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Chapter 3

Modern Neuroimaging Techniques in The Diagnosis of Brain Tumours

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Additional information is available at the end of the chapter

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1. Introduction

Intracranial tumors represent a significant health problem. The annual incidence of primary and secondary central Nervous system neoplasms ranges from 10 to 17 per 100.000 persons. The main histological types of brain tumors in adults include: high-grade (gliomas, primary cerebral lymphomas, medulloblastomas), low-grade (meningiomas, acoustic neuromas, neurofibromas) and Secondaries (common malignancies spreading to the brain include lung cancer, breast cancer, stomach cancer, prostate cancer, thyroid cancer, colorectal cancer, melanoma and kidney cancer). In recent years, the diagnosis of brain tumors has considerable progressed due to continuous advances in neuroradiology.

Neuroradiology is a part of general radiology dedicated to the diagnostic examination of the brain and spinal cord. The history of neuroradiology, as a whole, reflects the history of radiological development. It is, on one hand, the history of collaboration of radiologists, neurologists and neurosurgeons in the development of clinical methods of Central Nervous System (CNS) radiological examination. On the other hand, it is the history of collaboration of physicists, mathematicians, engineers and radiologists in the design and creation of new devices for brain and diagnostics of spinal cord diseases.

Neuroradiology began in the early 1900s as soon after Roentgen discovered X-rays. He made the first X-ray image - a skull - in December 1895. X-rays promptly became the new tool in physics research and in medicine, providing many opportunities to visualize the internal structures of the human body. This was followed by the development of ventriculography in 1918 while the 1920s was the era of pneumoencephalography development thanks

to the work of Walter Dandy, a prominent neurosurgeon at Johns Hopkins Hospital [1]. The 1930s were marked by the introduction of cerebral angiography. From 1935 to 1946, the phenomenon of nuclear magnetic resonance was discovered [2]. The 1950s and 1960s witnessed questions for practical solutions of tomography problems in neuroradiology and subsequent development of electronics and computer techniques. The 1970s and 1980s were the years of wide introduction of Computed Tomography (CT) in the clinical setting. When CT became available, the use of uncomfortable procedures was abruptly stopped because CT could depict the ventricular system and the intracranial suarachnoid spaces directly, without introducing air into the subarachnoid space itself [3]. As regard to the development of cerebral angiography, in the early 1960s, it was performed by means of direct puncture of the common carotid artery and the vertebral artery. In the late 1960s and early 1970s cerebral angiography was predominantly performed by means of selective catheter angiography following puncture of the femoral artery [3]. Progress in neuroradiology continued rapidly with the development of MR imaging in the late 1970s and early 1980s. The advantages of MRI imaging were that it could be performed in any plane and with various pulse sequences, obtaining more details of the cerebral anatomy [4]. By the end of 20th century, Magnetic Resonance Imaging (MRI) had been strongly incorporated into the clinical practice, and in some cases (spinal cord examination) became a method of choice compared to the CT. The high tissue resolution and the wide variety of types of contrast for MR images are typical for MRI. Currently, MRI employs several physical factors defining the brightness of tissue on the image such as: proton density; *T*1 and *T*2 relaxation time of protons in tissue; movement of protons in the large vessels with a blood–cerebrospinal fluid (CSF) flow and passage of protons through a capillary net; random thermal water molecule motion; anisotropy of the diffusion proton motion and magnetic susceptibility of tissues; chemical shift of proton's resonance frequency in molecular complexes. In addition, volumetric CT and super-fast MRI have opened wide diagnostic opportunities of CNS examination not only on a level of anatomic structures (simulation and support of surgery, endoscopy), but also on a level of molecular and gene biology. Neuroradiology has become the quantitative method of brain function examination, able to monitor and predict the results of therapeutic treatment and surgical intervention of many diseases [5].

Further development of neuroradiology is closely linked with the increase of processing speed and improvements in computer technologies, increase of (MRI) magnetic field induction, development of "open" magnets for biopsy, intra-operative control, examination of critical patients.

This chapter focuses on the role of the most commonly used advanced MR imaging techniques – perfusion imaging, diffusion-weighted imaging, and MRI spectroscopy- for the diagnosis of the most common brain tumors in adults.

1.2. Conventional MRI imaging

When dealing with a patient with a brain tumor, standard X-rays and CT scan is initially used in the diagnostic process. However, MRI is generally more useful because it provides detailed informations about tumor type, position and size, tumor anatomy, cellular struc-

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ture and vascular supply, making it an important tool for the diagnosis, treatment and monitoring of the disease. For this reason, MRI is the study of choice of brain tumors.

Discussion of MRI physic details is beyond the scope of this chapter. The concept that is important to remind is that conventional MRI exploits three physical properties of tissue protons to generate signal imaged as areas of different contrast, which reflect the anatomy and physiology of the organ under investigation. Those protons properties which contribute to MRI signal generation are Proton Density (defined as the number of hydrogen protons per unit of volume of tissue), T1 relaxation time (which is the time requested to recover 63% of the longitudinal magnetization) and T2 relaxation time (which is defined as the time requested to recover 63% of the transverse magnetization to be lost). T1 and T2 relaxation time and proton density are all specific for different type of tissues and increase as the magnet`s field strength increases [6]. In all three types of images, bright areas correspond to tissue with high signal intensity (i.e. areas with large transverse magnetization) and are referred to as hyperintense, whereas dark areas correspond to low signal intensity (i.e. small transverse magnetization) and are referred to as hypointense.

Different types of acquisition of MR imaging give different informations (table 1):

- T1-weighted images give a lot of anatomical informations as well as informations about venous sinus permeability or pathologic blush. CSF is dark and fat is white in T1-weighted sequences. Lesions bright in T1- weighted sequences are: fat (lipoma, dermoid), subacute haemorrhage (metHb), metastatic melanoma (melanotic), protein-containing fluid (colloid cyst) and paramagnetic agents (gadolinium).

- T2-weighted images give informations about oedema, arteries and sinus permeability. Water is white in T2- weighted sequences, fat appears intermediate to dark, and haematomas have a variable signal intensity. Some dark lesions on T2-weighted images are acute haemorrhage (deoxyHb), haemosiderin, iron and mucinous lesions.

- A proton density-weighted image is an image primarily dependent on the density of protons in the imaging volume. The higher the number of protons in a given unit of tissue, the brighter the signal is. Proton density-weighted images have excellent grey matter–white matter contrast, as their brain CSF contrast is much lower. It is useful to study basal nuclei anatomy and differentiate lacunar infarctions from Virchow-Robin spaces, and to evaluate also cerebral gliosis.

Conventional MRI gives morphological informations about brain tumors. Some authors name Conventional MRI as Morphological MRI, to differentiate it from Functional MRI that will be discussed later. Those morphological informations are both macroscopic and microscopic (T2 sequences give useful information in this sense, with a low signal intensity in the presence of calcification, melanin, lipids and haemosiderin). The vascularization of the neoplasm can be seen with the typical vessel aspect characterized by absence of signal in all sequences (the so called “Signal Void”).

