Pediatric Neuroimaging

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Introduction

Neuroimaging is a key tool in the diagnosis and follow-up of neuro-oncologic patients. Magnetic resonance imaging (MRI) and computerized tomography (CT) are the main imaging modalities involved in neuroimaging diagnosis of these patients. However, MRI is the main imaging tool in the daily practice of pediatric neuro-oncology. The main reason is that CT involves radiation exposure risks and MRI has the ability to show significant more details about the brain parenchyma.

PET (positron emission tomography) and molecular imaging are rapidly developing as new techniques to evaluate brain tumor. The results provided by PET and molecular imaging appear to corroborate the findings of MRI studies and may contribute to decision-making in the treatment and follow-up of patients. Therefore understanding general principles of different imaging modalities can help the clinician to improve patient care.

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CT Principles

Neuroimaging is essential for diagnosis of both primary and secondary central nervous system (CNS) neoplasms, and magnetic resonance imaging (MRI) remains the main imaging modality for characterization of these lesions. However, computerized tomography (CT) is often used in patients with acute presentations. The two main reasons that CT may be preferred over MRI in cases presenting acutely are: faster image acquisition than MRI, within few seconds, and diagnostic images are accrued more rapidly, which is important if the patient's clinical status is unstable. In addition, there is rarely a need for sedation [1] and CT may often be more instantly available than MRI [2]. However, a downside of CT is the ionizing radiation exposure, of particular importance in children who are more sensitive to its effects than adults (Fig. 4.1) [3].

Radiation Safety

Biological radiation effects can be divided into two categories: stochastic and deterministic effects. Deterministic effects are set by exposure threshold, and doses above the cutoff cause damage (e.g., cataract occurs if the crystalline lenses are exposed above 5 Gy (gray is the radiation unit for absorbed dose of radiation)) [3]. Stochastic effects are the result of cumulative doses of radiation and are related to genetic abnormalities and

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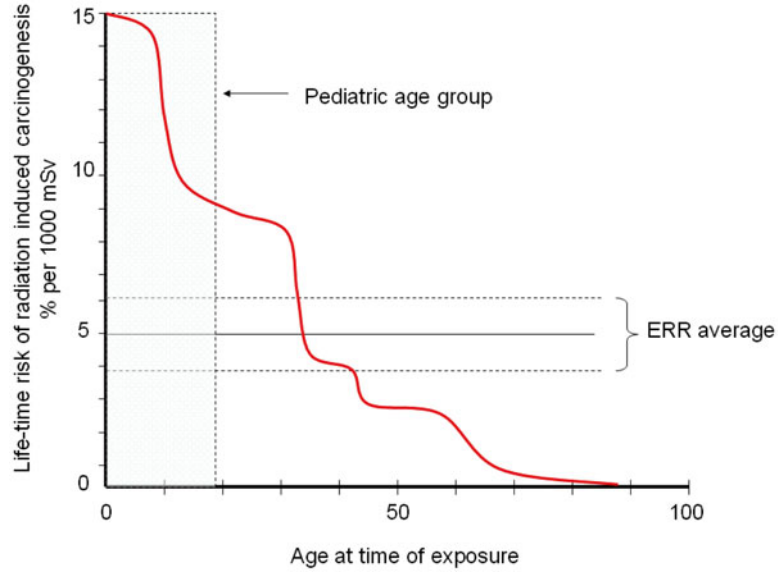

Fig. 4.1 The graphic demonstrates the increased carcinogenic risk related to radiation exposure for the pediatric population compared to the adult population. Reprinted from Peck DJ, Samei E. How to Understand and Communicate Radiation Risk. Image Wisely. Available at: http://www.imagewisely.org/Imaging-Professionals/Medical-Physicists/Articles/How-to-Understand-and-Communicate-Radiation-Risk. Reprinted with permission of the American College of Radiology, Reston, Virginia. No other representation of this material is authorized without express, written permission of the American College of Radiology

carcinogenic effects. There are no safe levels of radiation exposure related to stochastic effects, and the cancer risk increases as cumulative doses increase [3].

Recently, Pearce et al. (2012) demonstrated the association of low doses of radiation administrated on CT with occurrence of brain tumors and leukemia in a pediatric population (Fig. 4.2). This was the first time that this association was proven, although previous publications based on information gathered from the survivors following atomic explosions had raised the concern about the use of low dose radiation in medical imaging modalities [4]. Therefore, extra care should be taken when requesting a CT scan in the pediatric population, weighing the risks and benefits for each case.

There are three principles of radiation safety that should be kept in mind when requesting and performing a CT examination: justification, optimization, and dose limitation (Table 4.1) [5].

The North American radiological societies have mounted campaigns in an effort to educate doctors and the general population regarding radiation effects and radiation safety. The most important radiation safety campaigns (Image Gently® for pediatric population (http://www.pedrad.org/associations/5364/ig/) and Image Wisely® for the adult population (http://www.imagewisely.org/)) have made optimization ("as low as reasonably achievable" (ALARA)) a very popular principle. However, justification is also very important, not only because it justifies the investigation, but also because it helps to decide which adjustments are necessary in the imaging technique in order to make the diagnosis.

There are several techniques that can be applied in CT imaging acquisition. For example, a patient who needs to have only the size of the cerebral ventricles assessed can have a study performed with low radiation exposure. In contrast, for brain parenchyma assessment, a scan with a regular radiation dose exposure is required to prevent artifacts related to low doses [6] (Fig. 4.3).

The clinical information provided in the request form also helps the radiologist to decide if the study requires contrast. For

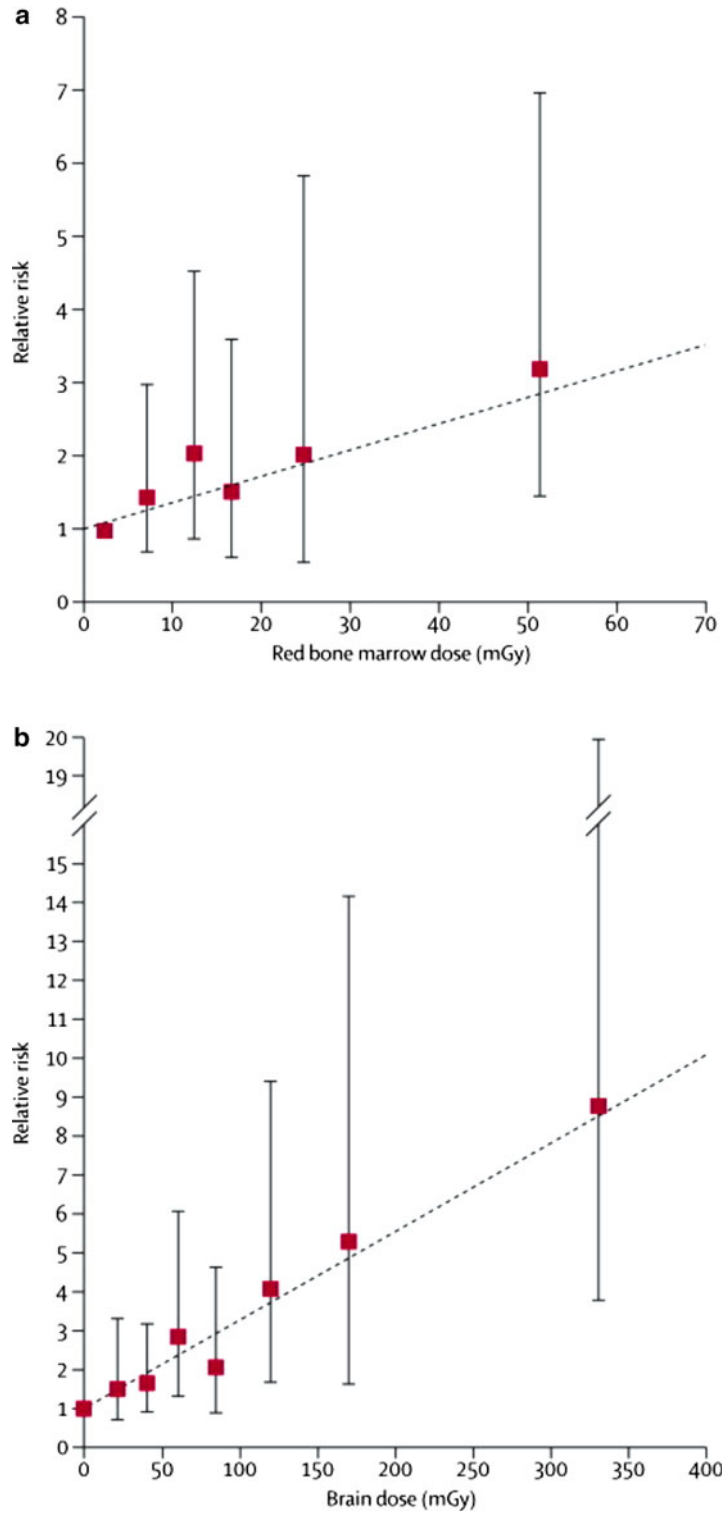

Fig. 4.2 Relative risk of leukemia and brain tumors in relation to estimated radiation doses to the red bone marrow and brain from CT scans: (**a**) Leukemia and (**b**) brain tumors. *Dotted line* is the fitted linear dose–response model (excess relative risk per mGy). *Bars* show 95 % CIs. Reprinted Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet. 2012 Aug 4;380(9840):499-505. With permission from Elsevier

