IMAGING STRATEGY IN ACUTE ISCHEMIC STROKE: DIAGNOSTIC CHALLENGE

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Stroke is the third leading cause of death and the most common cause of permanent disability among the world population. Imaging plays a central role in assessing this pathology and various techniques can be used to examine brain and its vessels in acute stroke.

Angio- and perfusion computer tomography (CT) are widely used due to their high availability worldwide. However, MRI diffusion-weighted imaging (DWI) allows earlier and more accurate detection of ischemia. It is used in conjunction with other sequences, especially with susceptibility-weighted imaging (SWI), 3D-time-of-flight MR angiography (MRA), and contrast-enhanced MRA of supra-aortic arteries (CE-MRA), which allows diagnosing occluded arteries or hemorrhage and localizing thrombosis. By means of non-contrast arterial spin labeling (ASL) perfusion, which is of special interest, it is possible to diagnose ischemic penumbra and suggest prognosis in a noninvasive way.

MRI is the most accurate and the most reliable technique for diagnosing ischemic stroke and, in combination with the ASL sequence, for differentiating it from other diseases such as epilepsy and migraine aura. However, CT may be a valuable alternative in case MR is non-available or contraindicated.

Key words: acute ischemic stroke, magnetic resonance imaging, arterial spin labeling

Introduction

During the last ten years, the incidence of stroke in Europe has ranged from 95 to 290/100,000 per year, 80% of cases having the ischemic origin (1). Recently, the overall incidence of stroke has declined and the overall patient outcome improved (2). However, an increased stroke incidence has been observed in patients aged 30-65 years, mostly due to cardiovascular risk factors such as hypercholesterolemia, diabetes, smoking, and consuming alcohol (3). Moreover, the population aging leads to a progressive increase of the stroke rate. Consequently, stroke is among the most common causes of death, being in the 3rd place after heart diseases and cancer, and the most common cause of permanent disability in the world. Since the therapeutic window of opportunity in early stroke treatment is as narrow as the first six hours, it is necessary to develop strategies for early diagnosis, the crucial factor for successful treatment (1, 4-7).

Imaging is essential for the assessment of patients suspected of acute stroke, particularly before the initiation of therapy (8). First, it is necessary to distinguish between hemorrhagic and ischemic stroke, second, to locate the potential intravascular clot and assess its extent, and, lastly, to evaluate the extension of the ischemic core and the penumbra (7, 9).

Currently, non-contrast computer tomography (NCCT) remains the most widespread and low-cost imaging technique of those being widely available. It is highly sensitive to acute intracerebral hemorrhage (ICH), but is not sensitive to acute ischemia in the first hours of onset. CT angiography is combined with NCCT in order to detect arterial occlusion. However, MRI is increasingly used in acute stroke, improving the imaging diagnostic accuracy.

The conventional MRI sequences include diffusion-weighted imaging (DWI), fluid-attenuated inversion-recovery imaging (FLAIR), T2-weighted
(T2-w) gradient-echo imaging (GRE), or susceptibility-weighted imaging (SWI), as well as MR angiography (MRA) of the intracranial arteries using 3D time-of-flight (TOF) sequence. In some cases, TOF or gadolinium-enhanced neck-vessel MRA is performed, especially prior to thrombectomy. If dissection is suspected, the neck is examined using fat-suppressed T1- or T2-w sequences, the method being more sensitive 3-5 days after the event, when the intra-mural thrombus can be evidenced. Additionally, the advanced MRI techniques, such as post-contrast perfusion-weighted imaging (PWI) or contrast-free arterial spin labeling (ASL) perfusion, are helpful in assessing ischemic penumbra (i.e., the hypo-perfused territory that is not yet infarcted and may be preserved with early recanalization) and also in differential diagnosis.