Most of the tumors are iso-hypointense in T1 and hyperintense in DP and T2. A hyperintensity in T1, however, can only be caused by fat (lipomas) and paramagnetic substances, such

as melanin (melanoma metastases) and different degradation products of hemoglobin. Tumors with high cellularity (medulloblastomas, lymphomas) are characterized by a hyperintensity in DP and relatively low signal on T2-weighted images. Meningiomas are usually isointense in all sequences, and- if small - may be disregarded on the basic examination.

The cystic-necrotic areas usually associated with malignant tumor such as glioblastoma multiforme (GBM) are markedly hypointense on T1 and hyperintense on T2. Signal can be differentiated, in most cases, from that of CSF in the proton density, as necrotic areas are slightly hyperintense, while CSF is slightly hypointense. It is important the concentration of proteins within cystic tumors, being the hyperintensity in the T2 sequences directly proportional to the protein concentration. It must be noted, on the other hand, that when the protein concentration in the cystic lesion is too high there can be a paradoxal hyperintensity in T1 and hypointensity in T2 sequences. The hemorrhagic areas cause the typical alterations of signal that follow the steps of degradation of haemoglobin. Calcifications are highlighted as areas of signal void, hypointense in T2 and DP. Perilesional edema is characterized as an area slightly hypointense on T1 and hyperintense in DP and T2. The mass effect can be evaluated in a much more accurate way than CT in studying the behavior of convolutions of the brain. A lesion may be considered intra-axial if it expands the adjacent cerebral convolutions. Anyway an intra-axial lesion may invade the meninges (eg, metastasis, glioblastoma multiforme) and an extra-axial lesions can invade the brain tissue (eg, dural metastases).

Another important sequences in MRI is “Fluid Attenuated Inversion Recovery” (FLAIR) also called the “dark fluid technique”. It is used to remove the effects of fluid from the resulting images. Lesions that are normally covered by bright fluid signals on T2-weighted images are visible by FLAIR. Its use is very common in many specific diseases, such as multiple sclerosis. Particularly, the correct evaluation of site and extension of the tumour is an important step to define the possibility of surgical resection. FLAIR sequences, available in 3D form on modern MRI equipment, seem to be mandatory to assess the extension of a glioma, usually with a hyperintense signal. 3D T1 weighted GRE sequences can provide images with high inplane spatial resolution without interslice gaps. This technique can be, therefore, very useful, after gadolinium injection, to obtain volumetric MRI data that can be reconstructed in any desired plane, suitable for presurgical planning or surgical navigation system.

Another important tool in MRI imaging is the use of contrast medium. Gadolinium, a rare earth metal, is frequently used in MRI. The paramagnetic properties of gadolinium affect free protons and hence shorten Tl-weighted signal. Gadolinium is not visualized but its effect on free protons. Increased concentrations of gadolinium will result in high signal, i.e. enhancement, on Tl weighting. It highlights areas of blood-brain barrier breakdown, areas of inflammation and increased vascularity. Marked enhancement is normally visible in the pituitary gland, choroid plexus, nasal mucosa and turbinates, and in slowflowing blood in vessels. Contrast enhancement is frequently used to improve detection and definition of tumors, infections, meningeal diseases, vascular diseases and "post-operative spine". Gadolinium is an extremely safe substance and has been used worldwide with less side-effects compared to iodinated contrast media. Gadolinium is a substance that allows the study of

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the blood-brain barrier permeability in brain tumors: low-grade tumors, which contain capillaries with a structure similar to the normal nervous tissue with tight junction, are characterized by no enhancement, while high-grade tumors have pathological capillaries with a high enhancement after gadolinium administration, expression of the blood-brain barrier disruption. As regard to extra-axial tumors, they usually have high enhancement because, being extra-axial lesions, they have no blood-brain barrier.

Basically the most important goals of conventional MRI in the diagnosis of brain tumors are:

- discover the lesion and define its nature (blood, ischaemia, tumor).

- localize the lesion (intra- or extra-axial, above or under the tentorium) and define its limits and relations with the surrounding structures, with the use of gadolinium.

- evaluate mass effect (compression, dislocations, cerebral erniation).

- evaluate the characteristics (necrosis, calcifications, surrounding oedema, haemorrhage, rupture of blood-brain barrier).

- give indications about the most probable histological nature and grade of malignancy of the tumor.

- define the vascularization and the relations with the closest cerebral vessels (very important in meningiomas, where it is necessary to evaluate the feeding arteries, in order to consider the possibility of a preoperative endovascular embolization, and the possible infiltration of dural sinus or cerebral vessels).

Substance	On T1 weighting	On T2 weighting
Water	Black	White
Fat	White	Gray/white
White matter	Gray	Gray/black
Gray matter	Gray/black	Gray/white
Bone		
Cortex	Black	Black
Marrow	White	Gray/white
Calcification	Gray/white	Black
Intervertebral disk	Gray	White
Air	Black	Black
Hematoma	Depends on the phase	Depend on the phase
Most pathology	Gray/black	White

Table 1. Signal intensity on MRI

1.3. Digital Subtraction Angiography (DSA)

Catheter angiography is an invasive technique which has progressively become safer with the introduction of DSA, non-iodate contrast media and improved catheters and guide wires.

The right femoral artery is punctured using the Seldinger technique. The catheter is then advanced up to the aortic arch and then, selectively, into the required artery. The catheters are usually 4F or 5F in size and pre-shaped to facilitate selective catheterization. Once in position in the desired artery, the formal DSA is undertaken with the contrast injection by hand or mechanical pump. Multiple projections are used to demonstrate the vasculature and images are obtained as far as the venous phase in several planes. Commonly, the internal carotid circulation is studied in lateral, posteroanterior 20° and oblique projection, e.g. 30° cranio-caudal, 30° lateral.

The posterior circulation is studied in lateral and Townes' projection (30° fronto-occipital). Numerous supplementary projections can be performed according to which vessel has to be demonstrated. This is particularly Important in the diagnosis of aneurysms where a clear demonstration of the neck of the aneurysm is required, especially if endovascular treatment has to be considered.

Local complications occur in about 5% of cases and range from self-limiting hematoma to fatal retroperitoneal hematoma. Vessel injury can result in pseudo-aneurysm, arteriovenous fistula and distal emboli.

Systemic complications are related to the contrast media or, very occasionally, to local anesthetics and sedation. Contrast media reactions are common to all radiological procedures using iodinated contrast. The risk is increased by history of previous reaction and in asthma sufferers, where the risk of severe reaction is about 0.2%. Neurological complications range from headache to disabling stroke or death. The risks are increased in the older population (over 50 years), particularly if there is atherosclerosis, vasculitis or sickle cell disease.

