Imaging of Acute Ischemic Stroke

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Abstract
Background: Over 80% of strokes result from ischemic damage to the brain due to an acute reduction in the blood supply. Around 25–35% of strokes present with large vessel occlusion, and the patients in this category often present with severe neurological deficits. Without early treatment, the prognosis is poor. Stroke imaging is critical for assessing the extent of tissue damage and for guiding treatment. Summary: This review focuses on the imaging techniques used in the diagnosis and treatment of acute ischemic stroke, with an emphasis on those involving the anterior circulation. Key Message: Effective and standardized imaging protocols are necessary for clinical decision making and for the proper design of prospective studies on acute stroke. Clinical Implications: Each minute without treatment spells the loss of an estimated 1.8 million neurons (‘time is brain’). Therefore, stroke imaging must be performed in a fast and efficient manner. First, intracranial hemorrhage and stroke mimics should be excluded by the use of computed tomography (CT) or magnetic resonance imaging (MRI). The next key step is to define the extent and location of the infarct core (values of >70 ml, >1/3 of the middle cerebral artery (MCA) territory or an ASPECTS score ≤7 indicate poor clinical outcome). Penumbral imaging is currently based on the mismatch concept. It should be noted that the penumbra is a dynamic zone and can be sustained in the presence of good collateral circulation. A thrombus length of >8 mm predicts poor recanalization after intravenous thrombolysis.

Introduction

Stroke is a major cause of mortality and long-term disability. More than 80% of strokes stem from ischemic damage to the brain due to the acute reduction of the blood supply. It was calculated that 1.8 million neurons are lost every minute that appropriate treatment is not given (‘time is brain’) [1]. For these reasons, ‘stroke imaging’ is crucial and has to be performed in a fast and efficient manner (fig. 1).

About 25–35% of strokes present with large vessel occlusion. Patients who fall within this category often present with severe neurological deficits and prognosis is often poor if early treatment is not possible. This group is thus the major target for endovascular interventions. Recent studies have postulated no significant differences between reperfusion strategies [2]. Appropriate patient se-
lection based on clinical findings and neuroimaging is crucial [3]. Effective and standardized imaging protocols are necessary for clinical decision making and for proper design of prospective studies on acute stroke. This review focuses on acute ischemic stroke involving the anterior circulation.

**Stroke Imaging**

Stroke imaging can be done using either computed tomography (CT) or magnetic resonance imaging (MRI). The choice is based mostly on the available infrastructure and staff, as well as the experience of the stroke team. CT is the imaging workhorse available in most hospitals on a round-the-clock basis. Use of CT imaging can readily exclude the presence of an acute cerebral hemorrhage. The recent technical advancements in CT and its speed confer additional advantages to this technique. Radiation exposure remains a relevant issue in stroke CT, especially if contrast-angiography and perfusion-CT datasets are acquired. Some institutions have MRI available at all times and prefer it over CT for many patients due to the additional information it provides (as described later).

Before scanning the (neuro-)radiologist needs to possess certain clinical information, that is, onset of the symptoms, the clinical findings including the NIHSS score and relevant patient history. The main goals of imaging are (1) to rule out intracranial hemorrhage, (2) to define the extent of the ischemic damage and to differentiate between the infarct core and the salvageable ischemic penumbra, and (3) to visualize the vessel status. We will describe the imaging steps based on the sequence of the images acquired on CT or MRI.

**The Role of Imaging in the Clinical Management of Acute Ischemic Stroke**

**Step 1: Rule Out Other Lesions**

Rule out intracranial hemorrhage (ICH) or other space-occupying mass lesions, for example, neoplasms. An acute ICH can be classically detected as a lesion with high CT density (60–90 HU) and with a high sensitivity. T2*-gradient-echo MRI sequences are extremely sensitive for detecting ICH [4].

**Step 2: Define the Infarct Core (IC)**

Defining the extent and location of the ischemic parenchyma irreversibly damaged by the significant hypoperfusion, the ‘infarct core’, is the primary step that guides further therapy. With ischemia (defined as cerebral blood flow [CBF] below 10–12 ml/100 g/min) [5, 6] and consequent energy failure, water molecules are trapped in the affected cells, a process called ‘compartmentalization’; this leads to the development of cytotoxic edema. The latter can be seen as a decrease in tissue density (hypodensity) on CT and is considered to be the marker of an IC (fig. 2a). For each 1% increase in tissue density...
water content, a decrease in tissue density of 2.6 Hounsfield Units is observed [7]. Early ischemic signs due to edema include blurring of the clarity of the internal capsule, loss of distinctness of the insular ribbon cortex and loss of cortico-medullary differentiation. The CT signs have a sensitivity of 40–60% within the first 3 h after symptom onset and have specificity, positive and negative predictive values of 85, 96 and 27%, respectively. The earliest time for detecting the hypodensity due to ischemia is about 45 min [8, 9]. With MRI, diffusion-weighted imaging (DWI) is the tool used to define IC. DWI detects cytotoxic edema due to the restricted motion of the water molecules trapped in the cell [10]. This restricted diffusion is seen as a bright signal on b1000 DWI images or as a low signal on the corresponding, automatically calculated apparent diffusion coefficient (ADC) maps (fig. 3a, b and h). An ADC ≤ 620 × 10⁻⁶ mm²/s was proposed as the threshold for identification of IC (with a sensitivity of 69% and a specificity of 78%) [11]. DWI can detect ischemia as early as 11 minutes after stroke onset [12], and is much more sensitive than CT for the identification of acute ischemia [13]. However, some areas with restricted diffusion may show reversal of these changes and thus are considered being part of the penumbra [14].