Diverse imaging techniques, such as positron emission tomography (PET), single photon emission computed tomography (SPECT), xenon-enhanced computed tomography (XeCT), dynamic perfusion CT, MRI-based dynamic susceptibility contrast (DSC) perfusion, ASL, and Doppler ultrasound, can be applied to assess brain hemodynamics. Among the above-mentioned perfusion techniques, perfusion CT and DSC allow, after contrast material administration, evaluating cerebral blood flow (CBF), cerebral blood volume (CBV), and mean transit time (MTT) parameters. DSC perfusion CT makes it possible to reveal acute infarction, localize the infarct core and salvageable brain tissues and estimate the degree of collateral circulation. Early ischemia signs on NCCT have been described, which allows assessing the Alberta Stroke Program Early CT (ASPECT) score. Although the early signs of stroke may not be always observed, NCCT can exclude ICH, which is most important. This technique can also be helpful for detecting such lesions as tumors that may mimic an acute ischemic stroke. The diagnosis of acute posterior fossa and brainstem infarctions remains problematic due to beam-hardening artifacts.

**Computed tomography**

Among the advantages of CT are its fast performance, low cost, and wide availability. It can be safely used in patients in severe condition, agitated, being on support or with implanted monitoring devices, such as cardiac pacemakers, that make MRI contraindicate. Multimodal CT, in which NCCT, CT angiography (CTA), and perfusion CT are combined, is also commonly used. Performing NCCT and CTA takes less than 10 min, which is enough to rule out ICH and detect potential arterial occlusion. In addition, perfusion CT makes it possible to reveal acute infarction, localize the infarct core and salvageable brain tissues and estimate the degree of collateral circulation.

As for acute-stroke patients, there are numerous imaging techniques suitable for the evaluation of vascular lesions and brain tissue status. However, in order to provide the most appropriate emergent management to a stroke patient, physicians should be aware of and well familiar with advantages and challenges of each technique and have the most appropriate standard imaging protocol for stroke management in each center.

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which could lead to false negative results. This drawback has been greatly reduced by using the latest CT-scanners, which allow evaluating a much larger or the complete brain volume.

Perfusion CT acquisition enables the physician to distinguish between penumbra and infarcted tissue. Increased MTT with decreased CBF and normal or mildly increased CBV, resulting from autoregulatory mechanisms, suggest penumbra in the early stage of ischemia, whereas increased MTT with markedly decreased CBV and CBF suggest irreversibly infarcted tissue (18). The color-coded perfusion maps are helpful for visual assessment of perfusion CT (Figure 2 a-e).

![Figure 2. Axial brain CT tomogram (a) shows normal brain parenchyma at supratentorial levels (ASPECTS 10); PCT (b, c, d) show decreased CBF, normal CBV, and increased MTT, suggest early stage of ischemia; axial MRI 3D DWI image (e) confirms the diagnosis of acute ischemic stroke, showing a restricted diffusion (ASPECTS 9)](image)

However, during the first hours after the onset of symptoms, perfusion CT is of limited value because CBV either stays within normal limits or may increase due to vasodilatation in response to CBF decrease (19). Moreover, the perfusion coverage of posterior fossa remains limited. Finally, the detection of small lesions remains challenging and, in contrast to MRI, CT is an irradiating examination.

CTA allows to study cervical and intracranial arteries at the same time, thus assessing the arterial occlusion site, dissection, potential collateral arteries, and atherosclerotic disease. The evaluation of arterial status is highly important before interatrial treatment (17). A thrombus may be identified as a filling defect by CTA.

However, distal thromboses are often missed, especially in older patients with vascular encephalopathy when it is challenging to distinguish the newly created lesion from the old one. Furthermore, while the prognosis seems to be better for patients with rich collateral leptomeningeal arterial network, its evaluation is limited if only CT imaging is used (17).

Finally, on CT images, there may be a number of potential stroke mimics, which would give false positive results (20, 21).

**Magnetic resonance imaging**

When available, brain MRI is the examination modality of choice for acute stroke management. In emergency context, it is sufficient to acquire four sequences (DWI, FLAIR, 3D TOF MRA and T2-w GRE), which takes less than 10 min.

These sequences allow to confirm the ischemic stroke diagnosis, locate it precisely, approximately evaluate the stroke date, detect occluded arteries, locate the thrombus, and rule out hemorrhage or other lesions.