Cerebral DSA remains the investigation of choice in a number of conditions despite improvements in Doppler ultrasound, MRAand CTA. The most common reason for its use is in the investigation of Subarachnoid hemorrhage (SAH), where DSA remains the gold standard. Other indications for angiography include: assessment of aneurysms (e.g.fusiform, dissecting, mycotic, giant) that have not presented with SAH; assessment of AVMs and other vascular lesions, such as carotido-cavernous fistula or dural fistula; investigation of various cerebrovascular disorders, such as vasculitis and demonstration of tumor vascularity, particularly if pre-operative embolization has been considered. This is particularly true for intracranial meningiomas. Meningiomas are commonly supplied by dural arteries such as middle meningeal artery, accessory meningeal arery, ascending pharyngeal, or occipital transmastoid perforating branches of the external carotid artery. Dural arteries also include the tentorial and infratentorial trunk branches of the internal carotid artery, as well as the posterior meningeal branch of the vertebral artery. Secondary supply to meningiomas may be derived from pial branches (of the anterior, middle and posterior cerebral arteries). Embolization involves the devascularization of the tumor’s supply through the placement of an embolic agent via a microcatheter into the feeding arteries. Because men-

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ingiomas are usually vascularized, preoperative tumor embolization can easily complete tumor resection by diminishing operative time and intraoperative blood loss [7]. Diagnostic angiography can also identify important informations for the surgeon such as a potential occlusion of a dural sinus adjacent to the tumor and the pattern of collateral venous drainage around such an occlusion.

Angiography in gliomas is not specific. Many gliomas, especially low-grade, are seen as avascular or hypovascular areas surrounded by displaced normal vessels. High-grade gliomas may show intense tumor neovascularization in a disorganized pattern, a prominent tumor blush in the mid-arterial phase, hypovascular areas representing necrosis or cysts and arteriovenous shunting with early draining veins which represent the most angiographically common finding in glioblastoma multiforme. These characteristics do not allow the differentiation of a primary glioblastoma from a secondary lesion. Some authors propose the possibility to use DSA in patients with brain metastases, in order to get a regional chemoinfusion to the arteries feeding the metastatic foci [8].

1.4 . New Functional Methods in Neuroradiology

The increase of the processing speed of CT and MRI scanners, the invention of new data-registration technologies and the algorithms of data-processing transfer neuroradiology allowed great development in neuroradiology. Functional MRI can detect areas of the brain having increased neuronal and metabolic activity, and areas of damage in the brain–blood barrier. It makes a quantitative assessment of microvascular permeability of brain tissue, evaluates the state of receptors on the cell surface as well as hormonal activity, and reveals the presence of certain antigen and protein structures [5]. Thus, CT and MRI perform diagnostics not only on a cellular, but also on a molecular level. Diffusion, perfusion, MR spectroscopy and functional MRI belong to the so-called methods of molecular visualization.

1.4.1. Diffusion Weighted Imaging

Diffusion is the basic physical process occurring during the cell's metabolic reactions. Kinetic energy leads to Brownian motion (random walk) of molecules (thermal motion; the speed is about 10–3 mm2/s). As a whole, the molecular motion of protons in physiological systems is divided into three types:

1. movements with moderate speed in macroscopic vessels (about 10–100 mm/s);
2. slow flow in a capillary net, or perfusion (the speed is about 0.1–10 mm/s); and
3. diffusion motion of molecules (the speed is about 10–3 mm2/s).

Blood flow in large vessels is measured as a volume-in-time unit, perfusion flow (a local blood flow) is measured as the volume of blood passing in and out of a given tissue weight (volume) per unit of time and the diffusion factor is estimated by the average square of the distance made by molecules for a time unit.

The image appearance in "*isotropic*" Diffusion Weighted Imaging (DWI) is based on the principle that molecules in any living tissue routinely undergo random (brownian) motion. Isotropic DW images are typically obtained by measuring loss of signal after a pulse sequence that consists of a series of two sequential gradient pulses added to a 90°–180° spin-echo sequence on either side of the 180° pulse [9]. The degree of MR signal loss after application of the second gradient pulse is related to two factors:

a. the duration and strength of the magnetic field gradients and

b. the diffusion coefficient of the substance.

The apparent diffusion coefficient (ADC) is a value that describes microscopic water diffusibility in the presence of factors that restrict diffusion within tissues (eg, cell membranes, viscosity). The ADC can be derived on a voxel-by-voxel basis and depicted on an ADC map, which allows ADCs in specific regions to be measured by using regions of interest. Measurement of the ADC would be expected to be useful in tumor assessment because variations in water content (and diffusivity), which can be found within tumors for various reasons (eg, necrosis, variations in cellularity) and adjacent to tumors (eg, vasogenic edema), provide information that is not readily available from conventional MR imaging.

The motion of the water molecules in live tissues occurs within the cell limits (the limited diffusion), as well as in intercellular spaces among structures, which restrict the molecules motion but still leaves them some freedom for manoeuvring between obstacles (the complicated diffusion). Water diffusion inside extracellular space is inversely proportional to the density of the intracellular space constituents.

The tendency for water molecules to diffuse in some directions rather than equally in all directions is termed "*anisotropy*." Highly compact white matter fiber tracts exhibit a high degree of anisotropy, and less compact white matter pathways exhibit lesser degrees of anisotropy. All types of white matter typically show greater degrees of anisotropy than are seen in gray matter structures, which have a low degree of anisotropy.

Diffusion Tensor Imaging (DTI) represents a magnetic resonance imaging method that is expression of fractional water anisotrophy (FA) and is available in many modern clinical scanners. DTI is similar to DWI but involves the collection of additional data necessary to define the tensor (vector) which describes the preferential direction and magnitude of water diffusion. FA maps has been used to investigate the microstructure of white matter that can be altereted in many pathologic conditions such as brain tumors. DTI provides a sensitive means to detect alterations in the integrity of white matter structures. In fact, in many settings, white matter abnormalities can be seen on diffusion-tensor images being not evident on routine MR images [2,3]. Diffusion-tensor imaging also provides a means of depicting white matter pathways (tractography). This may be useful in neurosurgical procedures by preoperatively depicting important white matter tracts, helping determine infiltration of white matter tracts by tumor, and providing evidence of degeneration of white matter tracts distal to tumor sites (ie, wallerian degeneration). In the real biological environment, water molecules can encounter natural barriers, such as cellular membranes and large albumin molecules, which can interfere with free motion of protons. Therefore, in practice, the appa-

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rent diffusion coefficient is calculated, and its value is lower than diffusion coefficient for pure water at temperature.

All diffusion-weighted examinations are performed without contrast injection. This is important for critically ill and restless patients, and especially for special examinations of brain development in children, beginning with the prenatal period. In the last case, DWI enables to obtain both the additional qualitative (visualization) and quantitative tissue characteristics.

