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INVITED REVIEW

Computed tomography in acute ischemic stroke

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Abstract Stroke remains the third most important cause of mortality in industrialized countries; this has prompted research for improvements in both diagnostic and therapeutic strategies for patients with signs of acute cerebral ischemia. Over the last decade, there has been a parallel in progress in techniques in both diagnostic and therapeutic options. While previously only used for excluding hemorrhage, imaging now has the possibility to detect ischemia, vascular occlusion, as well as detect tissue at risk in one setting. It should also allow to monitor treatment and predict/exclude therapeutic complications. Parallel to advances in magnetic resonance imaging of stroke, computed tomography has improved immensely over the last decade due to the development of CT scanners that are faster and that allow to acquire studies such as CT perfusion or CT angiography in a reliable way. CT can detect many signs that might help us detect impending signs of massive infarction, but we still lack the experience to use these alone to prevent a patient from benefitting from possible therapy.

Keywords Stroke · Computed tomography · Perfusion imaging · Thrombolysis

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Introduction

Acute stroke is an important cause of morbidity and mortality in all industrialized nations. For a long time, it was considered a hopeless situation with at best the prospect of lengthy rehabilitation periods for the affected patients. However, due to an impressive investment in energy during the decade of the brain in the 1990s, this purely attentive attitude has now been overcome, and over the last decade, thrombolysis has become an established standard of care [1–6]. This has been due to the simultaneous development of both new diagnostic and therapeutic strategies that have changed completely our vision of the disease.

According to the AHA guidelines, the first aim of global assessment of a patient with suspected stroke is to exclude another possible cause of symptoms (such as hemorrhage) [7, 8] (Fig. 1).

Indeed, signs of acute neurological dysfunction referable to stroke can be caused by a number of conditions. These so-called stroke mimics can be caused by a number of conditions such as epilepsy, brain tumors, or event infections/inflammatory diseases of the central nervous system. The aims of neuroimaging are manifold [9]: (1) rule out hemorrhage (and also demonstrate its cause, hence CT angiography, see below); (2) demonstrate the presence of ischemia since the non-absence of hemorrhage is not enough to make a diagnosis of stroke; (3) show the presence of hemodynamically compromised tissue (tissue at risk or penumbra); (4) demonstrate the underlying cause (vascular occlusion or embolus, carotid stenosis, or even cardiac source); in addition to this imaging must allow to monitor treatment (demonstrate success by showing reperfusion or demonstrating failure and or complications such as emboli or bleeding); and, finally, (6) to allow follow-up

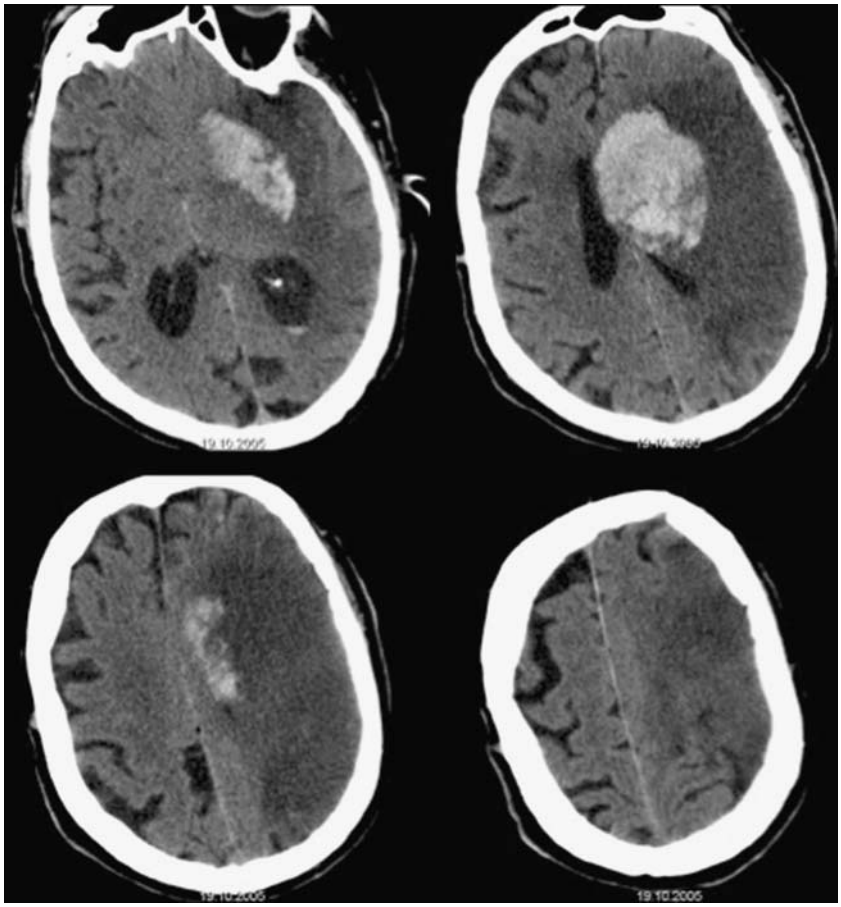

Fig. 1 Patient with hemorrhagic stroke; there is a visible hematoma in the basal ganglia with edema. This is a left MCA stroke with hemorrhagic transformation

imaging that correlates well with clinical status. Where one must be careful in the interpretation of these findings, be it with CT or MRI, is that the concept of the ischemic penumbra has evolved a lot since its original description and has moved from one of thresholds in intracellular energies to one of demonstrations of areas of relative hypoperfusion: While both these concepts are intimately and ultimately related, they do not represent the same concept, and it had been shown that vessel recanalization by any means even if effective does not always represent revascularization and a potential positive effect on brain tissue.