DWI is the most sensitive sequence for identifying acute ischemia shortly after the stroke onset (22). Ischemic lesions that appear in high DWI signal intensity, resulting from diffusion restriction with decreased apparent diffusion coefficient (ADC) are generally considered to be irreversible (23). However, the precise threshold of the ADC values for declaring a lesion as irreversible has not been established. Although there is no exact threshold of the DWI lesion volume for deciding on further treatment, still it is important to quantify DWI lesions either by visual determination of the DWI ASPECT score or by automatical software measurements, such as rapid processing of perfusion and diffusion (RAPID) or perfusion mismatch analyzer (PMA) software (24-27).

FLAIR sequence plays a significant role in the selection of patients for further treatment. It helps to approximately date the stroke event and determine whether or not the patient is within the therapeutic window for arterial recanalization by means of thrombolysis or thrombectomy. Indeed, the FLAIR hyper-intensity usually appears within 4-6 hours after the stroke onset (28).

A stroke in the early phase can be confirmed on the basis of FLAIR-diffusion mismatch, defined as a negative FLAIR signal in a zone of restricted diffusion (29). In addition, FLAIR sequence may reveal hemodynamic stenosis or an occluded artery by showing downstream hyper-intense arteries also known as slow flows. This hyperintense vessel sign is suggestive of brain tissue at risk of ischemia and has a prognosis value (Figure 3 a-c) (30).
Both MRI and CT may provide information about irreversible brain ischemia, but MRI provides more accurate data and is recommended as the exam of choice by the American Academy of Neurology (AAN). However, if the access to MRI is limited, it should be performed in the first place for those patients who are within twelve hours after the stroke onset (31).

DWI is more accurate and sensitive as compared to CT in detecting acute infarction. Using just NCCT, it is neither possible to rule out ischemic stroke nor to differentiate between and epilepsy or migraine. Moreover, there is strong correlation of the lesion volume on DWI acquired in the acute phase of stroke with the final infarct volume, which is not the case with CT (32). For posterior fossa stroke, NCCT is usually normal, while DWI allows making an early stroke diagnosis (19).

On the T2-w GRE sequence, early hemorrhage appears as a rim of hypo-intense signal surrounding the isointense core (33), the sensitivity of this technique and of CT being the same. More sensitive sequences, such as SWI, which have recently been developed, allow identifying an acute thrombus owing to its blooming effect, the sensitivity being higher than that of NCCT (34).

3D-TOF MRA, in contrast to CTA, is non-invasive since a contrast agent injection is not needed in the case of the former. This technique allows detecting occlusion or stenosis as well as its extension and localization. It is also helpful for evaluating collateral circulation, an important predictor of the outcome (35).

Extracranial vascular imaging plays an important role in the case of acute stroke and transient ischemic attack since it allows detecting atherosclerosis, which causes 40% of all ischemic strokes, but is most widely used in acute context for thrombectomy planning (36).

In view of the above, some medical centers have recently introduced contrast-enhanced MRA of supraaortic arteries (CE-MRA) as part of standard protocol in patients older than 70, with acute ischemia, in order to provide diagnostic information on steno-occlusive diseases within 2 min of acquisition (37). The signal-to-noise ratio of CE-MRA being higher than that of TOF MRA, the former technique is more advantageous than the latter, allowing better visualization of small intracranial vessels. Finally, CE-MRA can provide a morphological image of vessels by giving insight into plaque composition (38).

Adding CE-MRA to the imaging protocol has also some disadvantages, such as the need of using a larger coil, which can cause inconvenience for the acute patients, the more so that the need of perfusion and contrast injection extends the duration of the examination. Finally, CE-MRA alone does not provide dynamic information about the vascular supply of the infarcted territory. In order to overcome the above-mentioned shortcomings, a novel time-resolved broad-use linear acquisition speed-up (kt BLAST) CE MRA technique has been proposed. It allows using a non-dedicated body coil, has a shorter acquisition time and provides high-temporal-resolution dynamic data, which can help to differentiate occlusion from high-grade stenosis (39).