Table 4.1 Radiation safety principles

Justification	Any radiation exposure should be justified and judge. It only should be adopted if the benefit outweighs the harm it may cause
Optimization	Radiation doses and risks should be kept as low as reasonably achievable (ALARA). Technical aspects should be respected to achieve minimal radiation exposure and maximize benefits
Dose limitation	Exposure of individuals should not exceed specified dose limits above which the dose or risk would be deemed unacceptable. The limits are usually set by ICRP[a]

[a]International Commission on Radiation Protection

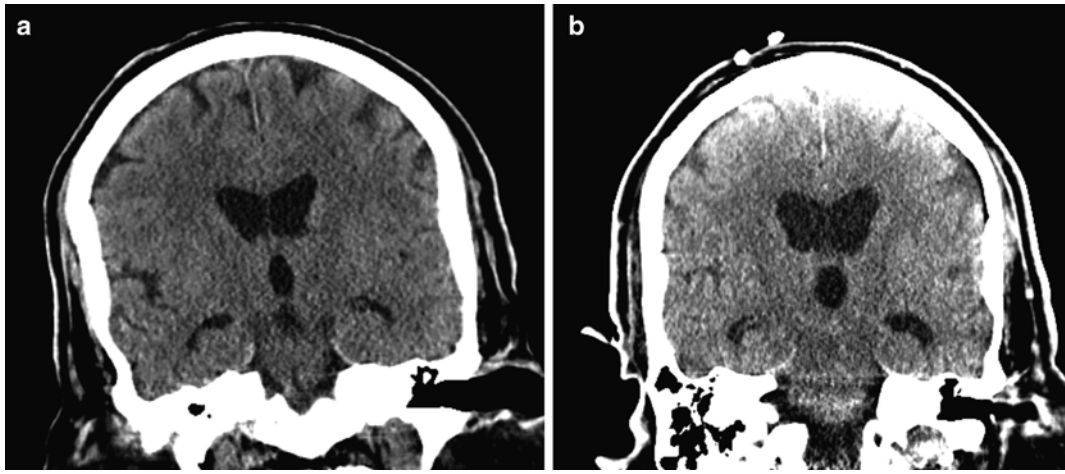

Fig. 4.3 (**a**) CT head regular dose is acquired showing detailed imaging of the brain parenchyma and ventricles. (**b**) Low-dose CT of the head does not have the same parenchymal imaging details but is enough to demonstrate presence of hydrocephalus

example, melanoma metastases are easier to depict after intravenous contrast injection. However, if the radiologist is not informed about a clinical suspicion of melanoma, intravenous contrast might not be used, thereby increasing the chance of missing lesions. The same problem applies for leptomeningeal disease in patients with history of malignancy as this can be difficult to visualize without the administration of intravenous contrast media as illustrated in Figs. 4.4 and 4.5.

The contrast used in CT scans is an iodine-based media. The use of this contrast should be cautious since it is not innocuous and contraindications to its use must be taken into account (Table 4.2) [7]. In addition, if a pre- and post-contrast study is needed, the patient will need to be scanned twice, receiving two doses of radiation.

In conclusion, every time a physician fills out a requisition with adequate clinical information, the radiologist is being helped to decide if the image modality chosen by the clinician is the most appropriate for the diagnosis and what is the best technical approach to perform it. The clinician must also flag any risk factors or contraindications for the use of contrast media. The chosen diagnostic test will have adequate sensitivity and specificity and patients will be saved from unnecessary radiation exposure if all these principles are followed.

Here are some questions that might help physicians to evaluate the appropriateness of a CT request:

– Are there publications or protocols to support the choice of a CT study for the condition?

The American College of Radiology website (http://www.acr.org/Quality-Safety/Appropriateness-Criteria) has published a list of

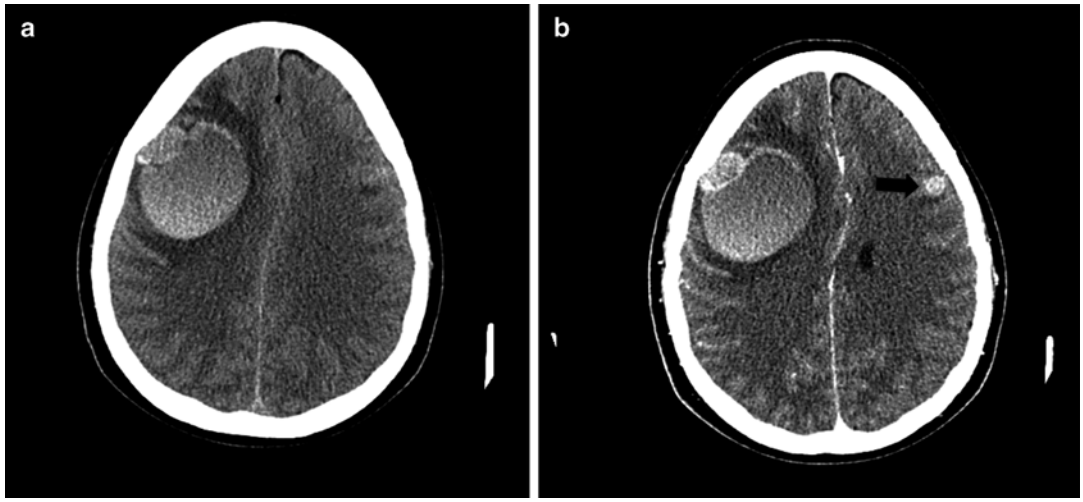

Fig. 4.4 (**a**) CT without contrast demonstrates a hyperdense hemorrhagic metastasis from melanoma on the right hemisphere. (**b**) Enhanced CT showing a second metastatic lesion on the left frontal lobe (*black arrow*). This was poorly visualized without contrast

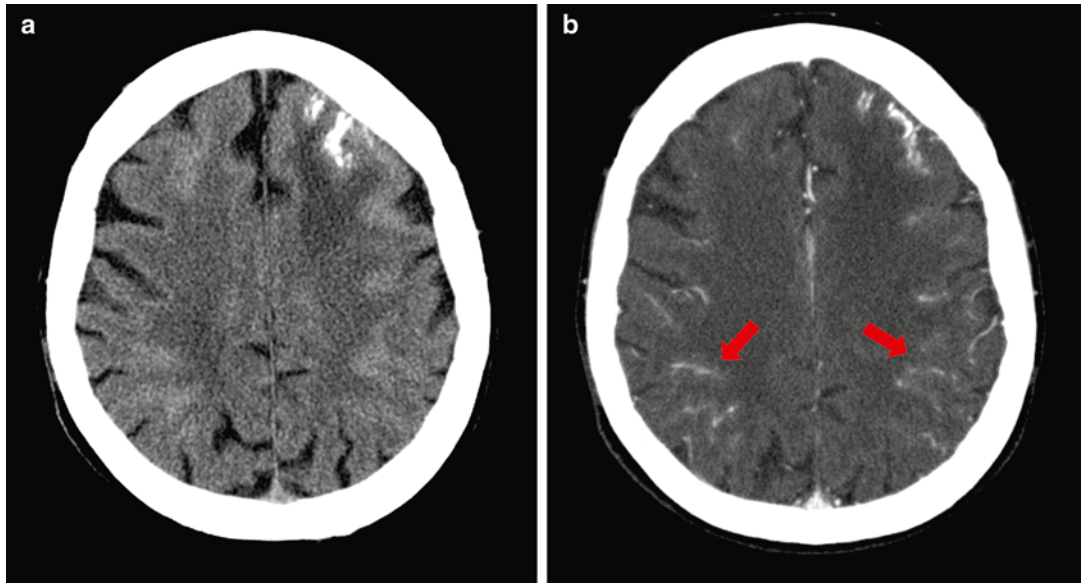

Fig. 4.5 (**a**) CT without contrast shows multiple hyperdense sulci in the cerebral convexity bilaterally with focal calcification on the left frontal lobe. (**b**) Enhanced CT of the same patient showing extensive leptomeningeal disease (*red arrows*)

appropriateness criteria for different clinical scenarios. The use of this website may be helpful when questions about appropriateness are raised.