The accepted time window for intravenous therapy has now increased to 4.5 h. While in the acute setting nuclear medicine techniques have moved to the background on the stage of neuroimaging for the moment, we momentarily rely on techniques such as magnetic resonance imaging and computed tomography to image the brain for ischemia. Imaging must of course not interfere with treatment options. Depending on local availabilities, both modalities may be equally used, but often, CT has remained the workhorse of acute stroke imaging. Magnetic resonance allows acquiring images of diffusion and perfusion that have been proven useful in acute stroke [10–13]. While MR is considered equivalent for the detection of hemorrhage

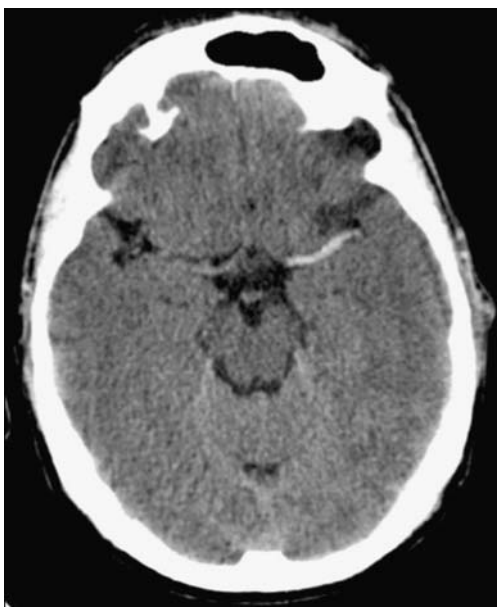

Fig. 2 Left-sided dense middle cerebral artery sign

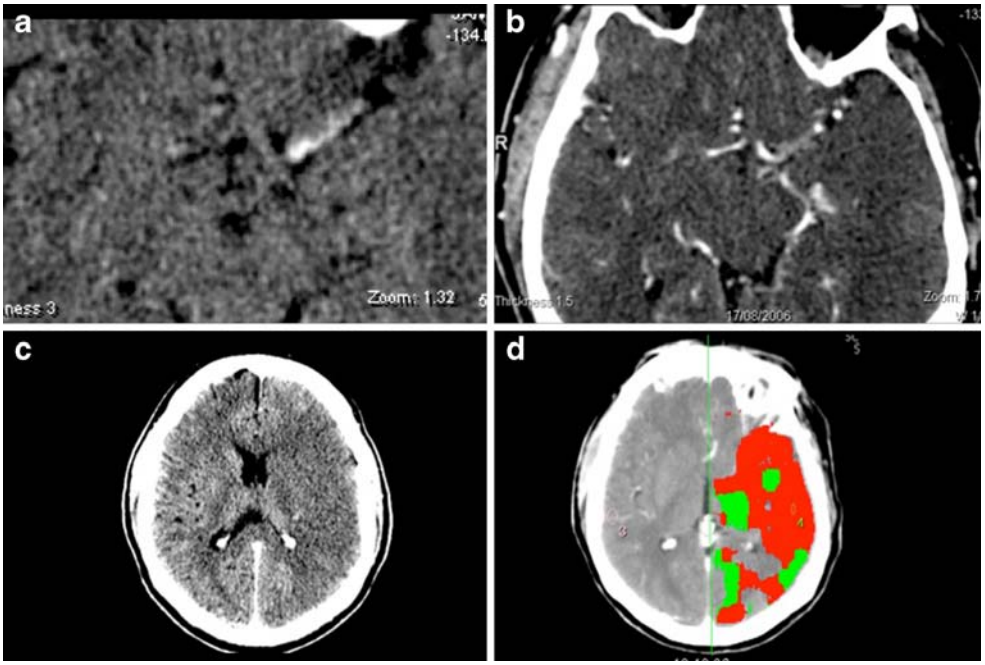

Fig. 3 Left-sided dense MCA sign (**a**). CT angiography shows occlusion of the left M1 segment of the MCA (**b**), while there is beginning left MCA hypodensity (**c**) and severe hypoperfusion (**d**)

[14] and superior for ischemia [15], CT still remains at the forefront. MRI will be clearly superior for the detection of small cortical infarcts and for small lacunar lesions located deep in the brain. However, for purposes of detecting large lesions, CT still has a power of detection that is almost equivalent in trained eyes.

Early signs The typical early signs that are looked for are the dense artery sign at the level of any cerebral artery, loss of gray/white matter differentiation, beginning hypodensity, sulcal effacement, and mass effect that are all due to the presence of beginning edema. These early CT signs have been found alone or in combination to be present in up to 92% of cases [16]. Von Kummer et al. [17] also found that early changes were often associated with poor outcome especially if swelling was present. There has been found a good inter-observer agreement for these signs [18].

The dense artery sign This represents visualization of the thrombus on unenhanced CT in the affected vessel (Figs. 2,

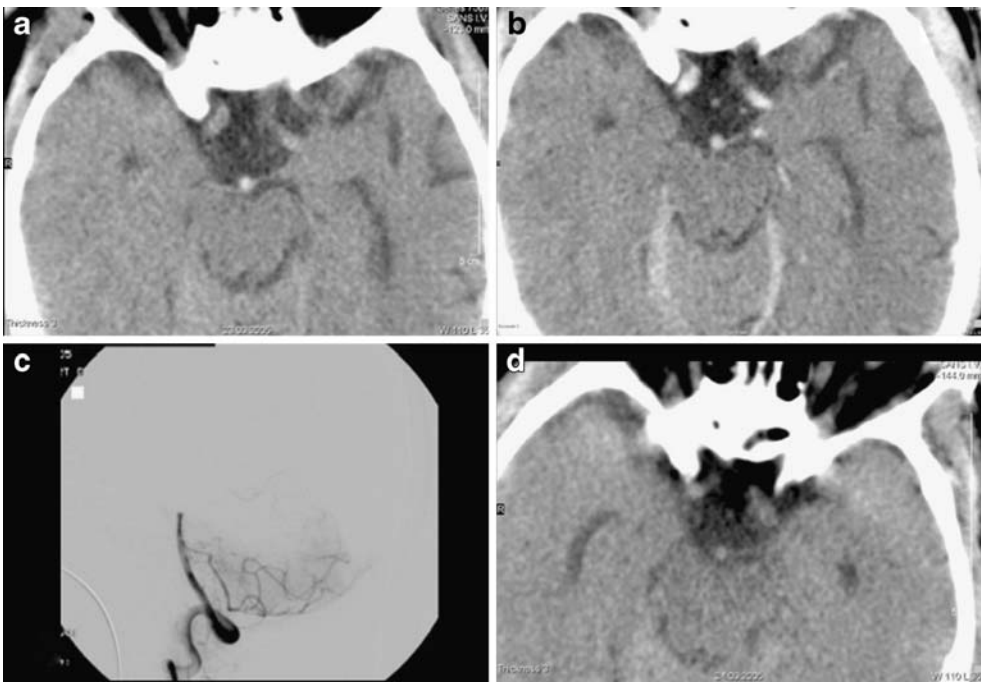

Fig. 4 Hyperdense basilar artery sign in a patient with signs of brain stem dysfunction. The unenhanced CT (**a**) shows hyperdensity of the vessel with no enhancement after contrast administration (**b**). There is a stop of the contrast column on vertebral angiography (**c**) and the posterior cerebral arteries are not visible. After thrombolysis, the vessel is no longer hyperdense (**d**)

