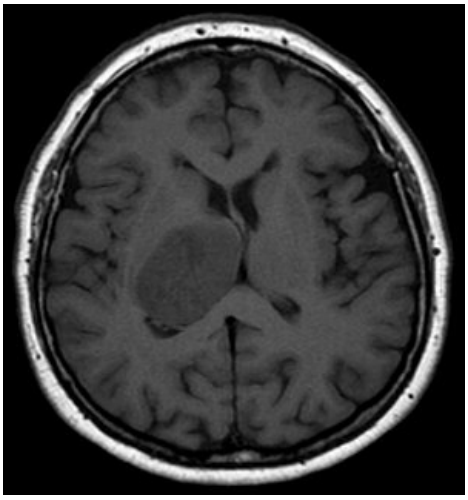
Glioblastoma multiforme

Glioblastoma multiforme (**GBM**, **Glioblastoma**) is the most common and malignant glioma of the brain. It is based on astrocyte cells, is usually located in the cerebral hemispheres and mainly affects adults. It arises either de novo or less often by malignancy of lower grades of astrocytomas (WHO grade II - astrocytoma with a lower degree of malignancy, WHO grade III - anaplastic astrocytoma). GBM therapy is a palliative surgical, radiotherapeutic and chemotherapeutic solution.

Epidemiology



Glioblastoma on T1 MR image

Glioblastoma multiforme is **the most common primary brain tumor**, accounting for approximately 12-15% of all intracranial tumors and 50-60% of astrocytic tumors. The incidence is approximately the same worldwide, with 2-3 new cases per 100,000 population per year. Approximately 350 high-grade gliomas are diagnosed annually in the Czech Republic.

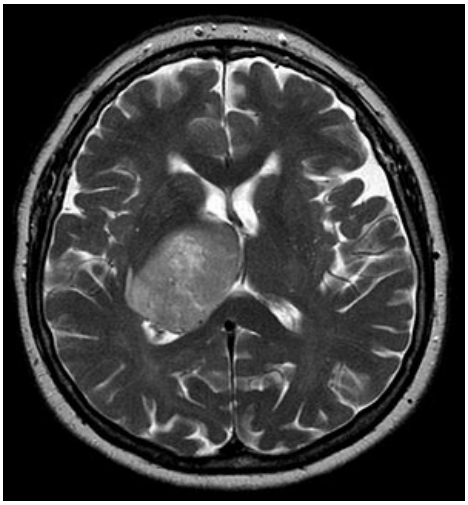
Glioblastoma multiforme (WHO gr. IV) is the most common of the high-grade gliomas. Anaplastic astrocytoma occurs less frequently (WHO gr. III). Anaplastic oligodendrogliomas and oligoastrocytomas are rare.

According to a study from the University Hospital in Zurich, men are more often affected in a 3:2 ratio, most often in the interval of **45-70 years**. According to a Dohrman study (1976), GBM affects children in only 8.8% of cases.

In the United States, the disease is more common in the white population.

Patients with GBM **without therapy die within 3 months**. **Optimally treated patients** (ie palliative surgery, radiotherapy and chemotherapy) **live for an average of 12 months**. Less than 25% of patients with GBM survive 2 years and less than 10% of patients survive 5 years.

Etiology



Glioblastoma on T2 MR image

The etiology of GBM is unknown in most cases. It can result from a **family genetic burden** or as a result of a known **genetic syndrome**, such as neurofibromatosis, Turcot's syndrome or Li-Fraumeni syndrome.[1]

The use of mobile phones and its effect on the development of brain gliomas is still under discussion. According to large studies, cell phone radiation is not considered a risk factor. Other studies challenge this claim, highlighting the lobbies of the telecommunications companies that funded the large studies, and see cell phone radiation as a significant risk factor, especially for children.

Pathophysiology

Glioblastomas can be divided into primary and secondary. **Primary glioblastomas** develop de novo, are more common (60% GBM) and occur in patients over 50 years of age. **Secondary glioblastomas** are based on malignancy of lower grade astrocytomas (WHO grade II - lower grade astrocytoma, WHO grade III - anaplastic astrocytoma), are uncommon (40% GBM) and occur in younger patients (under 45 years of age). Thus, primary and secondary glioblastomas are seen as **two different entities** that manifest in patients of different ages, differing in part in their genetic background and response to certain therapies.