**DSC perfusion weighted imaging**

PWI provides information about brain hemodynamics and allows early detection of penumbra and infarcted areas. In contrast to perfusion CT, MR PWI gives the whole-brain coverage (40).

DSC-MRI, the most widely used perfusion technique in clinical practice, is based on measuring the T2* decrease during the first pass of an exogenous endovascular tracer through the capillary bed. The other perfusion method, dynamic contrast-enhanced (DCE) MRI T1-weighted (T1-w) sequence, is not commonly used in stroke examination, due to a lower signal-to-noise ratio (41, 42).

The mismatch between DWI and PWI is used to identify penumbra in acute stroke. The DWI abnormality represents the infarcted zone, whereas the PWI abnormalities, which are not yet seen at this stage on DWI, correspond mostly to penumbra (43).

Parametric DSC-PWI maps provide the time-to-peak (TTP), MTT, CBV, and CBF parameters. TTP is considered a PWI marker of the highest accuracy for detecting penumbra in hyper-acute stroke (44), whereas CBV and CBF values have the best correlation with the final infarct volume and core. Since the DSC PWI sequence is not fully quantitative, the CBF and CBV are relative values, calculated as the
ratio of the values in the region of interest (ROI) located in the pathological area and in the contralateral ROI, which is used as a normal reference.

This method is not always used in stroke protocols since it requires perfusion and contrast enhancement and is time-consuming. Moreover, the results may depend on the post-processing tools. Errors may also be introduced by the variability in the choice of arterial input function, partial volume averaging caused by mixing the tissue and vessel signal intensities, as well as by the orientation of the vessel with respect to the direction of the magnetic field. Another drawback is that, the parameter values being relative, it is not possible to determine the zone of benign oligemia, which does not represent a part of the tissues at risk of ischemia (44, 45). The relative perfusion values may also vary due to proximal carotid occlusion.

**Arterial spin labeling imaging**

ASL perfusion is a particularly interesting noninvasive, contrast-free perfusion method, which allows identifying cerebrovascular abnormalities and hypo-perfused regions. ASL is currently gaining an increasing interest in the management of cerebrovascular diseases and ischemic events.

In contrast to perfusion CT and DSC MRI perfusion, ASL is non-irradiating and allows the evaluation of the whole brain, without contrast injection required, which is particularly advantageous in pediatric population (46). Moreover, ASL allows the follow-up of the CBF changes within ischemic regions over time, while DSC PWI perfusion requires repeated contrast administration for that (47).

ASL can be performed using continuous ASL (CASL), pulsed ASL (PASL), or pseudo-continuous (pCASL) techniques, each of them being based on different excitation methods. When constant radio-frequency (RF) pulses under constant gradient are used, CASL tends to continuously invert the blood water spin as it passes a certain plane. In PASL, a single pulse is employed in order to determine the volume containing arterial blood for labeling. In PASL, unlike the case of CASL, there is an inversion of a large slab along the feeding arteries, occurring over the very brief labeling phase. While CASL, similar to PASL, produces a greater signal-to-noise ratio (SNR), the labeling efficiency is higher with PASL. In order to reduce the technical restrictions of CASL and PASL, a novel approach, called pCASL, has been introduced. It employs a discrete RF pulse train in conjunction with a synchronous gradient field, which results in both greater SNR and labeling efficiency. Thus pCASL is more advantageous than both CASL and PASL (48, 49).

In pCASL, the time required for the labeled protons to enter the area of interest (called post-labeling delay (PLD)) is an important parameter for achieving good acquisition. If PLD is too short, the signal may remain in the vessels, producing arterial transit artifacts, while excessive PLD length leads to the signal loss. Consequently, PLD should be adapted to the patient’s age since the circulation is faster in young as compared to elderly patients. The appearance of hypo-perfused regions may be actually connected with supra-aortic stenosis (48, 50). Finally, one should be aware that anatomical variations, such as fetal origin of cerebral posterior artery, may lead to perfusion map asymmetry (51). Obviously, all the above factors may lead to misdiagnosis.

