malignancy grade, is of key importance in determining the therapeutic management.

In the case of benign gliomas (low-grade glioma – LGG), patient follow-up is often used to avoid postoperative complications (watch and wait approach). On the other hand, in the case of malignant gliomas (high-grade glioma – HGG), surgical intervention is indicated as soon as possible. However, in a standard MRI examination, the appearance of some HGGs may mimic LGGs and vice versa [32, 33]. Therefore, advanced magnetic resonance imaging techniques are increasingly used to determine the severity of gliomas, which is important for the decision on the type of treatment and correct qualification for surgery. These techniques provide more precise information about the tumour's aggressiveness and thus they help to distinguish LGGs from HGGs or to diagnose low-grade gliomas with a high risk of progression to HGG and to facilitate the decision on the application of the *watch and wait approach* or surgical procedure [16].

Among the advanced MRI techniques applied in diagnosis of gliomas, MR spectroscopy (magnetic resonance spectroscopy – MRS), perfusion MRI (perfusion-weighted imaging – PWI), diffusion tensor imaging (DTI) and functional MRI (fMRI) are the most commonly applied [34].

The main goals of the MRI examinations are:

- to confirm the neoplastic nature of the lesion,
- to assess the tumour's location,
- to assess the mass effect,
- to assess compression of the ventricular system and surrounding structures,
- to assess vascularity of the lesion [35, 36].

Among the basic MRI techniques, the following are of special importance: contrast-enhanced T1-weighted sequence, diffusion-weighted imaging (DWI) and magnetic susceptibility sequence (susceptibility-weighted imaging – SWI).

As the blood-brain barrier is damaged in abnormal tumour tissues, there is pathological enhancement of this area in sequences following administration of a contrast agent. The literature describes a positive correlation between presence of contrast enhancement and higher degree of malignancy of gliomas [37].

The DWI sequence is based on assessment of free movement of water molecules, and thus it enables definition of:

- cell structure of the lesion,
- oedema surrounding the lesion,
- hypoxia area inside the tumour,
- integrity of white matter tracts,
- presence of postoperative injuries [38].

In order to fully assess diffusion, DWI images should be interpreted together with the values of the apparent diffusion coefficient (ADC), which is automatically visible as an ADC map. Numerous studies have shown that a reduced ADC value is an independent biomarker that indicates a much worse prognosis in both gliomas and brain lymphomas [34].

Meanwhile, SWI sequence is highly sensitive to blood products, as well as calcifications. It allows visualisation of even very small microbleeds inside the tumour, as well as assessment of vessel structure. It has also been observed that presence of bleeding and necrosis within the lesion is more common in poorly differentiated gliomas (HGG) [38].

Among the advanced sequences, magnetic resonance perfusion imaging (PWI) is the most important. It is performed after administration of gadolinium contrast using the DSC (dynamic susceptibility contrast) or DSE (dynamic contrast enhancement) technique, or without contrast administration using the ASL technique (arterial spin labelling) [34]. With PWI, tumour angiogenesis and vessel proliferation can be defined. In malignant gliomas, vessels are tortuous and improperly formed, which results in leakage and abnormal blood flow in the brain. Perfusion studies are assessed on colour maps which display cerebral blood volume (CBV) and vascular wall permeability, expressed by the Ktrans parameter [16]. High-grade tumours show an increase in CBV as well as of Ktrans parameter. It is assumed that the rCBV value > 1.75 (determined in relation to normal white matter) may indicate pathological, neoplastic angiogenesis [16]. Increased perfusion parameters in imaging studies within the long-term follow-up of LGG patients are important for assessment of tumour progression, because approximately 50% of LGGs transform to a higher grade within 5 years. This can be detected in a PWI study [33]. Moreover, within the oedema surrounding gliomas with a lower degree of differentiation, an increased rCBV values were also observed, which indicates tumour infiltration into the surrounding tissues - this is not found in the oedema surrounding metastatic lesions. PWI enables a more precise biopsy of the tumour (which should be performed in the part of the tumour with the highest perfusion), which in turn translates into qualification for appropriate treatment [39]. The Ktrans perfusion parameter enables an additional assessment of malignancy of gliomas. With greater vascular permeability, probability of malignancy is higher [37].