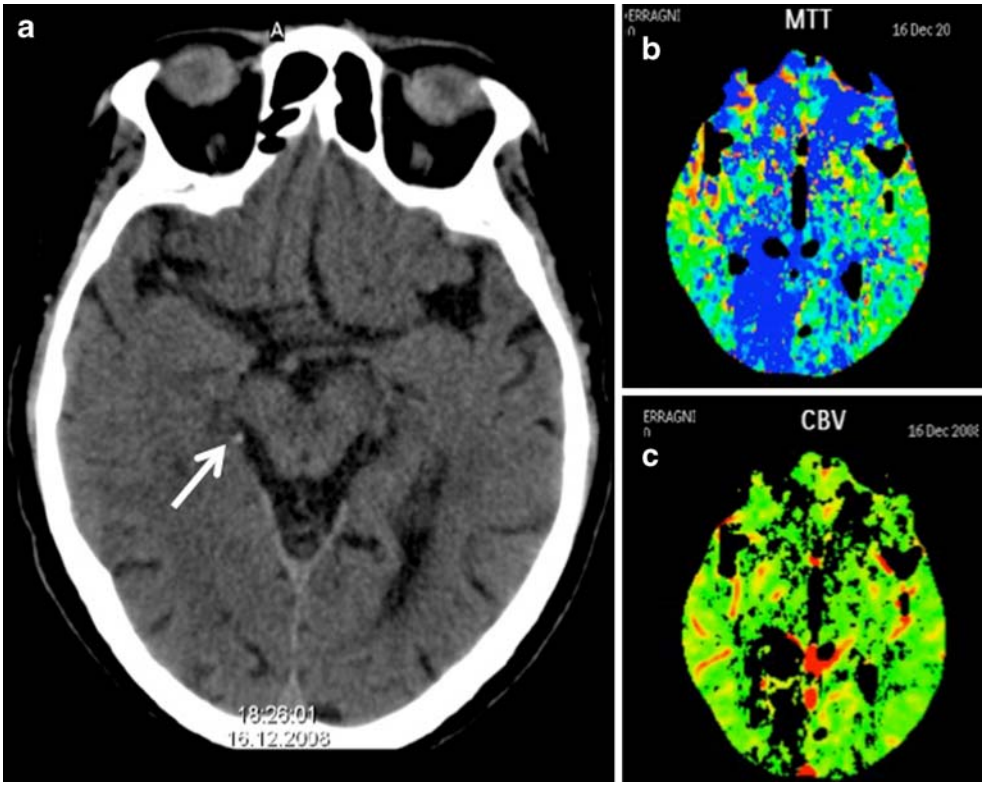

Fig. 5 Hyperdense right posterior cerebral artery (*a*, *arrow*). There is severe hypoperfusion in the right PCA territory

3, 4, 5, and 6). It is present in 35% to 67% [19] and is known to disappear after recanalization. The dense artery sign has been associated with a poorer outcome in most studies [20–23]. When such an occlusion is seen in a small middle cerebral artery (MCA) branch, it is referred to as the dot sign [24, 25]. False positives are known to occur in cases with vascular calcification, patients with a high hematocrit. This sign can be visible in any affected cerebral artery. Von Kummer et al. [17] found it to have a 32% positive predictive value (PPV) for fatal clinical outcome.

Brain swelling with sulcal effacement This is one of the earlier signs that may appear and is due to the mass effect caused by beginning water accumulation (Figs. 7 and 8). It was found to be present in 38% of cases and to have a 70% PPV for fatal outcome [17]. In a study of only 14 patients where it was found to be isolated, it was, however, not found to represent severe ischemic damage [26].

Hypodensity Brain density, or rather the presence of hypoensity in the affected vascular territory, has been widely used as a negative selection criterion for thrombolysis. Computed tomography shows differences in tissue composition due to the absorption of X-rays by the tissue. This is directly influenced by water content. In acute stroke, there is the early development of cytotoxic edema which, after a time, leads to infarction. CT is able to differentiate gray from white matter due to the slight differences in water content. The water

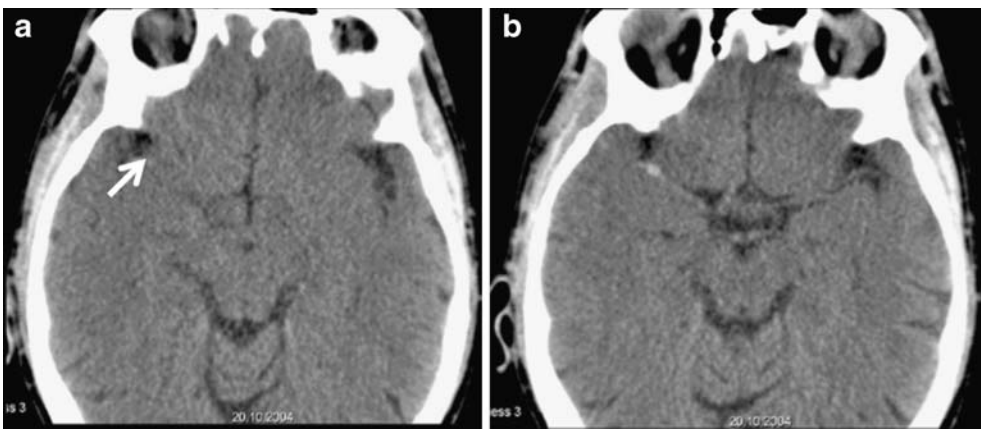

Fig. 6 Dot sign in the right sylvian fissure (*arrow*)