– In the knowledge that the younger the patient, the greatest the risk for tumors related to radiation exposure, does the benefit of a CT diagnosis outweigh the risk of cancer?
– Is there any contraindication to iodine contrast media if this is needed for the imaging study?
– What is the history of previous radiation exposure? Is this patient pregnant or at risk of pregnancy?
– Are there alternative tests available for the diagnosis?

Table 4.2 Adverse effects from the administration of iodine-based contrast agents

Adrenal glands	Hypertension (in patients with pheochromocytoma after intra-arterial injection)
Brain	Headache
	Confusion
	Dizziness
	Seizure
	Rigors
	Lost or diminished consciousness
	Lost or diminished vision
Gastrointestinal tract	Nausea
	Vomiting
	Diarrhea
	Intestinal cramping
Heart	Hypotension
	Dysrhythmia (asystole, ventricular fibrillation/ventricular tachycardia)
	Pulseless electrical activity (PEA)
	Acute congestive heart failure
Kidney	Oliguria
	Hypertension
	Contrast-induced nephropathy (CIN)
Pancreas	Swelling/pancreatitis
Respiratory system	Laryngeal edema
	Bronchospasm
	Pulmonary edema
Salivary glands	Swelling/parotitis
Skin and soft tissues	Erythema
	Urticaria
	Pruritus
	Compartment syndrome (from extravasation)
Thyroid	Exacerbation of thyrotoxicosis
Vascular system	Hemorrhage (due to direct vascular trauma from contrast injection or from the reduction in clotting ability)
	Thrombophlebitis

Based on data from [7]

Basic Principles of CT Interpretation

CT image formation is based on a gray scale of tissue X-ray attenuation. Tissues that can attenuate more X-rays appear whiter or hyperdense (e.g., bone) and tissues that allow the passage of X-rays appear blacker or hypodense (e.g., cerebrospinal fluid spaces). Fat tissue, for example, attenuates less X-rays than the normal brain tissue and therefore appears hypodense (Fig. 4.6) [8].

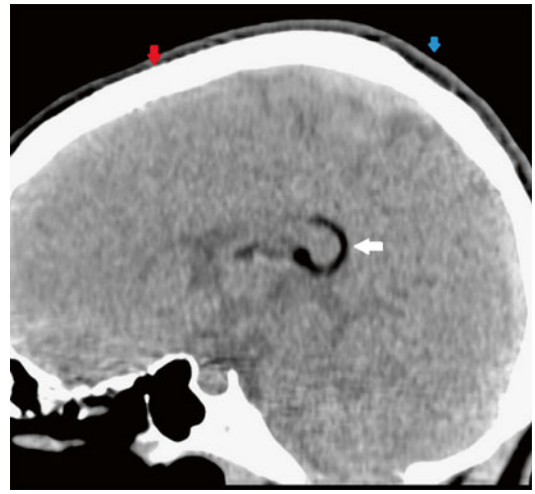

Fig. 4.6 Examples of different CT densities. A hypodense structure is seen in the posterior aspect of the corpus callosum (*white arrow*), in keeping with a lipoma. The *red arrow* is showing the parietal bone (hyperdense structure) and the *blue arrow* is pointing to the subcutaneous tissues of the scalp, which is also hypodense due to the presence of fat. Reprinted Senggen E, Laswed T, Meuwly JY, Maestre LA, Jaques B, Meuli R, et al. First and second branchial arch syndromes: multimodality approach. Pediatric radiology. 2011 May;41(5):549-61. With permission from Springer Science + Business Media

CT is a very good technique to assess the CNS vasculature. CT arteriograms and venograms have a high sensitivity and specificity in the diagnosis of vascular disease. Nevertheless, because of the increased radiation exposure, it is normally only used if the MR arteriogram/venogram was not diagnostic.

Interpretation of pediatric imaging has its own peculiarities as compared to adult imaging, as the different stages of development result in different appearances of the normal brain. The lack of myelin in the early stages of development and increased water content in the white matter is one example. This characteristic results in differences between the gray and white matter contrast that does not resemble what is seen in an older child, when the myelination process is complete (Fig. 4.7). Therefore, when looking at a pediatric study, it is very important to know the patient's age before coming to any conclusions.

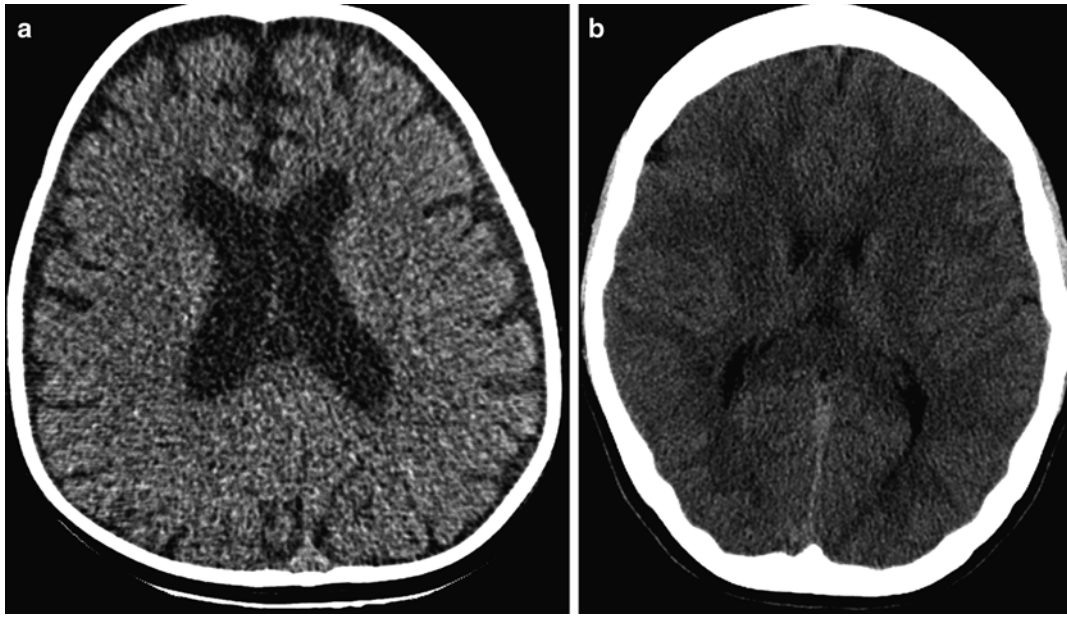

Fig. 4.7 (**a**) Axial CT image of an 11-month-old patient showing fairly homogeneous brain density with decreased gray white matter differentiation due to the small amount of myelin in the white matter. This is a normal finding in this age group due to the myelination process. (**b**) CT image of a fully myelinated brain of a 14-year-old showing the well-demarcated gray/white matter differentiation. The relative hypodensity of the white matter is due to the presence of myelin

Table 4.3 Imaging characteristics of hemoglobin degradation in intraparenchymal hemorrhages

			Appearance		
Phase	Time	Hemoglobin	CT	T1-weighted MRI	T2-weighted MRI
Hyperacute	< 12 h	Oxyhemoglobin	Hyperdense	Isointense or hypointense	Hyperintense
Acute	Hours to days	Deoxyhemoglobin	Hyperdense	Isointense or hypointense	Hypointense
Early subacute	Few days	Methemoglobin	Isodense	Hyperintense	Hypointense
Late subacute	4–7 days to 1 month	Methemoglobin + cell lysis	Hypodense	Hyperintense	Hyperintense
Chronic	Weeks to years	Ferritin and hemosiderin	Hypodense	Isointense or hypointense	Hypointense

Adapted from Parizel P, Makkat S, Van Miert E, et al. Intracranial hemorrhage: principles of CT and MRI interpretation. Eur Radiol 2001; 11: 1770-1783. & Osborn AG (ed). Osborn's Brain, Pathology and Anatomy. Salt Lake City, UT: Lippincott Williams & Wilkins; 2012

The same principles apply for the interpretation of MRI images [9].