1.4.1.2. Clinical Application of DWI and DTI

Today, DWI is one of the fastest and highly specific methods of early-phase ischaemic stroke diagnostics (within 6 h of onset), during which there is a therapeutic window for restoration of the affected brain tissue. In acute phase of stroke, the affected area on DWI typically has a high MR signal, whereas the surrounding tissues look dark. The ADC maps provide a reverse-in-brightness picture. Diffusion ADC maps are a tool in the diagnosis and monitoring of cerebral ischaemia.

DWI provides invaluable informations for inflammatory lesions of brain and spinal cord (abscesses, empyema). Purulent abscess content has a typical hyperintense MR signal on DWI and can be easily visualised on pretreatment (before draining) and as well on postoperative images. In addition, DWI can be used in the assessment of drainage intervention effectiveness or in the case of verification of the purulent complication in incision wound.

DWI and ADC maps provide great help in the diagnosis of brain tumors, providing additional diagnostic informations for differentiation of neoplasms with similar signs on *T*1 and *T*2 MRI (glioma, tumours with ring-shaped contrast accumulation), peritumoral oedema (vasogenic or cytotoxic) or the presence or absence of intratumoral cysts, only to name a few [10]. At the same time, as some authors demonstrate, DWI data alone do not allow differentiation between benign astrocytoma and anaplastic tumours, or between anaplastic astrocytoma and glioblastoma [5].

In many observations, the peripheral part of a tumor (as a rule in the case of malignant gliomas) is hyperintense on DWI; presumably it is linked to more dense cellular arrangement in the most actively growing tumor area (accordingly, there is a limitation on diffusive proton motion in this area). In fact, it has been demonstrated that the higher the tumor cellularity is the greater is the ADC value . It is demonstrated that value of ADC higher than 100×10^{-3} mm^2/s is typical of high grade tumors while ADC values lower than 100×10^{-3} mm^2/s are related to low grade lesion [11].

A low ADC in an intra-axial neoplasm should raise suspicion for lymphoma or metastatis, depending on the conventional MRI appearance, because the higher cellularity of these tumors generally produces an ADC which is significantly lower than in glioma. However, although most gliomas have a higher ADC (related to their lower cellularity), a number of case reports have demonstrated a low ADC in a small number of glioblastoma. Thus it is important to integrate DWI with other advanced and conventional neuroimaging data for accurate clinical interpretation [12].

In other brain neoplasms—in particular meningiomas and neurinomas— DWI may predict tumour histological type, with high reliability even before surgery. Based on this method data, the epidermoid and arachnoid cysts can be precisely differentiated. In fact DWI has a sensivity and specificy of over 90% for distinguishing epidermoid (low ADC) from aracnoid cyst (high ADC) and distinguishing abscess (low ADC) from necrotic tumor (high ADC). The viscous keratin and cholesterol in epidermoid and the viscous and cellular pus in abscess produce a very low ADC that distinguishes these lesions from increased diffusivity in necrotic tumor and from normal or slightly low diffusivity in demyelinating plaque. Meningiomas, a lower ADC has been demonstrated in atypical and malignant subtypes. It is also demonstrated that the eterogeneity of ADC within tumor reflects heterogeneity of cellularity within it [12].

Recently, DWI and DTI methods have begun to be applied to visualisation of a neural tract lines—tractography. This is a new and promising technique that enables non-invasive viewing of the brain neural tracts [13]. Despite some technical problems, the first results in tractography application to neurosurgery seem promising [5]. It is possible to plan operational access and to estimate the scope of brain hematoma to be removed, taking into account neural tracts and their involvement in the pathological process (dislocation–deformation, invasion, damage), with an aim to maximise the radical tumour resection and to minimise the subsequent complications [14].

In gliomas, the infiltration of the tumor disrupts the organization of the white matter tracts: FA derived from DTI defines of the degree of tumor infiltration. [12]. Some studies also suggest that DTI may distinguish vasogenic edema in brain metastases and meningiomas from non-enhancing tumor infiltration in gliomas. It has to be considered that white matter adjacent to glioma generally contains different proportions of vasogenic edema and tumor infiltration at different distances from the center of the tumor, making more difficult to define an unbiased region of interest for valid data analysis.

1.4.2. Perfusion Weighted Imaging

Perfusion studies are useful to quantify blood movement supplying each element of organ or tissue volume. It is widely known that, unlike the majority of parenchymatous tissue, brain tissue does not accumulate glucose, and brain cells can produce energy via anaerobic glycolysis only for several minutes.

Meanwhile, the brain consumes about 25% of all glucose consumed in the entire body, and for neurons, the uninterrupted and sufficient supply of oxygen and glucose is necessary.

There are complex mechanisms of autoregulation that manage brain perfusion to satisfy the demands of the nervous system for energy (released in a course of metabolic processes).

There are several modern quantitative methods of brain haemodynamic examination: MRI, CT with contrast enhancement, CT with Xe, single-photon emission computed tomography (SPECT) imaging and positron emission tomography (PET). The obvious advantages of CT and MRI are minimally invasive, high sensitivity in tissue microcirculation assessment, high resolution, the short examination time (within the framework of standard protocols), and

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last, but not least, the reproducibility of results. The most widespread perfusion examination in neuroradiology is based on intravenous bolus administration (CT and MRI). The dynamic studies of bolus passage demonstrate its distribution in tissue in each given image pixel, depending on time. The following main haemodynamic characteristics are used for quantitative assessment: cerebral blood flow (CBF), cerebral blood volume (CBV) and mean transit time (MTT).

The blood flow characteristics are measured in the ratio to 100 g of brain tissue. Accordingly, the value of CBV is measured in millilitres per 100 g of brain tissue, and CBF is measured in millilitres per 100 g per minute. The local (regional) CBV is defined as percentage of blood volume in a single element of brain tissue volume. MTT is measured in seconds.

Perfusion CT

CT approaches to perfusion imaging were first proposed in the early 1980s. However, clinical uses of perfusion CT were slow to progress because the technique suffered initially from relatively limited imaging volumes and poor temporal resolution. With the advent of multidetector CT, rapid scanning of larger volumes at faster speeds has been possible. Also, because CT uses ionizing radiation while MR imaging does not, MR imaging would seem to offer an advantage. However, CT techniques requiring lower milliampere-second values have been developed, associated to lower radiation dose. The use of iodinated contrast agents, with the associated risks of allergic reaction and nephrotoxicity, remains a drawback in some patients. However, perfusion CT has some clear advantages compared to perfusion MR imaging. CT scanners are generally more widely available, and CT does not suffer from magnetic susceptibility artefacts, which can compromise perfusion MR images when hemorrhage or other causes of magnetic susceptibility effect are present in the area of interest.