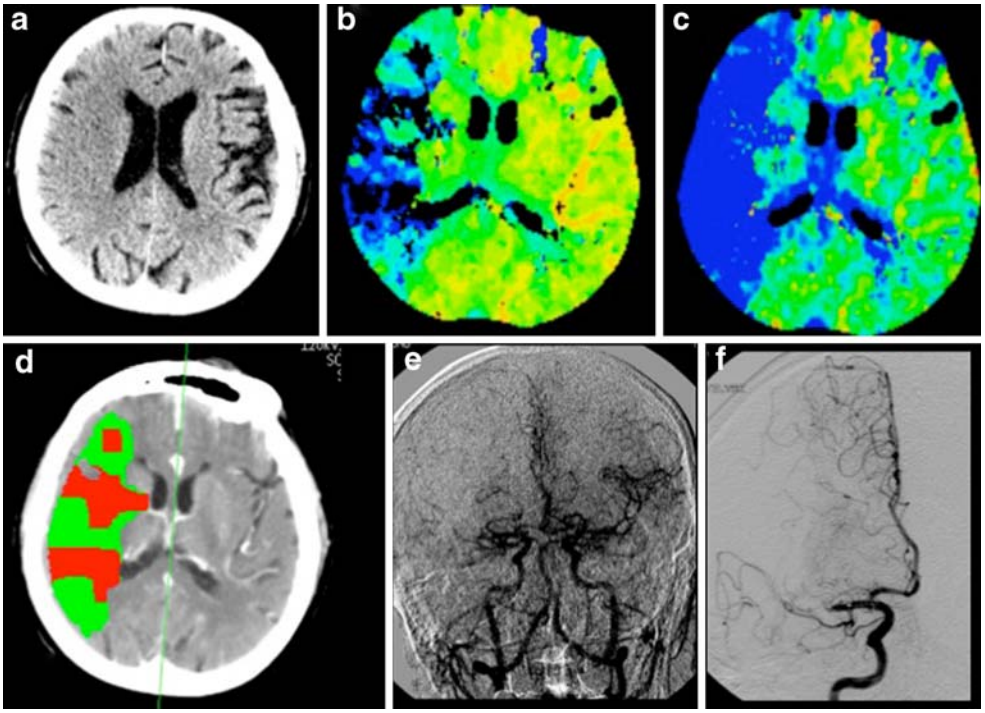

Fig. 7 Sulcal effacement: On the unenhanced CT, there is sulcal effacement in the right hemisphere (**a**); this is associated with severe hypoperfusion as seen on the MTT maps (**b**, **c**). The penumbra map shows inhomogenous perfusion (**d**); the angiogram shows occlusion with hypovascularization (**e**) on the parenchymography overview due to M1 occlusion (**f**)

concentration in gray matter is normally of 85% and 75% in the white matter. In acute stroke, as water accumulates, this leads to a decrease in Hounsfield units [27] with visual homogenization of brain tissue at first: This leads to the loss of gray/white differentiation that leads to the disappearance of the basal ganglia (Fig. 9), the cortical, and insular ribbons as well.

The method used is the one of the third of the affected MCA territory: When a hypodensity is visible that affects one third or more of the territory, this patient will show no benefit of thrombolysis but an increase of having lethal hemorrhage according to the European Cooperative Acute Stroke Study (ECASS) criteria [28]. Prior, Von Kummer et al. [17] had found that a hypodensity covering more than 50% of the middle cerebral artery territory had an 85% PPV for fatal outcome. Lev et al. [29] found that using variable window settings could improve the detection of hypoattenuation.

CT perfusion imaging Perfusion imaging allows investigating the presence or absence of alterations in cerebral perfusion in patients with suspected stroke [30–35] (Figs. 10 and 11). One drawback at the moment is that most scanners still only offer coverage over a few slices corresponding to a few centimeters instead of the whole brain; this does not always allow evaluating exact perfusion deficit volumes if they exceed the volume studied and also does not allow investigating areas outside the area chosen. Brain perfusion with MR has evolved into a whole brain method that allows full coverage of the neurocranium; this is now possible with a few select scanners either with extensive row numbers or with special techniques. After having found that penumbral thresholds could be determined by CT perfusion [36], Schaefer et al. [37] found a high correlation between CT and MR perfusion for the determination of the penumbra. There is,

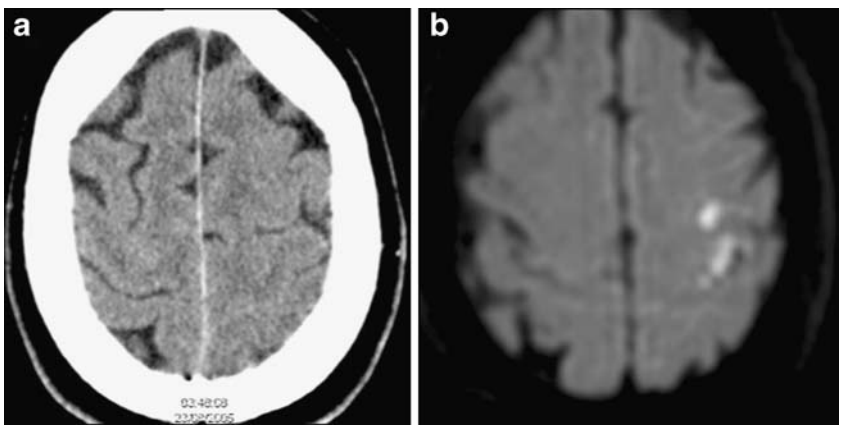

Fig. 8 Patient with a right-sided hand paresis: On CT, there is slight sulcal effacement in the left motor cortex (**a**); on diffusion-weighted MRI, the small cortical lesion lights up (**b**)

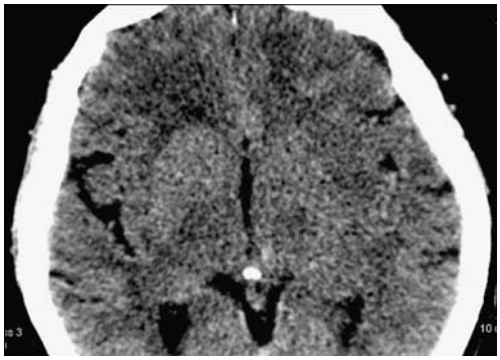

Fig. 9 Patient with left hemispheric stroke: The striatum on the left is no longer clearly visible as on the right

however, the trend for the development of CT perfusion strategies covering more and more of the volume of the brain, with scanners even achieving 320 slices, but these are at the moment more prototypes. Also, the development of CT perfusion techniques based on flat panel CT should allow combining all axial imaging modalities (CT, CT angiography (CTA), CT perfusion) with the interventional techniques in order to facilitate and combine diagnostic and interventional procedures in order to gain time.