Magnetic resonance spectroscopy provides information about the biochemical as well as metabolic profiles of the tissue. In the course of brain glioma development, an increase in choline (Cho) and a decrease in N-acetylaspartate (NAA) are observed. Higher values of the Cho/NAA ratio and the Cho/Cr ratio (choline / creatine) indicate the lower degree of tumour differentiation, which means a higher grade of malignancy [38]. Moreover, Castillo et al. demonstrated that in LGG tumours values of the ml/Cr ratio (myoinositol/creatine) are statistically significantly higher than in other types of brain tumours [40].

The challenge in treating gliomas is to perform surgery to remove the neoplastic lesion as accurately as possible without

excessively damaging healthy brain tissues. There are further advanced MRI sequences which are very useful in planning the procedure: DTI and fMRI.

Diffusion tensor imaging (DTI) along with diffusion *tensor* tractography (DTT) can detect disturbances of the direction and continuity of white matter nerve fibres. Therefore, this imaging study may be applied before the planned glioma resection, because it helps differentiate infiltration from displacement of the white matter nerve fibres adjacent to the tumour [41]. Changes in DTI can be quantified – most often using the fractional anisotropy (FA) parameter – a lower FA coefficient is associated with greater damage to white matter [41].

Promising results are observed with functional magnetic resonance imaging (fMRI), but this method is used rather in specialised clinical centres and in scientific research. fMRI evaluates brain activation by detecting changes in blood oxygenation levels (BOLD sequence). A reduced BOLD signal is recorded in the cerebral cortex occupied by the tumour – especially in HGG gliomas [38]. This technique allows for precise determination of the tumour's relationship to eloquent areas, such as: speech, sensory, motor and memory areas. This can be a key factor in planning of the course of the surgery.

Predictive and prognostic significance of genetic changes in gliomas

Despite huge advances in molecular diagnosis of gliomas, possibilities of personalised treatment, including targeted therapy, are still limited.

The classic therapeutic approach for patients with GBM, based on histopathological assessment of the tumour and patients clinical condition, is limited to surgical resection of the tumour (which never leads to removal of the entire tumour mass, due to infiltrative growth pattern), followed by radiation therapy and chemotherapy.

The primary drug used in these patients is temozolomide, approved in 1999 for treatment of patients with anaplastic astrocytoma [42] and subsequently in 2005 for treatment of patients with newly diagnosed brain tumours [43]. Temozolomide is an alkalising compound, i.e., its action consists in attaching an alkyl group to the DNA. As a result, multiple mutations occur, leading to cell death. This process is inhibited by the intracellular DNA repair system by cutting out abnormal bases (base excision repair – BER). The key enzyme for this mechanism is the MGMT protein (methyltransferase O6 – methylguanine, O6-alkylguanine-DNA alkyltransferase – MGMT), encoded by the *MGMT* gene. Loss of this gene's activity due to hypermethylation of its promoter (a mechanism of epigenetic regulation of gene expression) leads to impaired DNA repair and, consequently, to increased effectiveness of alkylating anticancer drugs. It was shown that patients with hypermethylation of the *MGMT* gene promoter respond better to treatment with these agents, although the effect is not as pronounced as expected [44]. To a large extent, this is due to the genetic heterogeneity of gliomas, as one of its symptoms involves high variability in the degree of hypermethylation of the *MGMT* promoter in different parts of the tumour. However, the methylation level of the *MGMT* gene promoter is currently an accepted predictor marker for application of temozolomide in patients with brain gliomas.

Another useful drug in treatment of brain gliomas is a monoclonal antibody, bevacizumab. Its effect involves blocking new vessel formation within tumour mass (anti-vascular endothelial growth factor – VEGF). Bevacizumab was approved by the FDA in 2004 as a drug used in metastatic colorectal cancer. In 2009, it was approved in treatment of various cancers, including brain gliomas [43].