Although the 3T scanner is recommended in clinical practice for increasing the SNR, ASL may also be performed on 1.5 T, providing images of satisfactory quality (48). The use of ASL in clinical practice is increasing, especially thanks to the availability of 3T MR scanners as well as to the development of improved pulse sequences and multichannel receiver array coils (50).

In the ASL, labelled blood water molecules are used as free diffusible tracers and their movement is followed from the arterial compartment to the tissue capillaries. Labelling is performed by applying radiofrequency waves in the neck area. The perfusion images are generated by subtracting control images from the labeled ones. By means of ASL, it is possible to measure absolute values of cerebral blood flow. ASL sequences are acquired by fast techniques, such as echo-planar, gradient- and spin-echo, or three-dimensional fast spin-echo imaging (50, 52). The turbo spin-echo 3D ASL acquisition is preferable to the echo-planar one since the former reduces artifacts.

The labeling plane must be located in the region where the relevant feeding arteries are perpendicular to the labeling plane and not at the level where dental artifacts may be produced. In order to appropriately position the labeling plane, a low-resolution MRA should be performed before ASL, so that tortuous artery segments that may cause protons deflection can be avoided (50).

Since acquiring an ASL sequence takes rather long time (around 4 min), it is difficult to obtain good-quality ASL images in highly agitated or confused patients. In order to decrease motion artifacts, background suppression should be used (50).

In the case of stroke related to brain hemodynamics disruption, ASL allows non-invasive contrast-free evaluation of brain damage and potential assessment of differential diagnoses (53). Using ASL, it is also possible to evaluate cerebral parenchymal perfusion by detecting both hypo- and hyper-perfused regions and delayed transit effects, which may predict clinical outcome in acute ischemic stroke (54, 55). Delayed transit effects are caused by the longer arterial transit time (the time it takes the labeled blood to reach the region of interest) in patients with cerebrovascular disease. The arterial transit time increases due to the decrease in perfusion pressure and the consequent development of collateral circulation. Spontaneous recanalization, therapeutic recanalization, and improved collateral flow without recanalization may be mistakenly interpreted as hyper-perfusion in the cases of acute ischemic stroke. Hyper-perfusion indicates greater proneness of the regions to hemorrhagic transformation (48, 54, 55).

Luxury perfusion refers to the CBF increase which occurs later on within the ischemic tissue and is considered to be a good prognostic factor, related
to the collateral flow, though with increased risk of bleeding (56).

An arterial bright signal (ABS) at the level of vascular occlusion in the ASL sequence can be helpful in identifying and locating a thrombus (Figure 4 a, b). The ABS corresponds to the labelled blood that is trapped in the vessel due to the vascular occlusion. In acute ischemic stroke, the thrombus and the vessel occlusion site can be detected as ABS localized proximal to the hypo-perfused area, related to the trapped labelled spins (57, 58). ABS may also appear due to a stagnant flow upstream from the stenosis since the bright intravascular signal may be attributed to slow flowing blood (59). If TOF and SWI are not conclusive, ABS may be helpful for the detection of vascular occlusion or narrow stenosis, especially in the small arteries (Figure 5 a-f) (59, 60).

In patients with acute ischemic stroke, due to delayed arterial transit time the late-arriving flow within or around the hypo-perfused territory is presented as a bright intravascular signal. This signal is usually referred to as arterial transit artifact (ATA). It can be an indication of stenosis or a stagnant flow, but also can represent the collateral flow. Thus ATA may signify both a better outcome after an acute stroke and the lack of its progression to infarct (Figure 6 a-d) (58).
Still another sign that may be seen on ASL images is the so-called border zone sign, presented as cortical areas of high signal intensity and resulting from ATA surrounding the normal low ASL signal in the watershed border zones. This signal is often found in elderly people with cardiovascular diseases and should not be confused with pathological hypoperfusion. Otherwise, the lesion may be overestimated when the hypoperfused area is adjacent to the border zone. Therefore, correlation with the contralateral hemisphere may help to avoid erroneous diagnosis (61).