Many CT manufacturers now provide automated or semi-automated calculations of perfusion and penumbral maps. While the perfusion maps are of use in the management of therapeutic measures, the use of penumbra maps has not been fully validated until now. We have found that an easy way of estimating penumbra is the simple subtraction of time to peak (TTP) area from mean transit time (MTT) area of hypoperfusion; while this may not be standard and may not be hemodynamically accurate, it does function as a simple model to assess perfusion differences [38]. While Wintermark et al. found that decision making could be done as well with CT as with MRI in all cases but one, this was not entirely supported by the findings of the DIAS-2 Study where a difference in the decisions was found based on CT perfusion or MR perfusion regarding the delineation of the penumbra; this may, however, been due also to technical and patient selection differences [39].

CT angiography Due to the development of faster multi-array scanner, CTA can now cover a larger and larger area going from the aortic arch or even the heart into the Circle of Willis (Figs. 12 and 13). This allows for the complete all-in-one approach that leads to a combined neuro-cardio-radiological

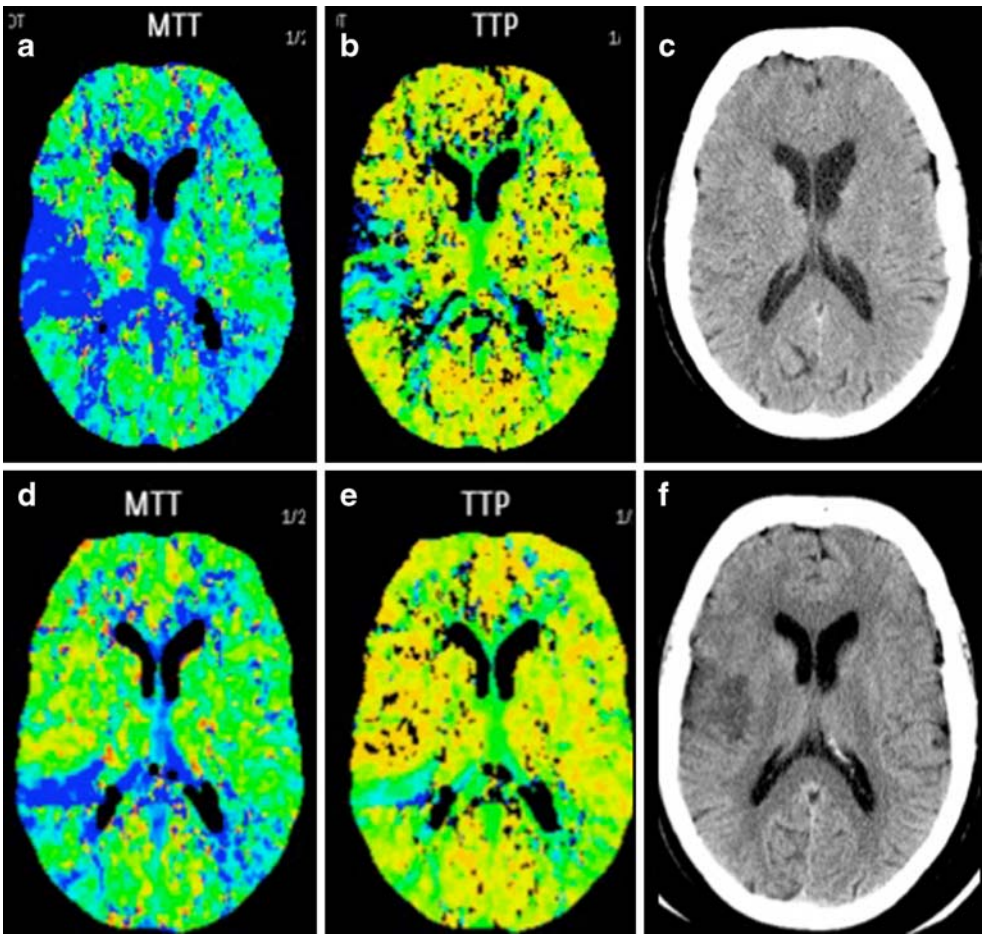

Fig. 10 Patient with signs of right hemispheric ischemia. There is hypoperfusion with a MTT-TTP "mismatch" (**a**, **b**); on the unenhanced CT, there is a small hypodensity (**c**). After thrombolysis, we see almost complete reperfusion (**d**, **e**) and a small cortical lesion on the CT (**f**)