The assessment of a CNS bleed also has some pitfalls. There are different stages of hemoglobin degradation (Table 4.3) [10, 11]. In acute stages a bleed will be hyperdense compared with the rest of the brain parenchyma. However, if the patient is anemic, the attenuation of the signal from an acute bleed can be similar to that of the brain parenchyma. Therefore, a small bleed can be easily missed. Another problem is the lack of myelin in young children, which produces a relative diffuse hypodensity of the parenchyma and makes the blood vessels (in particular the venous sinuses) appear more hyperdense than usual (Fig. 4.8). This should not be confused with acute thrombosis of the venous sinuses. A similar effect can be seen in patients with cyanotic conditions such as cardiac shunts or chronic lung disease, if they are polycythemic. However, in these cases the relative hyperdensity of

the vessels is caused by an increased hematocrit and is not due to lack of myelin [11].

A CT scan can determine the degree of mass effect over the parenchyma when evaluating a space-occupying lesion. It can also demonstrate the presence of intralesional cysts, calcification, necrosis, blood, or fat. CT almost always defines the anatomical location of the lesion, except in some cases of infiltrative lesions and posterior fossa lesions. However, MRI allows a more detailed assessment of brain anatomy and its associated pathology (Fig. 4.9). Therefore, once a space-occupying lesion is identified on CT, an MRI is carried out as the next step in the imaging investigation to further characterize the mass and its relationship to the rest of the parenchyma.

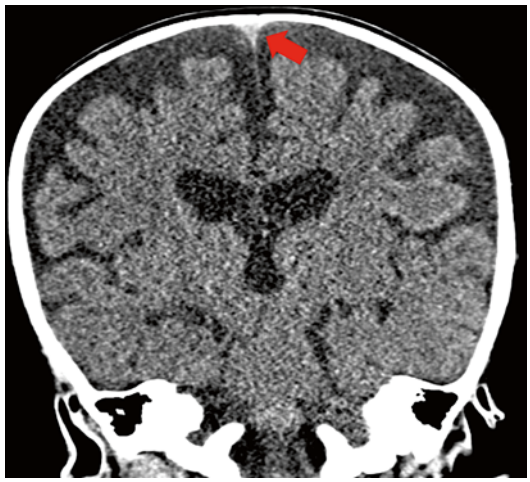

Fig. 4.8 Coronal CT image of an 11-month-old infant showing the relative hyperdensity of the superior sagittal sinus (*red arrow*) in the background of non-myelinated brain parenchyma. This should not be interpreted as venous sinus thrombosis

Magnetic Resonance Imaging

MRI Image Formation

The principle of MRI imaging acquisition is based on the spin movement of hydrogen atoms. Intermittent radiofrequency pulses are turned on to cause resonance of these atoms. The atomic resonance is extinguished when the radiofrequency pulse is turned off. At this moment, there is a relaxation period while the atoms are losing resonance in which a radiofrequency pulse is emitted by the atoms and then captured by the MRI coils (a device placed around the patient

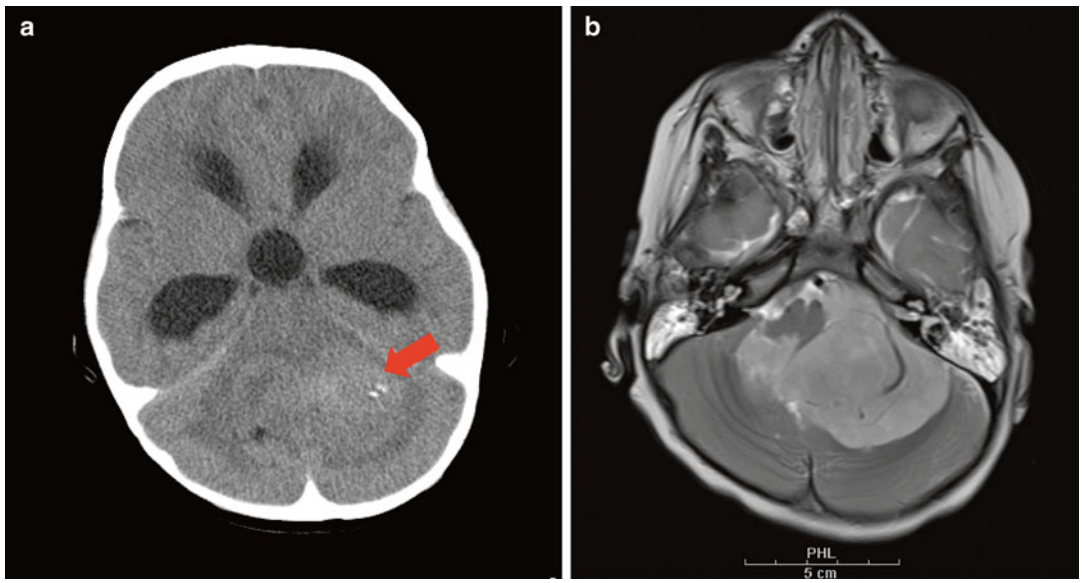

Fig. 4.9 (**a**) Non-enhanced CT demonstrates a posterior fossa mass (*red arrow*). (**b**) However, an axial T2-weighted MR image of the same lesion showed that the lesion is extra-axial in location involving the 4th ventricle and foramen of Luschka on the left side. This demonstrates the superior tissue characterization obtained with MR technique

Table 4.4 Characteristics of frequently used MRI sequences

Sequence	Characteristic	Main importance for CNS tumor imaging
Turbo spin echo (TSE) and spin echo (SE)	High-resolution and detailed anatomy	Helps in determining: – Anatomy of the lesion and its effect over the parenchyma – Evaluation of cystic/solid components – T1 and T2 signal characteristic of the lesion for differential diagnosis
FLAIR (T2 weighted)	Highlights with high signal abnormal water content and presence of gliosis in the brain parenchyma	– Helps in delineating infiltrative lesion's extension – Shows the presence of perilesional edema
Diffusion-weighted imaging (DWI)	Demonstrates presence of diffusion restriction of water molecules in the tissues	– Increased cellularity, decreased extracellular space, and a high nuclear to cytoplasm ratio are responsible for water diffusion restriction in high-grade tumors – If water restriction is present, it also may indicate the presence of necrosis, pus, acute blood products within the lesion – ADC map[a] measurements have an inverse relationship with tumor grading (the higher the measurement, the lower the grade)
Susceptibility-weighted imaging (SWI)	Highlights with low signal, the presence of gas, calcifications, and blood products	– Helps to establish the presence of intralesional calcifications and blood, adding information for the differential – Helps in demonstrating postsurgical changes or formation of post-radiation cavernomas

[a]Apparent diffusion coefficient (ADC) map is a mathematical subtraction of the true diffusion acquisition necessary to show the true diffusion of water throughout the tissues

which acts as a receptor), giving the necessary information for the image formation. The set of images obtained with a specific combination of radiofrequencies is called a sequence.

Depending on how the radiofrequency pulse is applied, the sequences can highlight the signal of water (T2-weighted images) or the signal of fat tissue (T1-weighted images). Other radiofrequency combinations result in different sequences and other contrasts (e.g., proton density-weighted imaging). The study protocol details are the combination of sequences. There are several types of MRI sequences (e.g., spin echo (SE), turbo spin echo (TSE), FLAIR (fluid-attenuated inversion recovery), and susceptibility-weighted image (SWI)).

The clinical history provided by the physician will help the radiologist to set up the MRI protocol and to make the decision regarding the need for intravenous contrast administration. Standard MRI protocols of the brain and spine vary among institutions. In our institution, the standard brain tumor imaging protocols are volumetric sagittal T1 with reconstructions, coronal T2 TSE, axial FLAIR, axial diffusion-weighted image (DWI), and axial SWI (Table 4.4). A volumetric gradient T1 with reconstructions is applied after intravenous gadolinium contrast media administration.