The extent of ischemic damage as detected on CT or MRI can be measured by eye-ball ing, semiquantitatively, that is, with the ASPECTS score [15], or with volumetry. For anterior circulation stroke, a large infarct affecting more than 1/3 of the territory of the middle cerebral artery, larger than 100 ml (or even 70 ml [16]) or declining to 7 points or less on the ASPECTS score is a predictor of poor clinical outcome and thus negatively affects the selection of patients for thrombolysis [9, 15, 17]. A similar concept can be applied to posterior circulation strokes. Thus, worse prognosis is observed for brainstem infarcts, especially for those affecting the pyramidal tract as well as large infarcts affecting more than 1/3 of the cerebellar hemispheres resulting in the compression of the fourth ventricle and hydrocephalus [18]. We are often faced with patients presenting with a wake-up stroke of unknown symptom onset. In such patients, a clearly hyperintense ischemia on T2-weighted and FLAIR MRI is considered a marker of IC (fig. 3c and i). In such cases, stroke experts are usually cautious to initiate a thrombolytic therapy [19].

Step 3: Penumbral Imaging

The ischemic penumbra [5], the ‘tissue-at-risk’ represents the critically hypoperfused (CBF 12–20 ml/100 g/min) parenchyma suffering neuronal silence and thus also causes neurological deficits. This functional damage can be reversed if timely reperfusion occurs. Otherwise, more and more of the penumbra will be recruited to the
IC. Thus, we need to think of penumbra as a dynamic region \[20\]. Discriminating the IC from the penumbra and from the surrounding benign oligemia (‘tissue-not-at-risk’; CBF >20 ml/100 g/min) requires the application of CT- or MR-perfusion imaging (CTP or PI respectively). Both techniques are dynamic imaging techniques necessitating the administration of intravenous contrast medium and yielding several parameter maps. The latter can be divided into (a) time maps, for example, time-to-maximum (Tmax), time-to-peak (TTP) and mean-transit-time (MTT), as well as the (b) cerebral blood flow (CBF) and (c) volume (CBV) maps. The reduced CBF in the penumbra triggers energy-dependent autoregulatory mechanisms to keep the CBV normal or even slightly elevated accompanied by elevated MTT and TTP. These compensatory mechanisms fail in the IC causing a CBV drop. Thus, CBV drop is a marker of infarction and correlates with the diffusion restriction only in hyperacute stroke \[21\] (fig. 2c–e and fig. 3d–f). The penumbra is traditionally defined on MRI as the area of DWI<PI mismatch. For PI, a Tmax with a delay of >6 s and >10 s has been used recently in large stroke trials, for instance, DEFUSE2, to define the thresholds for penumbra and IC, respectively \[22\]. TTP and MTT are also good alternatives to Tmax in determining the diffusion/perfusion mismatch. In CT, a mismatch between CBV (threshold at 2.0 ml/100 g for IC) and MTT (threshold at a relative MTT of 145% for the tissue at risk of infarction) defines the ischemic penumbra \[23\]. Almost all cases with an anterior circulation stroke show mismatch within the first 3 h. This declines to 75% within the first 6 h and to 50% 12–18 h after onset \[24\]. It has to be noted that the post-processing techniques used for the perfusion-CT and MRI analyses are not standardized, and can lead to variation in perfusion lesions of 50% or more \[25\]. In a recent study, academic programs outperformed commercial perfusion software \[26\]. The diffusion/perfusion mismatch concept is currently considered by several authors as inadequate for patient selection in ischemic stroke treatment trials \[27\]. Several experts suggest that the indication for endovascular intervention is set in case of severe neurological deficit, presence of a large vessel occlusion and a small (<70 ml) infarct core. Thus, the necessity of perfusion imaging for therapeutic decision making has to be proven \[28\]. Such issues are addressed by automated software solutions and consortia of stroke imaging specialists, for example, STIR \[29, 30\]. Several brain regions are known to have the highest ischemic vulnerability. These include the caudate body, putamen nucleus, and insular ribbon as well as selected areas of the frontal lobe including the middle frontal gyrus, precentral gyrus, paracentral lobule and the subcortical white matter \[31\].