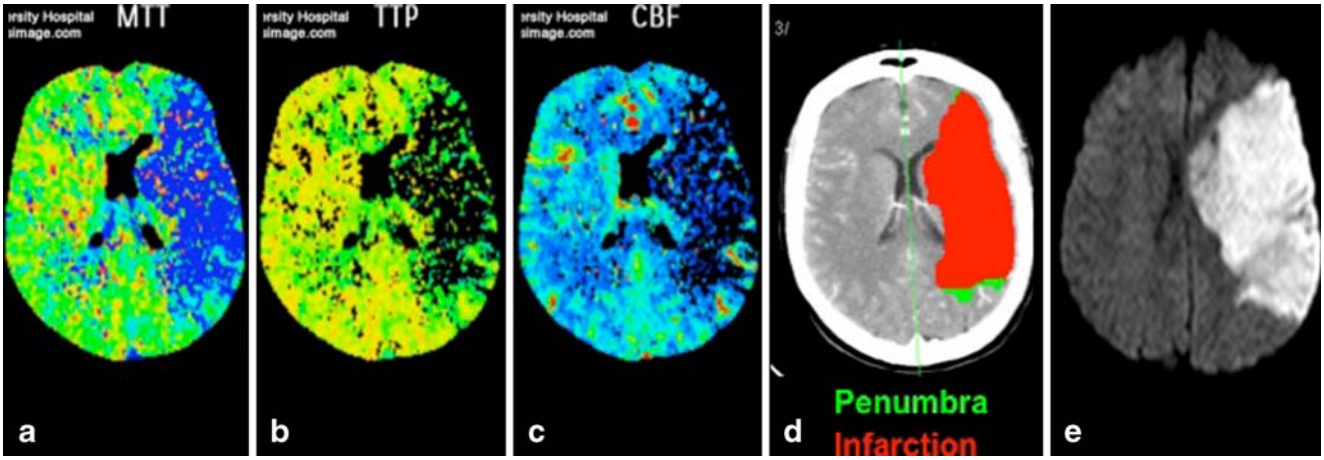

Fig. 11 Patient with massive left hemispheric stroke but no penumbra: There is a match between MTT TTP and CBF maps; the penumbra map shows almost no tissue at risk and only infarction. On the follow-up DWI, this large MCA infarction is confirmed

workup. The presence of more distal occlusions was associated with better outcome [40].

Source images Some authors have advocated using the source images of CTA acquisitions in the assessment of infarction (Figs. 14, 15, and 16). While this gives an improved visualization of the affected area, there is a perfusion effect, and it should not be confused with acute hypodensity. This was shown by both Schaefer and Rosenthal [41, 42]: In vertebrobasilar occlusion, this hypoattenuation was found to be the best predicted by Schaefer et al. [41] and for MCA infarction by Rosenthal et al. [42]. Camargo et al. [43] found them to be more sensitive than non-enhanced images: 70% vs 48% sensitivity for detection. When applied to the Alberta Stroke Program Early CT score, there is also an improvement of determination of outcome when com-

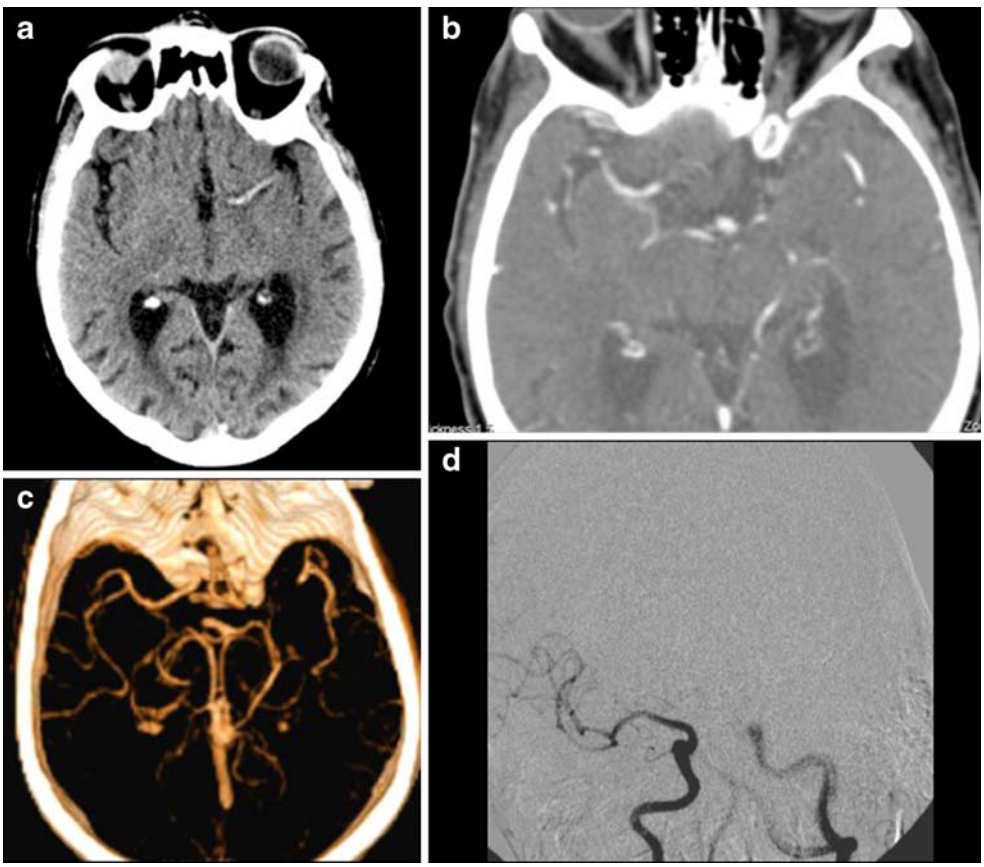

Fig. 12 Patient with left MCA stroke: Unenhanced CT shows left hyperdense MCA sign; on angio-CT, there is non-opacification of the same vessel segment, seen better on the 3D reconstructions and confirmed by DSA

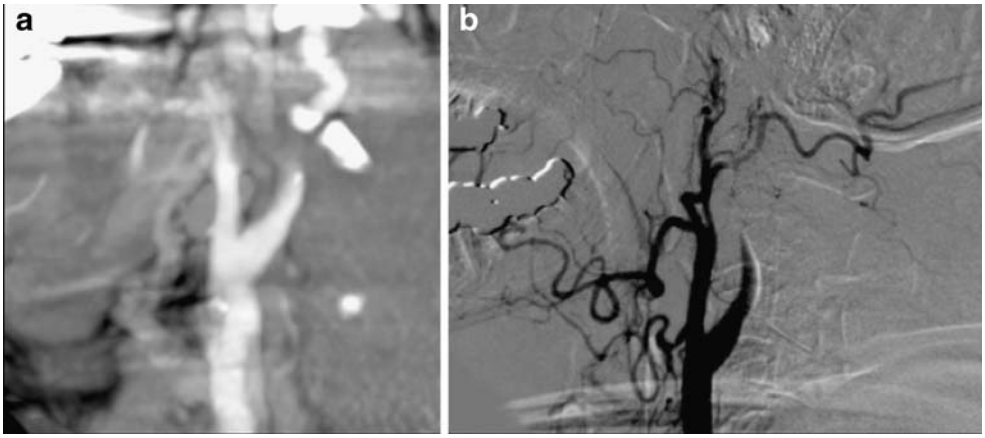

Fig. 13 Patient with carotid artery dissection: Reconstruction of the CTA shows a flame signs, confirmed by DSA

pared to unenhanced images [44, 45]. Schwamm et al. [46] also found that the hypoattenuation on CTA images could improve prediction of post-therapeutic hemorrhage.