Both variants of GBM are caused by the accumulation of a large number of **genetic mutations**:

- **Loss of heterozygosity** (LOH) on chromosome arm **10q** occurs in up to 60-90% of GBM cases and is relatively specific for GBM.
- Mutations in the tumor suppressor gene **p53** occur in 25–40% of cases, mainly in secondary GBMs.
- Clinically significant mutations in the EGF receptor (**EGFR**) gene are manifested by its increased activity. It occurs in up to 40-50% of cases of primary GBM (less common in secondary GBM).
- Uncontrolled cellular profiling can also be caused by a mutation in the **MDM** gene, the product of which binds the tumor suppressor p53 and thus deprives the cell of an important regulatory mechanism. According to some studies, a mutation in this gene is associated with a worse prognosis.

- PDGFR is a receptor for PDGF-alpha (Platelet-derived growth factor-alpha), a growth factor that acts as a major mitogen for glial cells. Amplification or overexpression of **PDGFR** occurs in up to 60% of secondary GBM cases.
- **PTEN** (also known as MMAC and TEP1) encodes a tyrosine phosphatase on chromosome arm 10q. Phosphatase inhibits signaling cascades. If the mutation results in a loss of function, the cell begins to proliferate uncontrollably. It occurs in 30% of GBM, mostly primary.
- *MMAC1-E1, MAGE-E1, NRP / B* (nuclear-restricted protein / brain) genes are less common (but more malignant).
- Other mutations include defects in the *p16* and *Rb* genes.

Clinical manifestation

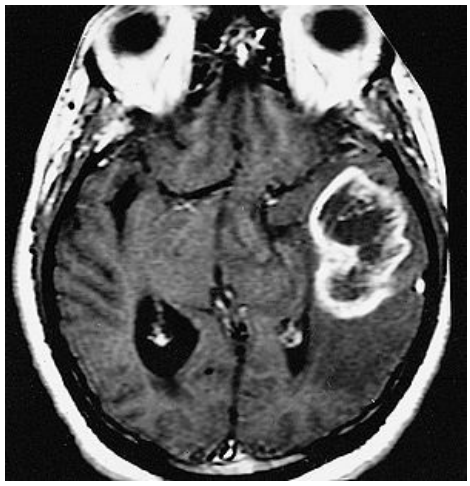
GBM most often manifests as a **slowly progressing neurological deficit**, mostly muscle weakness. Subjectively, however, patients complain most about **headaches** (usually in the morning after waking up). The general symptoms are mostly the result of **intracranial hypertension**, which includes the already mentioned headache, constipation on the optic papilla, nausea and vomiting, mental disorders and consciousness. Secondary partial or **generalized seizures** may occur. In GBM with infratentorial localization, cerebellar or stem symptoms, cranial paresis, dominate.

Diagnostics

Imaging methods are of the greatest importance for the diagnosis of GBM.[2]

On CT, glioblastoma appears as a hypodense lesion with a peripheral annular zone of enhanced contrast and a penumbra zone of cerebral edema.

MRI is the method of choice. Typically, the **T1**-weighted image shows **annular hyperintensity** and the **T2**-weighted image shows edema surrounding the lesion. In the T1-weighted image, the interior of the lesion is hypointense due to necrosis. The annular hyperintensity in the contrast examination consists of a tumor mass with rich neovascularization permeable to the contrast agent. Pathological studies have shown that the hyperintense zone does not form the edge of the tumor, but that the tumor cells extend up to two centimeters from this edge, sometimes beyond.



Glioblastoma multiforme, on contrast MRI, GBM usually appears as a tumor with an annular hyperintense margin and a central hypointense nucleus of necrotic tissue.

In more complex cases, positron emission tomography (PET) or MR-spectroscopy may help diagnose. PET displays increased glucose metabolism in the area. Measurement of tumor size after surgery with O-2 - [(18) F] fluoroethyl-1-tyrosine (FET) PET is of prognostic significance (Pirotha et al). **MR-spectroscopy** shows changes in peaks, such as increased peak ratio for choline and creatinine, increased peak for lactate and decreased for N-acetylspartate.