Current studies are investigating new methods of targeted treatment of gliomas, for example compounds to block hyperactivity of the EGFR receptor with tyrosine kinase inhibitors (TKIs). The use of depatuxizumab mafodotin (a conjugated EGFR blocking antibody) in combination with temozolomide showed positive therapeutic effects in patients with a relapse of EGFR-positive GBM in the second phase of clinical trials. However, in the third phase of clinical trials concerning application of depatuxizumab mafodotin in combination with standard therapy in newly diagnosed FGFR-positive GBMs, this therapeutic approach has been proved ineffective [10].

Other unsuccessful clinical trials concerned application of drugs targeted at mutations within the *PI3K/mTOR* signalling pathway, which is frequently deregulated in GBMs without *IDH* mutation, frequently with *PTEN* gene deletion and *PIK3CA* or *PIK3R1* mutation. However, a weak but positive therapeutic effect was achieved in the case of buparlisib monotherapy (PI3K tyrosine kinase inhibitor; pan-PI3K TKI) in patients with a relapse of *PI3K*-active GBM. Once more, there was no clearly positive effect recorded by clinical trial on application of VEGF inhibitors and tyrosine kinase multi-inhibitors targeted at changes in genes which modulate tumour microenvironment. However, there are promising preliminary results of trials concerning pharmacotherapy for glioma patients, e.g., administration of vemurafenib (in patients with GBM and *BRAF V600E* mutation, as well as a combination of *BRAF / MEK* inhibitors), dabrafenib and trametinib, which were applied successfully in targeted therapies for other cancers.

It seems that an interesting direction can be found in research on inhibitors of fusion genes, occurring in almost 55% of GBM (e.g., *FGFR, MET, NTRK* and less frequently fusions of *EGFR, ROS1, PDGFRA* and *NTRK*), 10% of which are fusion kinases which have known inhibitors approved for clinical use in other tumours (e.g., larotrectinib and entrectinib, approved by FDA for application in patients with solid tumours and *NTRK* fusion) [10].

Molecular changes are also prognostic markers. It was found that GBMs without *IDH* genes mutations have a more aggressive clinical course than tumours with mutations in these genes. Similarly, tumours with *TERT* gene mutations, without *IDH* mutation, have a worse prognosis. Meanwhile,

oligodendrogliomas with the 1q / 19p codeletion and *IDH* gene mutations have a milder clinical course. Similarly, a milder course of the disease and thus a better prognosis can be expected if mutations in the *ATRX* gene are present in GBM cells. It is characteristic for these tumours that *ATRX* gene mutations almost never occur simultaneously with the 1q / 19p codeletion. Better survival prognosis is observed in patients whose GBM cells have hypermethylation of *MGMT* gene promoter associated with 1q / 19p codeletion [6,45].

Conclusions

Genetic and radiological studies are currently very important in diagnosis, treatment and prognosis of patients with brain gliomas. Therefore, there is an intensive effort to correlate specific imaging features of gliomas with their molecular classification.

One of those features is the finding observed in MRI, referred to as T_2-FLAIR mismatch sign, found to be highly specific for diffuse astrocytomas with *IDH* mutation and without 1p / 19q codeletion [46, 47]. On the other hand, absence of this finding is characteristic for oligodendrogliomas. Presence of the 2-HG metabolite in MRS is also characteristic for gliomas with the *IDH* mutation [48]. In MRI of gliomas with amplification of *EGFR*, diffusion restriction in DWI along with high perfusion (rCBV > 3.0) in PWI were found with statistical significantly higher frequency, and so was left temporal location [49]. MRI proved also correlation of the molecular pattern of texture, fractal features and volume of diffuse low-grade gliomas assessed by a special computer algorithm [45].

Recently, development of advanced magnetic resonance techniques has been observed, allowing for non-invasive assessment of morphology and biological features of brain tumours, and in some cases – suspicion of genetic changes, too. This translates into an increasingly precise initial tumour malignancy assessment, allowing more precise determination of the patient's prognosis and their qualification for the right method of treatment. However, radiological-molecular-genetic relationships in brain gliomas require further in-depth studies to accurately assess their clinical usefulness.

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