Prognostic signs on imaging Overall, the presence of hypodensity of more than one third alone is considered a negative prognostic sign. The remaining early signs are also considered to some degree to be of unfavorable prognostic value [16].

Time window Once there has been a decrease in blood flow due to embolus or occlusion, the timeframe available to

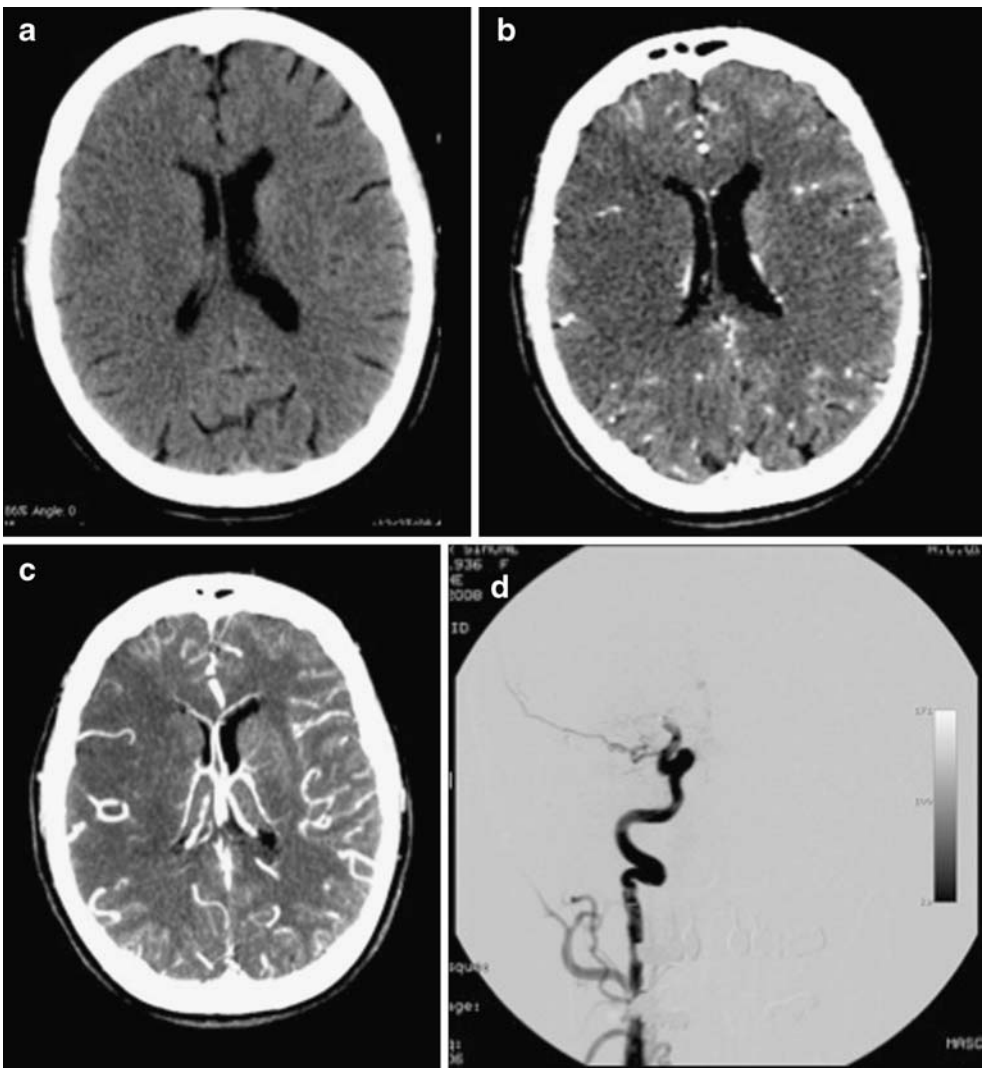

Fig. 14 Seventy-two-year-old female patient with right hemispheric stroke. On the unenhanced CT, there is slight sulcal effacement and ventricular asymmetry (**a**). This is more apparent on the angio-CT source images (**b**), even more on the angio-CT reconstructions (**c**). On DSA, there was a corresponding occlusion

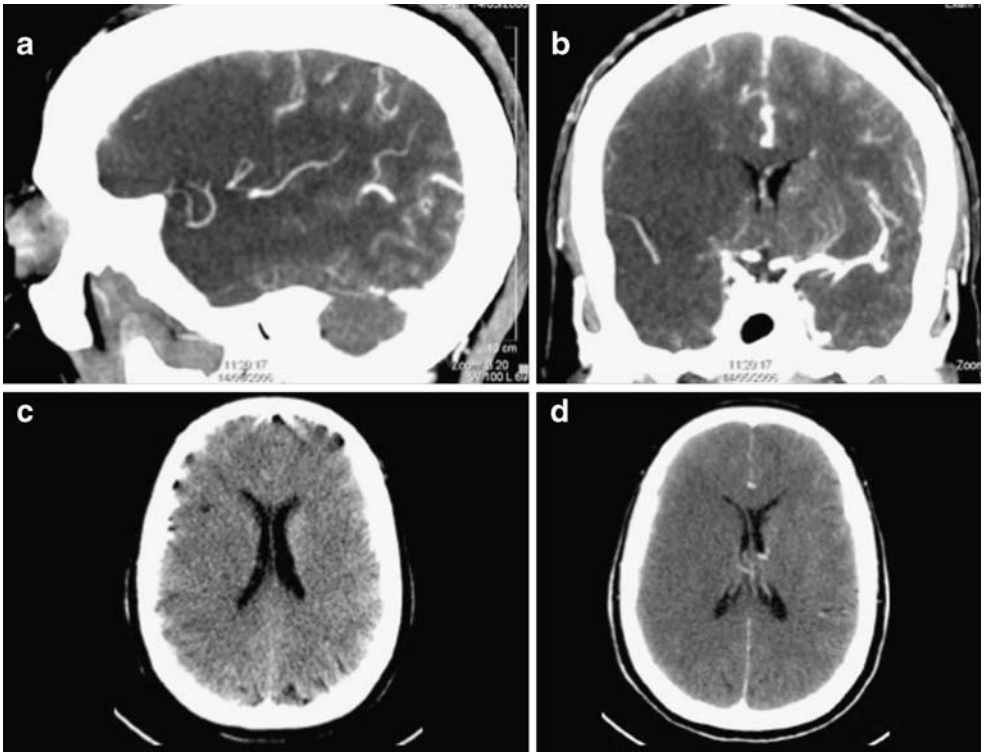

Fig. 15 Patient with signs of right hemispheric stroke. The thick reconstructions of the CTA show the compromised better visualized (**a**, **b**) than the axial unenhanced slices (**c**, **d**)