To sum up, these artifacts are of significant interest in stroke patients. However, in cases requiring optimal CBF quantification, it is possible to avoid ATA by applying the vascular suppression method (62). Precise quantification of CBF can also be achieved by applying the multi-PLD method, which provides greater accuracy of CBF quantification as well as improved visualization of collateral flow through series of dynamic images. Moreover, multi-delay pCASL makes it possible to differentiate between temporal profiles of hyper-intensities on ASL images due to different conditions such as hyperemic responses or delayed transit effects (63).

ASL can be used to evaluate penumbra volume in acute stroke, which is observed as zones of hypoperfusion. In recent studies, positive correlation between DSC, PCT, and ASL hypoperfusion volumes was found (64). Moreover, it was shown that the ASL-CBF decrease of more than 40% had about the same diagnostic performance as DSC thresholds of PWI Tmax > 6 sec and CTP Tmax > 5.5 sec, which are considered to be reliable markers of penumbra (64).

ASL can also be helpful for eliminating other differential diagnoses such as epilepsy or migraine. During the ictal phases in epileptic patients, focal hypoperfusion in the epileptogenic grey matter zones, which is not systematized to a vascular territory, can be seen on ASL imaging, at the stage following the early post-ictal hyper-perfusion. Furthermore, in patients suspected of a recurrent stroke in the previous-infarction zone, ASL identifies epileptogenic foci in the ischemic scar tissue by showing high flow rate zones located on the borders of parenchymatous sequelae (48).

In addition, ASL makes it possible to detect decreased CBF areas with the brush sign in acute migraine aura, which follows the CBF increase during the headache phase, with no vascular systematization (in contrast to ischemia), and is predominantly observed in posterior regions (65).

**Conclusion**

There is a growing number of imaging techniques for assessing the parenchymal and vascular status in acute stroke. The chosen method should provide a fast and precise diagnosis, improve the outcome, and provide timely intravenous thrombolysis and/or mechanical thrombectomy. In different medical centers, the choice of a particular method may depend on several factors such as MRI availability, cost and local preferences. MRI is more accurate and more reliable than CT in diagnosing acute ischemic stroke. Advanced imagings, such as the ASL sequence, allow assessment of penumbra and differential diagnoses (e.g., epilepsy or migraine aura).
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Imaging strategy in acute ischemic stroke: diagnostic challenge

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Irradiation strategy in acute ischemic stroke: diagnostic challenge

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IMIDŽING STRATEGIJA U AKUTNOM ISHEMIJSKOM MOŽDANOM UDARU: DIJAGNOSTIČKI IZAZOV

Akutni ishemijski moždani udar je treći vodeći uzrok smrti i najčešći uzrok trajne invalidnosti u svetu. Različiti modaliteti imidžinga imaju važnu ulogu u evaluaciji parenhima mozga i intrakranijalnih krvnih sudova u akutnom ishemijskom moždanom udaru. Angiografija i perfuziona kompjuterska tomografija (CT) imaju široku primenu, zbog dostupnosti širom sveta. Međutim, MRI difuzioni imidžing (DWI) omogućava ranije i preciznije otkrivanje ishemije i koristi se zajedno sa drugim sekvencama protokola, kao što su imidžing susceptibilnosti (SWI), 3D MR angiografija 3D (MRA) i kontrastna MRA supraortalnih arterija (CE-MRA), što omogućava dijagnostikovanje okludiranih arterija ili otkrivanje hemorrhagije, kao i lokalizaciju tromboze. Pomoću nekontrastne perfuzije, sekvence arterijskog obeležavanja spinova (ASL), koja je od posebnog interesa, moguće je dijagnostikovati ishemijsku penumbriu i predvideti prognozu ishoda na neinvazivan način. MRI je najtačnija i najpouzdanija tehnika za dijagnostikovanje ishemijskog moždanog udara i u kombinaciji sa ASL sekvencom, značajna je za diferencijaciju ovog stanja od drugih bolesti, poput epilepsije i migrene. Međutim, CT može biti značajna alternativa u slučaju da MR nije dostupna ili je kontraindikovana.

Ključne reči: akutni ishemijski moždani udar, magnetno rezonantni imidžing, obeležavanje arterijskih spinova