Initial analyses of CT data with deconvolution methods used indicator-dilution methods that suffered from the same problems as dynamic susceptibility contrast (DSC) MR approaches. The modern spiral CT scanners present new opportunities in tissue perfusion examination during the first passage of the iodide contrast bolus. This method has high resolution and provides quantitative assessments of tissue perfusion, and currently, it is one of the most perspective methods. Perfusion CT is based on analysis of CT density increase during contrast media passage through brain vascular structures. Contrast bolus (iodine agent with concentration 350–370 mg/ml, speed of administration is 4 ml/s) is administered intravenously. Spiral CT obtains a series of scans with 1-s intervals, within 50–60 s after contrast administration

Perfusion MRI (PWI)

There are MRI methods of haemodynamic perfusion examination, aided by exogenous and endogenous markers. The methods of perfusion assessment during contrast bolus passage are called perfusion-weighted MRI, or PWI. Perfusion-Weighted MRI can be performed by using either a gradient-echo or a spin-echo pulse sequence. Gradient-echo DSC sequences tend to be more sensitive to larger vessels, such as veins, in the imaged region. Spin-echo DSC techniques tend to show greater sensitivity to smaller vessels (and therefore are more representative of capillary density) or tumor-specific vessels.

These examination methods are currently widely used in MR diagnostics, especially in combination with MR angiography and MR spectroscopy. PWI uses changes of *T*1 or *T*2 tissues contrast due to infusion of gadolinium into blood as a contrast agent. Normally, gadolinium does not pass through blood–brain barrier. It can pass into intracellular spaces only in cases of blood–brain barrier disruptions. The CM bolus is administrated quickly (about 2–3 s); the speed of administration is 4–5 ml/s and is higher than in the standard infusion. The bolus passage on consecutive (in time) scans corresponds to the sharp decrease of MR signal intensity. In the process of CM bolus passage through the vascular system, multiple registration of the image from the same location occurs (usually it is 10 different levels).

The scanning takes place for 1–2 min. The graph of intensity decrease during CM bolus passage provides the curve "signal intensity–time" in each pixel of the scan. The form of this curve for arteries and veins provides arterial and venous function data. With these data, the haemodynamic tissue parameters are calculated. The regional CBV (rCBV) is estimated on the basis of area under curve "concentration–time"; the MTT calculation is performed on the basis of centre of gravity in CM distribution position, regional CBF (rCBF) = rCBV/MTT. The perfusion maps are built in "off-line" mode in the specialised workstations. The method of dynamic *T*1 MRI is used in cases of examination of CM distribution in extracellular spaces.

1.4.2.3. Clinical Applications of CT and MRI Perfusion

Currently, perfusion examinations are performed to estimate the haemodynamic of brain tumours, monitor tumour-state after chemo- and radiotherapy, detect the tumour recurrence and radiation necrosis. This procedure gives informations in cases of brain injury and CNS damage like ischaemia, hypoxia, large-arteries stenosis, blood diseases, vasculitis and moyamoya disease. Epilepsy, migraine, vasospasm, various mental diseases (including dementia), autism, and so forth are prospective in terms of perfusion methods application.

CT and MRI perfusion allow building of parametric maps and quantitative characterization of areas of hyper- and hypo-perfusion, which is very important in diagnosis of tumours and cerebrovascular diseases. Perfusion maps provide important additional information about characteristics of normal and pathological tissues (in areas of tumour, oedema, necrosis). In neurosurgery, Perfusion Weighted Imaging (PWI) is used in primary differential diagnosis of tumor grading, in particular gliomas. However, perfusion CT and MRI do not specifically allow differentiating tumours according their histology, nor does it enable estimation of the tumour spreading into brain tissue [5].

The hyperperfusion in the structure of astrocytoma can indicate increase of tumour malignancy because the degree of perfusion is related to the development of abnormal vascular net (angiogenesis). In other words, the tumor perfusion is related to the grade of the tumor itself and the most important value to evaluate it is rCBV (higher rCBV values indicates high grade tumors while rCBV values < 1,5 are usually related to tumor with low grade of malignancy) [15]. Maia et al demonstrated that rCBV correlates with the vascular endothelial growth factors (VEGF) which is expression of the angiogenesis in gliomas [16].

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If the abnormal vascular net in a tumour can be the evidence of its aggressiveness, on the other hand the decrease of perfusion in a tumour tissue under the influence of chemo- or radiotherapy can be a sign of response to treatment. The use of PWI in target selection for stereotactic intervention is helpful, especially in cases of gliomas characterized by full absence of contrast accumulation with the use of standard CT and MRI. (Fig 1 c)

PWI potential is higher in assessment of histological type and spreading of extra-axial neoplasms than of intra-axial ones. PWI successfully visualizes meningiomas and neurinomas of cerebellopontine angle, according to the high haemodynamic parameters of these tumors. In addition, it has been demonstrated that there is a clear correlation between local blood flow (CBF, CBV) and direct angiography data in patients with meningiomas. The tumours with radiopaque shadows in the early capillary phase of angiography have high perfusion, and such tumours are characterised by high risk of a intraoperational bleeding. CT PWI data are highly specific in demonstrating the blood supply of haemangiomas located in posterior cranial fossa; in this case, early and marked contrasting is combined with high perfusion.

PWI is also successfully used in differential diagnosis of postoperative residual tumour growth and radionecrosis. In both cases, standard CT and MR examinations can show the accumulation of contrast in the lesion and blood–brain barrier disruption. Blood–brain barrier disruptions cause CM extravasation in pathological tissues, with subsequent contrast accumulation. However, the pathophysiological reasons in both cases are different. For tumoral tissues, the perfusion increase or the reaching of normal perfusion level are typical, while in necrotic tissues the blood supply is absent. Blood–brain barrier disruption in tumours is related to the invasive growth of tumour cells and vascular wall damage. In case of radionecrosis, the disruption of blood– brain barrier is an initial step, but the radionecrosis is characterized by a decrease perfusion level (iso- or hypoperfusion). The areas of radionecrosis appear as areas of weak blood filling on CBV maps.

Undoubtedly, ischaemic brain damage takes the first place in the frequency of PWI methods used. Currently, PWI is an integral part of diagnostics in patients in whom cerebral ischaemia is suspected. The first clinical PWI application in brain lesion diagnostic in humans was performed for stroke diagnosis. At present, perfusion MRI is the only method to verify early ischaemia, is capable to show the haemodynamic decrease in certain brain areas (as the main mechanism of ischaemic damage), even in the first minutes after appearance of focal neurogical deficit.

1.4.3. Proton MR Spectroscopy

MR spectroscopy (MRS) is a non-invasive method of brain metabolism assessment. Proton (1H) MRS is based on a "chemical shift" which is the change of proton resonant frequency. This term was developed by N. Ramsey in 1951, for defining a distinction between frequencies of separate spectral peaks. The chemical shift measured unit is in parts per million (ppm). The main metabolites and corresponding values of the chemical shift are: *N*-acetylaspartate (NAA), 2 ppm; choline (Cho), 3.2 ppm; creatine (Cr), 3.03 and 3.94 ppm; *myo*-inositol (mI), 3.56 ppm; glutamate and glutamine (Glx), 2.1–2.5 ppm; lactate (Lac), 1.32 ppm; and a complex of lipids (Lip), 0.8–1.2 ppm.