Accurate anatomical localization of a space-occupying lesion is the key for the differential diagnosis of a brain tumor in the pediatric population. Nevertheless, signal intensity, presence of restricted diffusion, calcifications, fat, hemorrhage, and enhancement pattern of the lesion are additional features that help to narrow down the differential diagnosis [12].

The routine MRI sequences are usually enough for an accurate differential diagnosis (Fig. 4.10). Nevertheless, newer sequences and techniques provide additional information to help in the diagnosis and treatment management of difficult and atypical cases.

Commonly, neuro-oncology MRI studies will need post-contrast imaging for the characterization of a space-occupying lesion. Particular attention should be paid to studies post-surgery. Ideally, these should be performed within the first 24 h after a surgical procedure in order to avoid misinterpretations of residual tumor enhancement with leakage across the blood–brain barrier. Enhancement of the surgical bed due to such leakage starts within

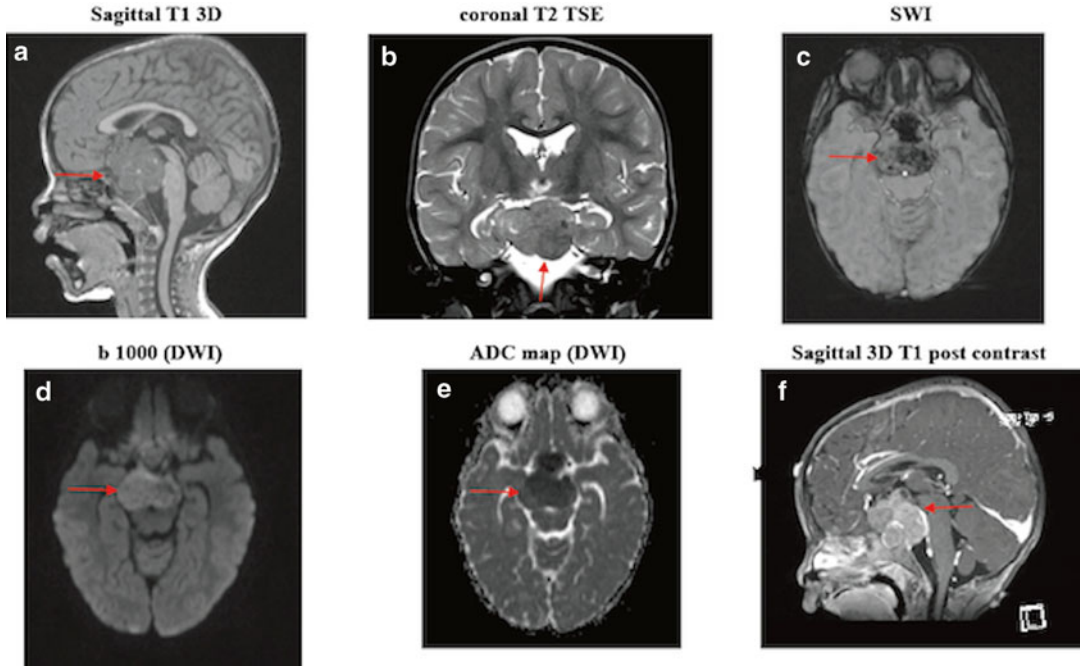

Fig. 4.10 (**a**) Sagittal T1 3D MPRAGE showing large heterogeneous slightly hypointense lesion centered in the suprasellar/hypothalamic region. Small punctate areas of high T1 signal within the lesion may represent small areas of hemorrhage or calcification. Mass effect is seen over the pons but the lesion also appears invading adjacent structures like sella turcica and anterior aspect of third ventricle. (**b**) Coronal T2 turbo spin-echo showing that the same lesion has areas of slightly high and low T2 signal. (**c**) sequence is showing abnormal susceptibility. The DWI (**d**, **e**) is showing restricted diffusion within the lesion. The post-contrast sagittal T1 (**f**) shows heterogeneous enhancement of the lesion. FLAIR images were not acquired as this was an 18-month-old child. The characteristics of this lesion are aggressive and the main differential was primitive neuroectodermal tumor which was confirmed after biopsy

72 h after surgery and is maintained clearly for up to 6–8 weeks, decreasing progressively for up to 12 months after surgery. A further aspect post-intervention is the enhancement of lesions 4–6 months after radiotherapy, which may be related to radiation necrosis [13]. In these cases frequent follow-up is necessary, and other MRI techniques can be used in an attempt to differentiate radiation necrosis from tumor recurrence.

MRI Special Considerations

MRI contrast media are gadolinium-based agents, and its use in the pediatric population is off-label for individuals younger than 2 years. Gadolinium-based contrast media is not nephrotoxic in the approved dosages for MRI studies [7]. However, patients with previous renal failure can develop nephrogenic systemic fibrosis (NSF) if gadolinium-based contrast is administered. NSF is a rare irreversible disease. The hypothesis is that it is caused by deposition of gadolinium in the tissues. To date, there are approximately 370 cases reported in the literature associating this pathology to the use of gadolinium contrast. The age range of reported cases is from 8 to 87 years [14]. The majority of NSF cases are described in patients with previous chronic renal failure. Patients with acute renal failure can also develop NSF especially if superimposed to chronic renal failure. Due to the risk of NSF, the procedure of administering gadolinium-based contrast "just in case" has been removed from the daily practice. The American College of Radiology also advocates cautious use of gadolinium-based agents in newborn and infants due to renal immaturity, even though no case has been reported in patients younger than 8 years [7].

Enhanced CT is the alternative for patients at increased risk of NSF that need an enhanced study,

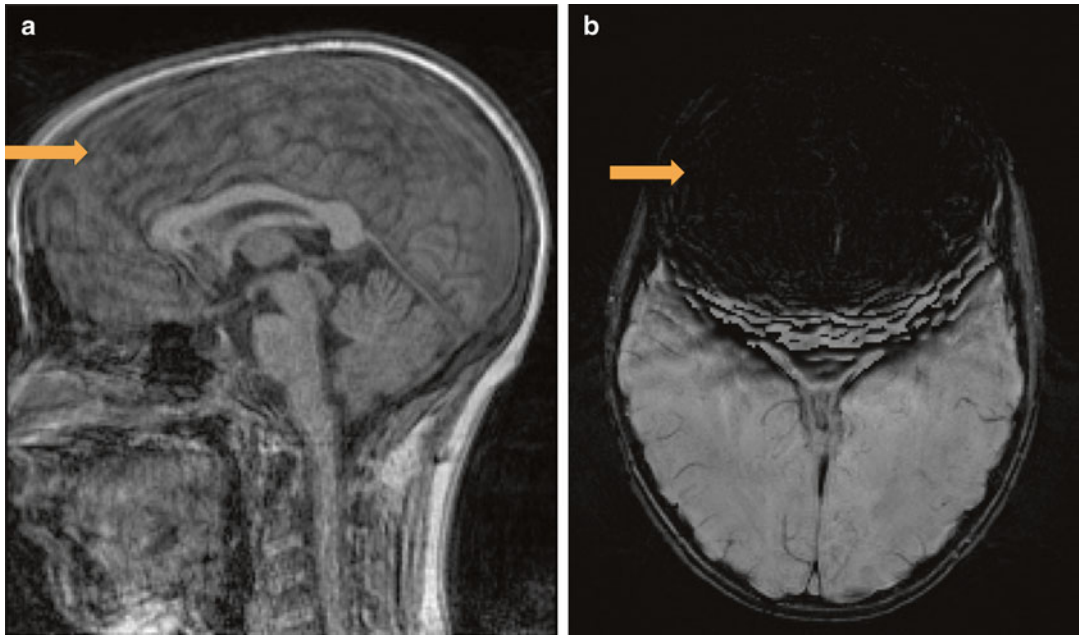

Fig. 4.11 (**a**) Sagittal T1 3D of the brain showing imaging quality degradation secondary to motion artifact. The multiple curved lines overlying the midline gyri correspond to artifacts. (**b**) Nondiagnostic axial SWI showing marked imaging degradation secondary to metallic artifacts produced by dental braces (*arrow*)

but iodine contrast media can potentially worsen the renal function. In addition, the risk of ionizing radiation needs to be weighed up in the risk-benefit analysis when a CT study with contrast is carried out instead of an MRI especially in the pediatric population. However, CT iodine contrast can be removed from the blood stream through hemodialysis. It is unknown if hemodialysis performed soon after an enhanced MRI scan to remove gadolinium from the blood stream can prevent NSF. Nevertheless, this practice is advised if the enhanced MRI study is indeed performed [7].