EEG changes are non-GBM specific.

Histopathology

As the name glioblastoma multiforme suggests, the histopathology of this tumor is **very variable**. GBM is composed of **low-differentiated, pleomorphic astrocytes** with significant **cellular atypia** and **numerous mitoses**. **Necrosis** is typical of GBM. **Microvascular proliferation** is noticeable.

Macroscopically, the tumor consists of **peripheral gray tumor cells** and **central yellow necrosis**. The color of necrosis is determined by the breakdown of myelin. Old and recent **bleeding sites** can be seen in the tumor.

Immunohistochemical staining is variable in GBM. In addition, the more the tumor is dedifferentiated, the worse it stains. Undoubtedly the best marker of astrocytic neoplasms is glial fibrillary acidic protein (**GFAP**), which is often positive in staining even in aggressive forms of GBM. Less specific is staining for **vimentin** and **fibronectin**.

GBM tends to be **invasive locally**, spreading along white matter such as the corpus callosum, internal capsule, radiatio optica, anterior commissure, fornix, and in the subependymal region. This may give the impression of multiple glioblastoma foci on imaging. Truly multiple, independent foci of glioblastoma occur in only about 2-7% of cases. Although the tumor grows highly infiltratively, it does not tend to invade the subarachnoid spaces, nor does it metastasize through the cerebrospinal fluid. Similarly, hematogenous metastases to extraneural tissues are very rare in patients without surgery.[3]

Therapy

Basic treatment algorithm

At present, glioblastoma can only be treated with **palliative care**. The basis is **radical surgical resection.** The aim of the surgical intervention is to reduce the tumor mass and thus reduce the pressure on the surrounding structures, to enable the histopathological diagnosis of the tumor and to facilitate the effect of adjuvant therapy. Surgery is followed by adjuvant radiotherapy (standard fractional conformational radiotherapy, 60 Gy) and concomitant or (stand-alone) adjuvant chemotherapy with **Temozolomide** (an orally administered alkylating agent). **Concomitant chemoradiotherapy** seems to be the most effective (Stupp et al). Concomitant chemoradiotherapy is followed by 6 cycles of adjuvant chemotherapy. In patients older than 70 years, it is recommended to choose only one of the modalities, ie only chemotherapy or only radiotherapy, due to the aggressiveness of the therapy. According to some studies, therapy tends more in favor of radiotherapy for longer patient survival (Scott et al).

The median tumor recurrence after standard therapy is approximately 7 months. Then the selection of individual modalities is approached individually, ie. surgical treatment, radiotherapy, chemotherapy or **biological and experimental treatment**.

The cooperation of neurologists, neurosurgeons, neurooncologists and radiation oncologists is appropriate to ensure an optimal treatment strategy.

Symptomatic treatment

Symptomatic treatment complements palliative care. Seizures are compensated by **levetiracetam** (Keppra®), **phenytoin** (Dilantin®) or **carbamazepine** (Tegretol®). Lunlike the other two, evetiracetam has no effect on the cytochrome P450 system and therefore does not interfere with chemotherapy. Vasogenic brain edema is compensated by **corticoids** (dexamethasone) often in combination with **antiulcer drugs** (famotidine, ranitidine).

Biological treatment

Currently (September 3, 2010), targeted biological therapy is in the phase of clinical trials. Bevacizumab and cilengitide look promising. **Bevacizumab** is a humanized anti-VEGF monoclonal antibody. In studies, bevacizumab had a higher radiological effect. The combination with irinotecan also shows good results. **Cilengitide** is a relatively new drug belonging to the group of integrin inhibitors. Integrins act as cell receptors on the cell surface, inhibiting tumor growth and angiogenesis upon binding of cilengitide.

A recent study (Wernicke et al) demonstrated the expression of prostate specific membrane antigen (**PSMA**) in tumor vessels that could be used as a target for biologic therapy.

Links

- ws:Glioblastoma multiforme

External links

- Neurologie pro praxi - kazuistika (http://www.neurologiepropraxi.cz/pdfs/neu/2010/06/15.pdf)
- Pediatrie pro praxi - kazuistika (http://www.pediatriepropraxi.cz/pdfs/ped/2011/01/08.pdf)

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