Multinuclear MRS, based on phosphorus, carbon and other element nuclei, are entering the clinical practice.

Currently in proton MRS, two basic methods are used, single voxel (SV) and multivoxel (MV, or chemical shift imaging). MRS is a single-stage detection of spectra from several brain areas.

MV-MRS simultaneously obtains MR spectra for several voxels, and thus it is possible to compare spectra from different elements in an examination area. Processing of the MV-MRS data enables construction of a parametrical map of brain. The concentration of particular metabolites on this map is marked by colour, and thus it is possible to visualize the metabolite distribution in brain, i.e. to obtain an image weighed on the chemical shift. *NAA* is the most visible peak in the 1H spectrum (at 2 ppm). In the adult brain, NAA plays at least two roles:

1. as a predecessor of brain lipids, and

2. as a participant in coenzyme A interactions.

Some researchers believe that NAA is metabolically inert, and it participates only in maintenance of "deficiency anion" balance in neutral tissues, so it is the indicator of processes with neurotransmitter–neuromodulator participation, and its basic function is to be the form of free storage of aspartate. In an adult brain, the concentration of NAA in the cortex is higher than in the white matter, as the majority of NAA is located in neurons and their branches.

Due to the mainly neuronal and axonal NAA location, the NAA peak decreases in cases of neurodegenerative diseases.

The *choline* contribution is a sum of signals from several choline-containing chemical compounds (phosphoryl choline, glycerophosphoryl choline and free choline), and probably together with choline, which is present in a form of a polar head group in lipid membranes. MRS might not detect the compounds of choline embedded in a membrane; however, in the case of cell membrane destruction caused by the disease, choline is released, accumulated and may be them detected. Choline is a structural component of cellular membranes, especially myelin membranes. The choline peak tends to increase in highly malignant tumours and neurodegenerative diseases. Focal inflammation, which leads to considerable local cellularity and often to significant cellular membranes damages, could also result in increasing of choline peak.

The *creatine* peak at 3.03 ppm is caused by protons of methyl (CH3) group of creatine, phosphocreatine, lysine and glutathione. It appears that phosphocreatine is the basic molecule for maintenance of energy-dependent systems in all brain cells. Its concentration is maximal in cerebellum, followed by grey, and then by white, matter. Usually, it is assumed that the general creatine level is stable in different situations; therefore, the height of creatine peak is often used as reference in comparison with the height of other metabolites peaks.

MI has two peaks at 3.56 and 4.06 ppm, and it is supposed to function as storage of membranous phosphoinositides, which are the second messengers of the hormonal sys-

tems and participate in CNS enzyme regulation. It is one of the major growth factors, and it is a predecessor of phosphatidylinositol, which in turn is a part of the lipid layers of cellular membranes. It is primarily located in glial cells and, therefore, could serve as a specific glial marker.

The low combined peak at 3.56 ppm is from glycine and inositol-1-phosphate.

Another important metabolite that can be detected is lactate, which is a marker of anaerobic glycolisis. Lactate is detected by its typical doublet located in 1H MRS spectra around 1.32 ppm. It is believed that lactate, if found in greater quantities, especially in the first hours of life, is an indicator of brain damage. Lactate concentration varies as the brain matures: it is higher in newborns and in less-matured areas of the brain, such as parietal, anterior frontal and temporal. In more mature brains, lactate concentration is higher, for example in the basal ganglia and central gyri. Lactate is also a pathological metabolite in cases of high grade tumours, together with lipids (frequency range 0,8-1,3 ppm) that represent a marker of myelin disruption and necrosis.

Currently, the following areas of proton MRS clinical application are: injury, metabolic and mitochondrial damages, as well as inflammatory and volumetric disorders.

1.4.3.1. Proton MR Spectroscopy and Brain Tumours

MRS is now widely used to estimate various volumetric brain formations [17]. The most important goals of H-MRS are:

- *differentiate neoplastic from non-neoplastic lesion.* MRS accuracy is 95% to 100% in distinguishing neoplastic from non-neoplastic lesions. Cho is considered the most specific marker of intracranial neoplasm and increase in Cho levels and Cho/Cr and Cho/NAA ratio is very suggestive of neoplasm.

- *differentiate primary neoplasm versus metastases.* Absent or practically absent NAA and Cr levels are suggestive of a metastatic lesion. If the spectral analysis of the peritumoral region shows an increase in Cho level, it is probably an infiltration related to primary neoplasm. If there's no increase in Cho level it is probably vasogenic edema associated with metastasis.

- *indicate tumor grade and extension.* Sensitivity, specificity and accuracy of proton MRS are 100%, 86% and 96% respectively, in discriminating between high and low grade neoplasm. The most important metabolites to estimate tumour grade are Cho (higher Cho levels are related to cell density and correlate with the grade of the tumors), Lactate (there's a correct correlation between lactate levels and tumor grade), lipids (they are tipically found in high grade tumors), NAA and Cr (they usually decrease in high grade tumors), Mi (In low grade tumors Mi/Cr ratio is typically greater than in high grade tumors).

- *assess the ideal site for biopsy:* if performed in the site where the Cho/NAA ratio is maximum the biopsy will show high tumor infiltration.

- *demonstrate tumour extension*: intracranial neoplasm often extend beyond enhancement demonstrated in gadolinium-enhanced MRI. The high signal area on T2 surrounding the ne-

oplasm may represent vasogenic edema, tumor infiltration, and or abnormalities induced by radiotherapy and chemiotherapy.

- *demonstrate tumour progression*: Cho and lactate levels are considered prognostic factors in patients with intracranial neuroepithelial tumors. An increase in Cho levels > 140% in the lesion is related to high risk of tumor progression.Tumor progression is characterized by an increase in Cho levels greater than 45%, while in tumors that do not progress Cho levels decrease, maintain or rise less than 35%.

- *demonstrate therapeutic response:* Proton MRS is very useful in follow therapeutic response, identify residual or recurrent tumor earlier than conventional MRI and, above all, differentiate residual or recurrent tumor from post-treatment abnormalities. Evidence of radiation necrosis is typically observed within 6 months and is characterized by reduced Cho and increased lipid and lactate levels or by a normal spectral pattern. Postradiation and postchemotherapy necrotic areas are usually characterized by absent or decreased brain metabolites (NAA, Cr, Cho, Mi), elevated lipid and lactate levels, large peak between 0 and 2 ppm indicating cell necrosis products.

Definitively, even if it is impossible to predict with sufficient confidence the neoplasm histological type, nevertheless, the majority of researchers agree that tumoural processes as a whole are characterised by a low NAA–Cr ratio, increase in Cho–Cr ration, and in some cases, by the lactate peak.