Imaging Artifacts

MRI is a technique that is highly susceptible to imaging artifacts. In brain imaging, artifacts related to dental hardware are very common and it may be impossible to diagnose any pathology. Motion artifact is another common artifact in pediatric studies, and this can also degrade the quality of images significantly (Fig. 4.11). For this reason some pediatric MRI studies need to be performed under sedation.

MRI Safety

Another important consideration is the MRI safety area and procedures. When approaching the area of an MRI scanner, safety zone alerts should be evident. Metallic objects can fly towards the magnet due to the magnetic field strength and this can be deadly. Patients with metallic implants can have the implant damaged or displaced. Injury can also occur by heat of a metallic foreign body or implant. Anyone that approaches an MRI scanner should be initially screened for the presence of metallic hardware and other contraindications (Table 4.5) [15].

Pediatric Sedation

Imaging pediatric patients can be challenging. Motion artifact can ruin an MRI or CT study. Therefore, sedation may be needed to perform an imaging examination.

The age group most likely to require sedation is for children younger than 8 years.

Table 4.5 Important screening information for an MRI study

Problems in previous MRI scan (e.g., claustrophobia)
Previous surgery and dates
Injury by metallic object or presence of foreign body?
History of kidney disease, asthma, or allergies?
History of previous allergy of MRI or CT dye? Which kind of reaction?
Pregnancy? Lactation?
Any type of electronic, mechanical, or magnetic implant or device?
Cardiac pacemaker/implanted cardiac defibrillator/artificial heart valve
Aneurysm clip
Neurostimulator/biostimulator
Internal electrodes or wires/any type of surgical clip or staple
Any type of coil, filter, or stent
Cochlear implant/hearing aid/any type of ear implant
Implanted drug pump
Halo vest/spinal fixation device/artificial limb or joint
Penile implant
Artificial eye/eyelid spring
Any type of implant held in place by a magnet
Any IV access port/shunt
Medication patch
Tissue expander
Removable dentures, false teeth, or partial plate
Diaphragm, IUD, pessary
Surgical mesh
Body piercing
Wig/hair implants
Tattoos or tattooed eyeliner
Radiation seeds (e.g., cancer treatment)
Any implanted items (e.g., pins, rods, screws, nails, plates, wires)
Any hair accessories (e.g., bobby pins, barrettes, clips)
Jewelry
Any other type of implanted item

Adapted from Expert Panel on MRS, Kanal E, Barkovich AJ, Bell C, Borgstede JP, Bradley WG, Jr., et al. ACR guidance document on MR safe practices: 2013. Journal of magnetic resonance imaging : JMRI. 2013 Mar;37(3):501-30. With permission from John Wiley & Sons, Inc.

Overall, the failure rate of sedation varies in the literature from 1 to 20 % [16]. In addition, major cardiovascular and respiratory events can occur in approximately 0.4–1 % [17]. Alternative techniques are safer for the patients and can avoid a significant number of sedations. Audiovisual systems in the MRI suits, for example, can reduce the number of sedations in children between 3 and 10 years old by 25 % and by 50 % in children older than 10 years [18]. Other examples of alternative techniques are feed and sleep (which works very well in neonates and young infants), sleep deprivation, melatonin administration, and MRI simulation training. Alternative techniques should be applied whenever is possible [19].

Advanced Imaging Techniques

Functional MRI (fMRI)

Imaging acquisition in fMRI is based in the principle that oxygen consumption increases in the brain area used for a particular activity. The sequence used for this technique is known as blood-oxygen-level-dependent (BOLD) contrast. In neuro-oncology this technique can add information about involvement of eloquent areas of the brain by a space-occupying lesion (Fig. 4.12) [20].

Functional studies are carried out with the patient awake and able to collaborate [20]. Standard MRI scanners might have the BOLD sequence available; however, special software is necessary to perform the functional examinations.

Diffusion Tensor Imaging (DTI)

DTI imaging principle is based in the three directional movements of water molecules throughout the tissues. Isotropy is the term used when the water molecules diffuse equally in all directions. However, in the brain, due to the parallel micro movement of water molecules within the axons, there is anisotropy of water molecule movement, which is measured by the fractional anisotropy (FA) index. DTI also allows determination of fiber bundle directionality, also known as tractography study [21].

Nowadays, tractography studies have been used alone or in association with fMRI to determine the degree of white matter tract involvement by a CNS tumor (Fig. 4.13). This information is extremely helpful for surgical and radiotherapy treatment planning, especially if the tumor is located in an eloquent region of the brain [21].

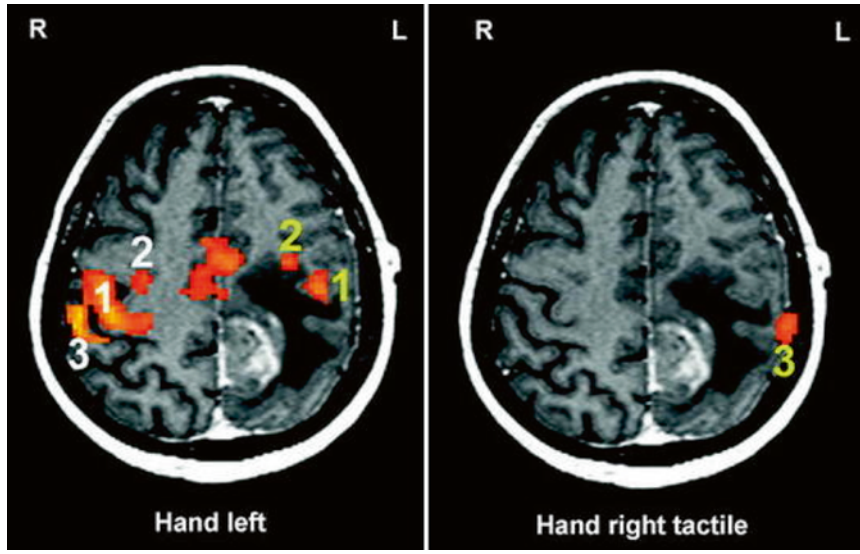

Fig. 4.12 Presurgical fMRI in a hemiparetic patient (grade 3/5) with a left malignant glioma only weak BOLD activation was available from contralateral (*right*) hand movements precluding reliable localization of the motor hand area (not shown). By using complex finger opposition of the unimpaired hand ipsilateral to the tumor (*left*) and fully automated tactile stimulation of the right digits BOLD activation is achievable in the motor hand area (1), premotor cortex (2), and primary somatosensory cortex (3) on the tumor side. Note the corresponding activations in the unimpaired hemisphere (*right*) associated with the left finger movements (*white numbers*). Bilateral supplementary motor activation is in the midline. Reprinted from Stippich C. Preoperative Blood Oxygen Level Dependent (BOLD) functional Magnetic Resonance Imaging (fMRI) of Motor and Somatosensory Function. In: Ulmer S, Jansen O (eds). fMRI: Basics and Clinical Applications: Heidelberg, Germany: Springer-Verlag; 2013. p. 91-110. With permission from Springer Science + Business Media