**Step 4: Arterial Imaging**

4.1. **Arterial lumen** imaging is achieved by CT- or MR-angiography (fig. 2b). The scan has to cover the entire arterial tree from the aortic arch to the vertex \[32\]. MRI provides the advantage of noncontrast imaging of the intracranial arteries using the flow-sensitive time-of-flight (TOF) technique (fig. 3g). The combined assessment of the intracranial and extracranial cervical arteries provides a true ‘lumenography’ and requires automated...
injection of intravenous contrast medium using an injection pump. The fast scanning protocols are timed to optimize the acquisition in the arterial phase. The following points are important to comment upon: a) site of occlusion; this is of utmost importance since large vessel occlusions produce severe neurological symptoms and eventually result in poor outcomes. Mortality rates for distal ICA, proximal MCA and basilar artery occlusions are reported at 41.7–53% [33–35], 27–78% [36, 37] and 92% [38], respectively. b) Details of collateral circulation are of particular importance since the extent of collateralization is a predictor of final infarct volume and thus the clinical outcome [39]. It was shown that the rate of neuronal loss varies greatly depending on the state of the collaterals, which can maintain a stable penumbra for several hours after the onset of occlusion [40]. Several grading systems for the collateral circulation have been proposed [41]. Furthermore, c) tandem occlusions or stenosis and d) anatomical peculiarities that can handicap or modify the technique of the endovascular intervention, for example, arterial loops, angulated origin of the artery, can be documented.

4.2. Dissection: Fat-suppressed T1-weighted MRI images are the gold standard to visualize the mural hematoma in cases of arterial dissection [42] (fig. 4). In addition, contrast-enhanced CT- or MR-angiography may detect the dissection membrane. Enhancement of the arterial wall distal to the arterial occlusion, the so-called ‘carotid ring sign’ can indicate a recent (<1 week) arterial occlusion [43].

4.3. The acute thrombus can be seen on noncontrast CT as a (hyper)dense artery sign [44–46] or on T2*-gradient-echo MR imaging, including the more sensitive susceptibility-weighted imaging (SWI) as an MRI signal drop, the so-called ‘artery susceptibility sign’ [47] (fig. 5b). A recent study has shown that a dense middle cerebral artery longer than 8 mm predicts poor recanalization after intravenous thrombolysis [48]. The quantification of the extent of the intracranial thrombus using the clot burden score predicts final infarct size and functional outcome [49].

4.4. Other ‘vessel signs’: SWI not only depicts the thrombus, but it demonstrates additional vessel ‘signs’. The increased oxygen extraction in the ischemic tissue leads to a local increase in deoxy-hemoglobin, which in turn causes the so-called BOLD (blood oxygen level dependent) effect, which is a commonly used functional MRI technique. In acute major vessel occlusion SWI, formerly called ‘venous BOLD’ imaging, prominent, low-signal vessels are visible in the hypoperfused area. These are seen peripherally (‘cortical vessel sign’ or ‘abnormal visualization of leptomeningeal vessels’) in the deep white matter (‘brush sign’) (fig. 5c). Collectively both were termed the ‘region of multiple hypointense vessels (RMHV).’ Before SWI was widely used in the clinical stroke MRI routine, the same findings were described with the T2* gradient-echo imaging [50, 51]. The reversal of the cortical vessel sign has been observed after full recanalization and is associated with a favorable outcome [52].

Step 5: Miscellaneous

5.1. Prediction of hemorrhagic transformation in an infarction can be achieved by observing the hyperintensity of the CSF space on FLAIR-MRI or parenchymal enhancement after intravenous administration of gadolinium [53, 54].

Fig. 4. Carotid dissection on the left side seen on the first-pass contrast-enhanced MR-Angiography (a) as vessel irregularities (black arrows) of the proximal cervical segment. Pre-contrast fat-suppressed, T1-weighted coronal (b) image shows the mural hematoma as a bright signal (white arrows). The corresponding axial image (c) demonstrates the classical appearance of a spindle-shaped bright mural hematoma (asterisk).
5.2. Presence of cerebral microbleeds does not seem to lead to a relevant increase in symptomatic ICH and thus appears to be a contraindication for thrombolytic therapy [55].

5.3. Future trends in imaging include the arterial spin labeling (ASL) perfusion MRI, a technique that provides quantifiable CBF maps without the need to administer intravenous contrast medium. Recent publications have demonstrated the feasibility and usefulness of this method if combined with the other stroke MR sequences [56]. A special ASL method, the so-called ‘territorial arterial spin labeling’ can provide insight on collateral circulation in patients who may not otherwise be candidates for digital subtraction angiography [57].

Conclusion

The recent advances in stroke imaging allow almost real-time information on many aspects of stroke pathophysiology. The main role of imaging is to exclude an intracranial hemorrhage, define the ischemic region, to distinguish between infarct core and penumbra and to depict the vessel status. CT and MRI are modalities that can be used with confidence, both having their strengths and weaknesses. CT is more widely available but MRI can provide additional information and is more sensitive to small infarctions. The choice of modality depends on the infrastructure, the logistics, the expertise as well as the scientific interest of the stroke team.

References

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