In the majority of performed MRS examinations, proton spectroscopy is used in differential diagnostics of astrocytoma, ependymoma and primitive neuroepithelial tumors (PNET). Typical signs of astrocytoma and ependymoma are the decrease in the NAA–Cho ratio and increase in the ratio of Lac–Cho peaks in relation to those in a healthy hemisphere. Although the typical pattern of glioma spectra is well defined with high choline and low or absent NAA peaks, with lipid and lactate peaks often seen in GBM, studies of MRS for prediction of tumor histology have not shown sufficient specificity to make MRS a clinically useful adjunct in most cases.

MRS of extra-axial tumors that do not arise from glial precursors, such as meningiomas, generally reveals very high choline and no NAA, because the tumors contain no neurons. Although the presence of a very high alanine peak in rare meningioma's subtype can be useful to suggest the diagnosis, a recent well-controlled study suggests that the presence of low levels of alanine detected in up to 80% of meningioma is not useful because it is detected in similar frequency in metastases and schwannoma [12].

In comparison to these tumours, PNET are characterized by an increase in the NAA–Cho ratio and a lower Lac– Cho ratio, which is related to a higher level of Cho in patients with PNET, as with malignant neoplasm. For astrocytoma, in general, the increase of the Cho peak, the change of mI peak (depends on the malignancy level), the significant reduction of the NAA peak and the appearance of a Lac peak are typical.

For low grade astrocytoma, the reduction of NAA peak is typical, and the increase of Cho peak is observed. The height of the mI peak can remain unchanged, or it can not rise signifi-

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cantly in comparison with contralateral tissues not affected by tumours. The Lac peak is characterised by small elevation, and in rare cases, it cannot be detected at all. The Cho and Lak peak rises, while the mI peak falls with the increase of malignancy level—in particular, in cases of anaplastic astrocytoma. The NAA peak is reduced in comparison with its height in the spectrum of benign astrocytoma.

The marked or full reduction of NAA and mI peaks, and the sharp increase of the Lac peak, are observed in spectrum of glioblastoma, which is characterised by the presence of necrotic areas. At the same time, the Lip peak appears and overlaps the Lac peak and these peaks look like single complex. Generally, the height of Cho peak is sharply increased.

It is important to use MRS during postoperatory period for diagnostics of the continued neoplasm growth, tumour relapse or radiation necrosis. As a rule, treatment of brain tumours is a combination of surgery with chemo- and radiotherapy. However, current methods and doses of radiotherapy could cause death of tumour cells and also of normal cells, especially in cases of lowered sensitivity threshold for radiotherapy. First, vassels endothelium cells suffer, then brain oedema appears, and as a result, a zone of radiation necrosis could appear. According to statistics, in more than 5% of all patients who undergo radiotherapy because of a tumor, brain damage is diagnosed by the end of the first year near the tumour as well as in other areas.

The diagnosis of lymphomas is an important neuroradiology problem. Differential diagnosis of these tumours based on only routine CT and MRI is complicated, and combined chemo- and radiotherapy treatment is more preferable than surgical removal [5]. Therefore, the correct diagnosis influences the tactic choice in the treatment and prognosis of the disease. In the majority of cases, it is necessary to differentiate lymphomas with glial tumours and metastases. The common trend of changes in peaks of Cho, Lac and NAA is observed in lymphoma spectrum as well as in that of astrocytoma. However, these changes are different. With the lymphoma spectrum, the changes of peak heights are not so expressed. The Cho peak moderately increases, and the increased of peak of the Lac–Lip complex is substantial, whereas the decrease in the NAA peak is not significant.

1.4.4. Functional MRI

Brain activity mapping enables to reveal the areas of neuronal activation in response to tests, motor, sensor, and other stimuli. Until recently, similar mapping was performed with the help of radionuclide methods: PET and SPECT imaging. Functional MRI (fMRI) is based on increase of brain haemodynamics in response to cortical neuronal activity due to a certain stimulus [18; 19]. BOLD (*Blood Oxygenation Level Dependent contrast*) EPI-GRE registers hyperintense MR signal from active areas of the brain cortex. The registration time of one MR image is about 100 ms. fMRI signal intensity, registered by physiological load, is compared with the intensity, registered in the event of its lack. During MRI examination, the stimulation periods (duration of 30 s) alternate with control periods (without stimulation) of the same duration. The areas of statistically significant MR signal increasing during activation, revealed in the course of subsequent mathematical processing of images, correspond to areas of neuronal activity. They are marked with colour— in this way the neuronal activity

maps are built and these maps are imposed on *T*1 MRI sequences. Map construction methods (for instance, brain wave algorithms) subtract images obtained during neuron stimulation from control images obtained in the absence of stimulation. The subtracted image is imposed on a control scan according to its location, and areas of increased neuronal activity are marked with colour. The revealed functionally significant areas could be "imposed" on a *T*1 MRI sequence of the same section or on a three-dimensional (3D) brain model, and thus it is possible to estimate the ratio between the affected area (tumour) and functionally active brain areas, for example, motor, sensory or visual cortex.

1.4.4.1. Clinical Application of fMRI

Neuronal activity mapping enables planning the surgical approach and studying the pathophysiological processes in brain. This method is used in neurosurgery to study cognitive functions. Its perspective is in revealing the epileptic foci. Currently, fMRI is an integral part of MRI protocol in patients with brain tumours located close to functional critical brain areas. In the majority of cases, the examination results adequately reflect the location of sensomotor, speech and acoustical areas of brain cortex. However, according to the literature, 8–30% of all observation are not informative due to motion artefacts, lack of precise tests execution by the patients and damage to the above-mentioned cortical centres by tumours. In cases in which fMRI can localize active cortical areas, in 87% of cases there is a correspondence with the results of intraoperational electrophysiological methods, within 1-cm limits, and in 13% of cases, within 2 cm. This is evidence of the high accuracy of the fMRI technique [20]. Performing fMRI (currently it is conducted for somatosensory and visual cortices) and tractography with mapping of the functionally active cortical areas, pyramidal or optic tracts is becoming a standard in patient suffering from lesions located in eloquent areas. Imposition of these maps over 3D brain images is promising within the framework of one MRI examination for patients with brain tumours who are going to be operated. Based on these data, neurosurgeons plan the interventional approach and estimate the volume of neoplasm resection, and radiologists assess the areas of radiation and its distribution in tumour.

Conclusions

Advances in imaging technology have led to a better understanding of brain tumors and have advanced neuro-imaging from a purely anatomical to functional assessment of the nervous system.

MRI is the preferred imaging study for brain tumors diagnosis, providing detailed informations on lesion type, size and location. Although gadolinium-enhanced T1-weighted images and T2-weighted images are the MRI modalities of choice for the initial assessment, their usefulness in identifying tumor types, distinguishing tumors from nontumoral lesions, and assessing treatment effects is limited. For this reason, these sequences are used in combination with other MRI technicques, including Diffusion Weighted Imagin (DWI), Diffusion-Tensor-Imaging (DTI), Perfusion MRI, and Magnetic Resonance Spectroscopy (MRS). The most important application of MRI is intraoperative MRI (iMRI). Used with or without cortical stimulation, iMRI can maximize tumor resection while minimizing damage to healthy tissue, reducing the risk of neurological deficits and improving patient survival [21].