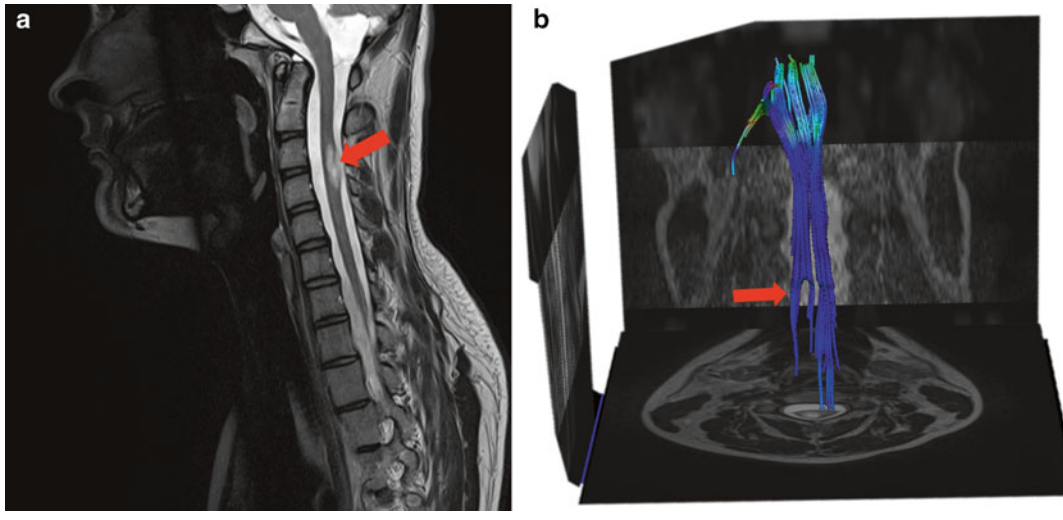

Fig. 4.13 (**a**) Spinal cord tumor (pilocytic astrocytoma) is demonstrated on a sagittal T2-weighted image (*red arrow*). (**b**) The same lesion is demonstrated causing disruption of tract direction by using a 3D tractography imaging reconstruction technique (*red arrow*)

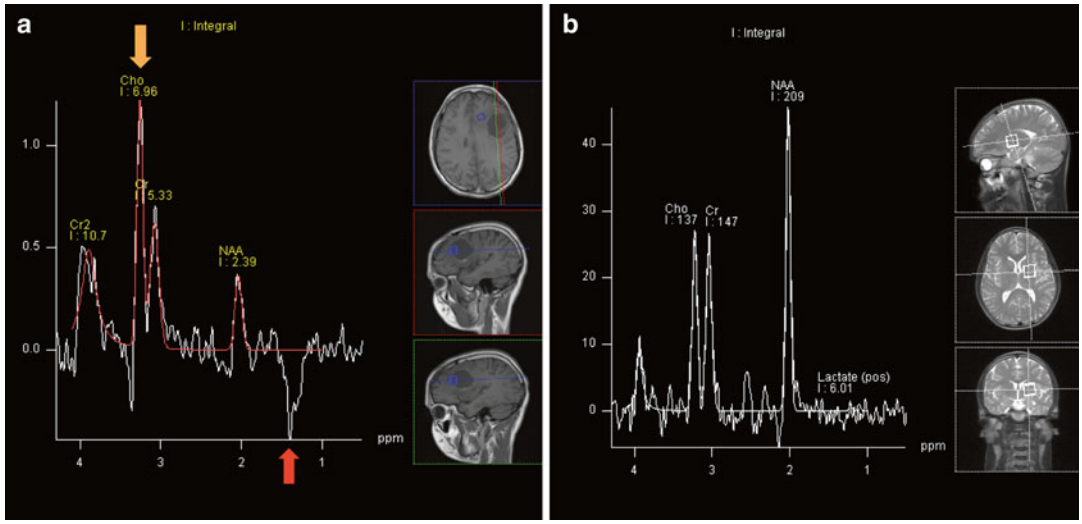

Fig. 4.14 (**a**) MRS study (PRESS technique—single voxel—TE 135 ms) showing a malignant signature with high choline (Cho) (*orange arrow*), low NAA peaks in relation to creatine (Cr), and the presence of a lactate peak (*red arrow*) in the surgical margin of a left frontal lobe lesion. (**b**) Normal MRS study acquired with the same technique for comparison in left basal ganglia

A promising application of DTI technique in neuro-oncology is the FA index measurement in high-grade gliomas. This measurement may help to detect infiltrative portions of the tumor and differentiate it from perilesional edema [22]. It also could potentially help to depict tumor recurrence. However, further research in this area is being performed to prove this use of DTI. Patients with medulloblastoma who have received radiation and present with decreased cognitive function have shown low FA index measurements in the brainstem, even though the overall imaging of the brainstem may be normal [23].

Unfortunately, FA index measurements and tractography studies are not carried out in the daily practice of most institutions since such techniques demand special software reconstructions that are not always available.

3D Imaging and Stereotaxy

3D imaging (or volumetric imaging) is extremely helpful for anatomical reconstructions. There are several different MRI sequences that can be acquired as volumetric images. Several different kinds of reconstructions also can be performed from it if adequate software is available.

In neuro-oncology, 3D imaging is especially used for stereotaxy. Stereotaxy is a technique that makes use of 3D imaging to create a coordinate system that will guide the localization of a lesion in a surgical procedure or radiotherapy treatment. Nowadays it is associated with other techniques, such as fMRI and direct cortical stimulation, to reduce morbidity in CNS tumor resection especially if the lesion is located in eloquent areas of the brain [24]. Association of 3D MRI imaging with other imaging modalities such as positron emission tomography (PET) scan is possible and it has been studied to improve surgical and radiotherapy planning.

Spectroscopy

MR spectroscopy (MRS) is a technique widely used in brain imaging. It is used to assess metabolites in the brain parenchyma and lesions. The results of an MRS acquisition are typically displayed in a graphic of metabolite peaks. Each metabolite has its own location in the MRS graphic and the height of the peak indicates its concentration in the parenchyma (Fig. 4.14). The most commonly assessed metabolites are choline, creatine, N-acetylaspartate (NAA), and lactate.

Choline is a substance related to the cell membrane and it is elevated therefore in situations in which there is increased cell density and high cellular turnover. Creatine is related to the cell's metabolic rate. NAA is a protein present in the cells, which reflects the neuronal density. The most common spectral signature of a brain tumor is increased choline and decreased NAA compared to creatine peaks. If present, lactate peak usually reflects areas of ischemia and necrosis within the tumor, suggesting a higher grade tumor. The lipids peak is related to cell proliferation. Therefore this peak is usually present in high-grade CNS tumors [13].

Attempts have been made in the use of MRS to determine the type and grading of CNS tumors. However, there is a significant overlap of metabolite peaks pattern that exists between low- and high-grade CNS tumors as well as between neoplastic and nonneoplastic lesions. For example, pilocytic astrocytoma and oligodendrogliomas are low-grade tumors that may have a similar MRS spectrum to that of a high-grade tumor [13].

In general, MRS does not add much information to the differential diagnosis of an initial investigation. Nevertheless, it has been shown to be useful in some atypical cases differentiating brain tumor from brain abscess. It can also potentially help to differentiate areas of radiation necrosis or postsurgical changes from recurrent or residual tumor. Ratios between choline peak and other peaks such as creatine and NAA peaks can also be helpful in assessing response of therapy.

Perfusion Techniques

Perfusion technique can be applied with both MRI and CT. However, CT perfusion is usually not performed in the pediatric population due to the risks involved in radiation exposure.

The standard perfusion technique uses intravenous contrast. Nevertheless, there is a new MRI sequence called arterial spin labeling (ASL) that can be used to study brain perfusion without the use of contrast media. This technique does not require IV access and avoids the off-label use of gadolinium contrast media in patients younger than 2 years [13].

The perfusion images are frequently interpreted in a color map. The red zones usually demonstrate increased perfusion and the blue zones decreased perfusion. More detailed analysis can also be made with numerical estimations of cerebral blood volume using post-processing techniques.

Research studies suggest that perfusion technique may help to differentiate between low- and high-grade tumors. It also has been described to help in the differentiation of radiation necrosis (decreased perfusion) from tumor recurrence (normal to elevated perfusion) (Fig. 4.15) [25]. Another application of this technique is to help in defining an ideal area for surgical biopsy, avoiding areas of necrosis. It can be used in association with MRS for this purpose. Future applications of this technique are related to evaluation of tumor angiogenesis and treatment response in patients using antiangiogenic drugs [13].

Unfortunately, MRI perfusion technique is not available in all institutions since it is not a standard MRI sequence.