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Advanced brain tumor MRI evaluation can now routinely produce an impressive array of in vivo data reflecting tumor cellularity, metabolism, invasiveness, neocapillary density and permeability. Ongoing technical improvements and additional metrics, currently reported in the literature in a preliminary way, promise to bring to the clinic further dramatic increases in the quantity and quality of imaging data over the next years [12]. The greatest current challenge in advanced tumor imaging is the need for a new tumor classification method that can allow better integration of advanced imaging data into brain tumors research and clinical decision making. In essence, what is needed is a significant revision of brain tumor nosology. It is conceivable that a new tumor classification, advanced-MRI metrics in addition to nucleoside positrone emission tomography data and cellular and molecular microarray data could define novel pathophysiologically relevant subtypes that would better predict brain tumor patient prognoses and responses to targeted chemotherapeutic agents, than our current histopathologic grading system. A number of recent reports have been published evaluating imaging markers by direct comparison with molecular genotype [16] and phenotype and patient outcomes [22]. This approach seems likely to become the dominant paradigm in the future [12].

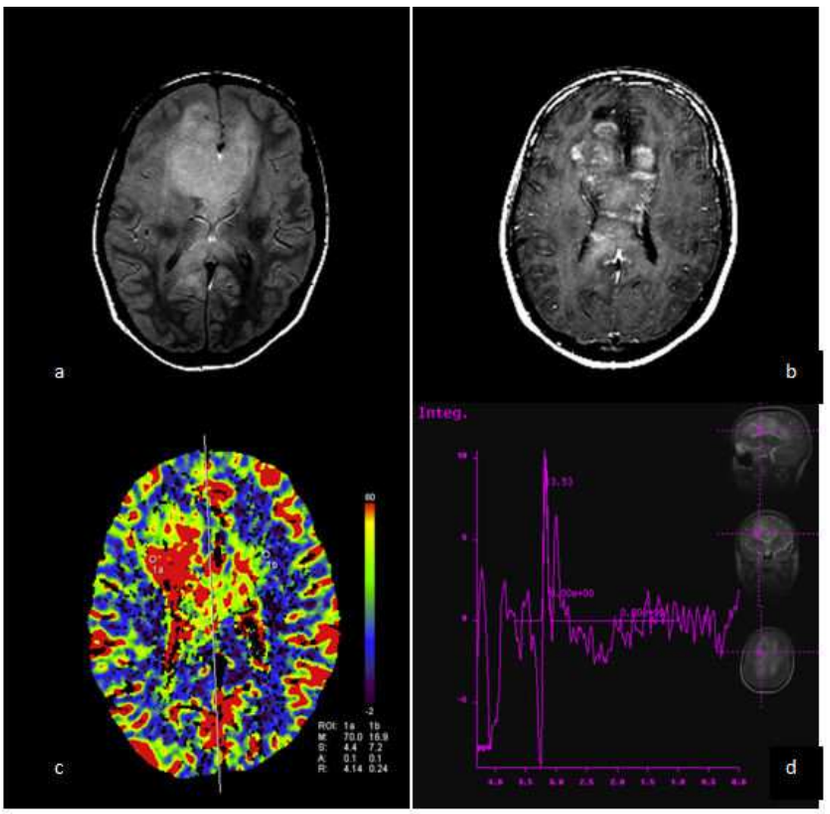

Figure 1. a) MRI Flair sequences demonstrate a frontal lesion with homogenous hyperintensity. b) T1 weighted MRI with gadolinium administration demonstrating no enhancement of the lesion. c) Perfusion CT scan showing a circular area of the tumor with higher r-CBV, expression of hypervascularization of that part of the tumor. d) MRI Spectroscopy showing an increased choline/NAA ratio. The neuroradiological findings suggested the diagnosis of low grade glioma with an area within it of higher grade (the area with hypervascularization). Definitive histological results was positive for anaplastic oligodendroglioma.

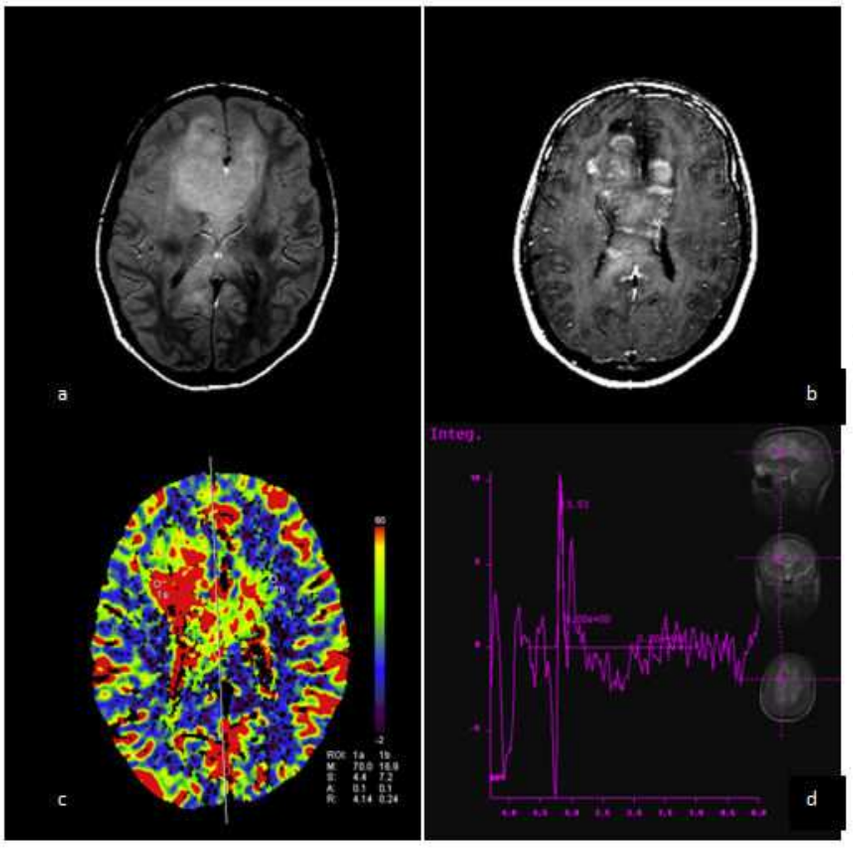

Figure 2. a) MRI Flair sequences demonstrate a frontal lesion with involvement of corpus callosum and bilateral extrinsecation (butterfly glioma). b) T1 weighted MRI with gadolinium administration demonstrating disomogenous enhancement of the lesion.. c): Perfusion CT scan showing a high vascularization of the tumor with high r-CBV. d) MRI Spectroscopy showing an increased choline/NAA ratio (higher than in case 1). The neuroradiological findings suggested the diagnosis of high grade glioma. Definitive histological results were positive for glioblastoma multiformis.

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