PET Scan and Future Molecular Imaging

PET scan is considered to be a conventional molecular technique. Its principle is based on the injection of a radiopharmaceutical containing a positron-emitting radionuclide (tracer) into the body. This tracer emits two gamma rays in opposite directions to the imaging receptor located in the PET scanner forming the image. The highlighted areas in the images usually demonstrate higher concentration of the radiopharmaceutical in the tissues. The main difference between PET and single-photon emission computed tomography (SPECT) is that the gamma-emitting radionuclide used in SPECT produces a random emission of gamma rays, while in PET the emission of gamma rays is always in opposite directions (180°) giving better resolution. Use of a PET scan is often carried out together with low dose CT images or MRI to improve the anatomical

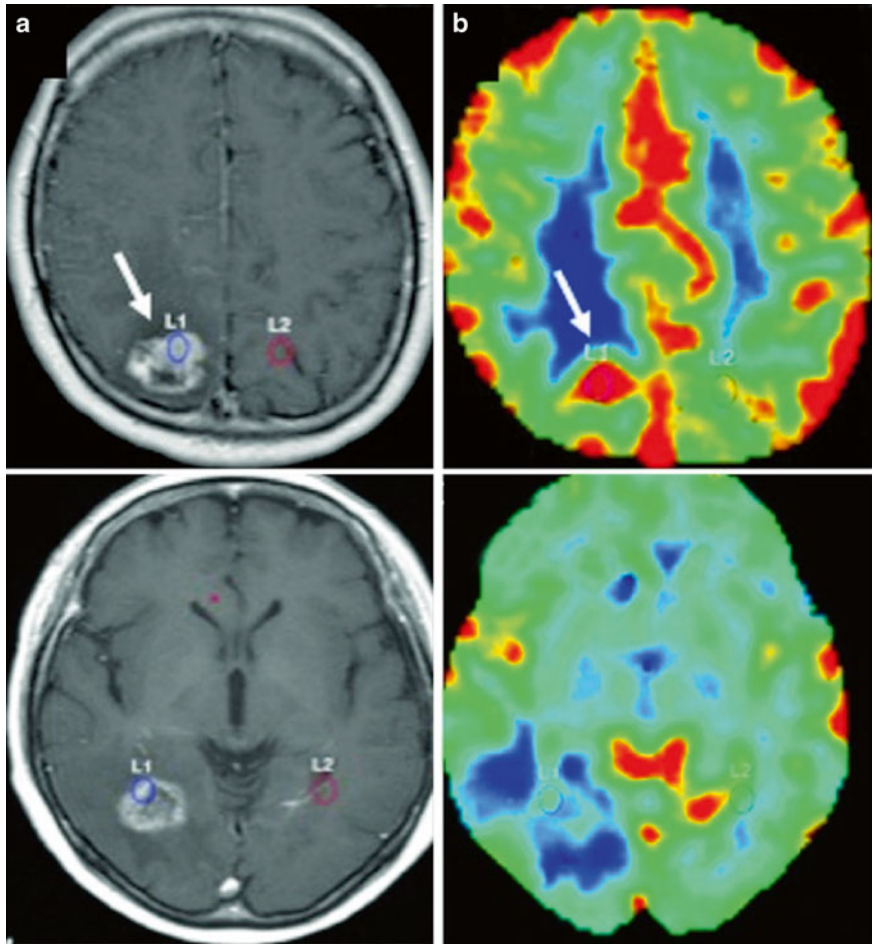

Fig. 4.15 Contrast-enhanced T1-weighted (**a**) and perfusion-weighted (**b**) MRI in cases of tumor recurrence (upper) and radiation-induced necrosis (lower) after radiosurgery of metastatic brain tumors. Note the clear difference in the cerebral blood volume of lesions. Reprinted from Mitsuya K, Nakasu Y, Horiguchi S, et al. Perfusion weighted magnetic resonance imaging to distinguish the recurrence of metastatic brain tumors from radiation necrosis after stereotactic radiosurgery. Journal of Neuro-Oncology 2010; 99(1): 81-88. With permission from Springer Science + Business Media

analysis. The difference between PET/SPECT scan from CT scan is that the radiation source is within the patient while in CT the source is external.

Radiopharmaceuticals are radionuclides bonded to specific biological markers. Numerous radiopharmaceuticals are available and each one has a special diagnostic or treatment target. Common radiopharmaceuticals applied in brain imaging are fludeoxyglucose (FDG), L-[methyl-^{11}C]methionine ([^{11}C]MET), and 3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT).

Neoplastic lesions demonstrate increase uptake of FDG in PET studies due to increased glucose metabolism (Fig. 4.16). Thus an FDG scan can be used in the evaluation of tumor grading, localization for biopsy, differentiation of radiation necrosis from tumor recurrence, therapeutic monitoring, and assessment for malignant transformation of what were originally low-grade gliomas [26]. However, its applicability in clinical practice is low because normal gray matter also demonstrates increased glucose metabolism, effacing lesions.

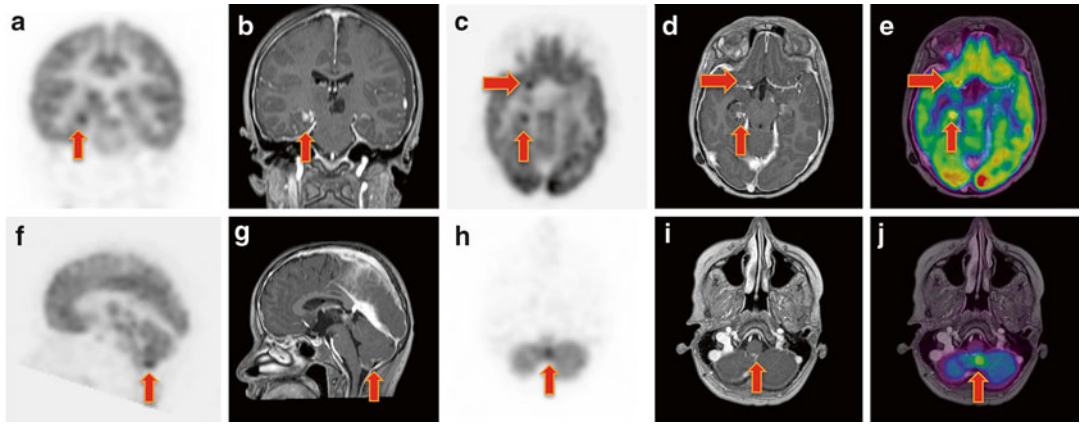

Fig. 4.16 An 11-year-old patient with metastatic pineoblastoma. 18F-FDG PET (**a**, **c**, **f**, **h**) brain images with correspondent MRI images (**b**, **d**, **g**, **i**) and PET-MRI fusion images (**e**, **j**). 18F-FDG PET study demonstrated lesions with focal increase in activity corresponding to abnormal leptomeningeal enhancement in the MRI images. Courtesy of Dr. Amer Shammas (Hospital for Sick Children—Toronto, Canada)

L-[methyl-^{11}C]methionine ([^{11}C]MET) is an amino acid-based agent. The advantage of this radiopharmaceutical over FDG is that it does not have a high uptake by the normal brain parenchyma. It has been used to differentiate neoplastic from nonneoplastic lesions and to differentiate recurrence from radionecrosis [26].

3′-deoxy-3′-[^{18}F]fluorothymidine ([^{18}F]FLT) is a marker for cell proliferation since it is trapped by thymidine kinase, an intracellular proliferation pathway enzyme. It is useful to differentiate recurrence from radionecrosis and in differentiation of low- and high-grade tumors [26].

MR-based molecular imaging is another example of molecular imaging technique. MR molecular imaging can be based on physical principles of imaging acquisition or on the use of special combinations of gadolinium with specific macromolecules or nanoparticles.

MRS is an example of MR-based molecular imaging since it demonstrates presence and quantities of different metabolites. Its applicability in neuro-oncology was described previously in this chapter. Nowadays, a significant amount of research has been carried out using a new MRI technique called chemical exchange saturation transfer (CEST) imaging. This technique is able to image specific molecules. Amide proton transfer (APT) imaging is a type of CEST imaging that has been used in studies of brain tumor. This technique is able to depict endogenous mobile proteins and peptides in the tissues. Potentially it may be able to assess tumor boundary and detect tumor recurrence [27].

A large number of special combinations of gadolinium and nanoparticles have been investigated in preclinical research projects. The hypothesis is to explore the possibility of this type of gadolinium contrast acting in a similar way as a radiopharmaceutical. This is another promising research field in MRI techniques, which could revolutionize brain tumor imaging in the near future.

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