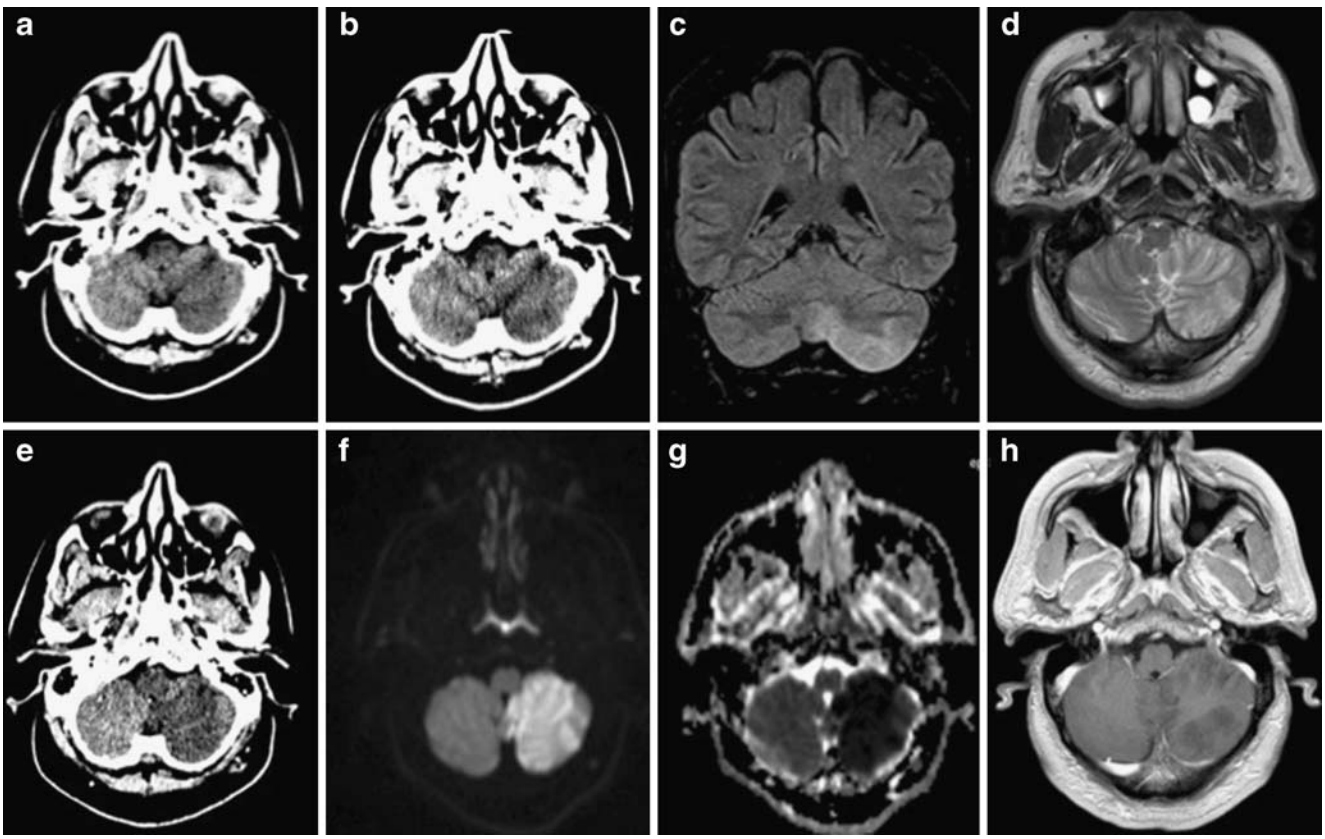

Fig. 16 Patient with a left hemispheric cerebellar infarction. On the unenhanced CT, the lesion is almost not visible (**a**), whereas it becomes more apparent on the thick slab reconstructions (**b**, **c**). The lesion is confirmed by MRI (**c**–**h**)

treat is very short. Up until now, there was an agreement for intravenous thrombolysis that this therapeutic window was of 3 h for the MCA territory and longer for the posterior circulation due to the collateralization of these territories. ECASS 3 has recently shown that the time window has now increased to 4.5 h [4]. While CT perfusion can monitor the presence or not of revascularization, this technique might be complemented by the use of transcranial Doppler to follow the effect on revascularization. Also, if one is beyond the timeframe for the accepted drugs, other mechanical techniques might be added with benefit on revascularization [47].

Reperfusion therapies Once it has been established that a patient has a stroke and that he can be treated, imaging should try to detect not only which cases are amenable to treatment but also which ones should be used. While there is no clear consensus, it is possible that density of the thrombus will play a role. What is certain is that length of the thrombus will play a role: A longer thrombi will probably necessitate intravascular therapy. Vora et al. [48] found that hemorrhagic infarctions were related to the CT infarction, while parenchymal hematomas are associated with the presence of tandem occlusions, hyperglycemia among others, after treatment.

Follow-up imaging with CT Despite literature reporting higher incidence of post-stroke hemorrhage, a retrospective study of 91 patients showed only 3.6% of patients with ischemic stroke to have hemorrhage [49]. After intra-arterial thrombolysis, large hyperdense areas are often seen on CT, and it is sometimes unclear whether this is blood, contrast, or a mixture of both (Fig. 17). A recent study has tried to provide answers to this burning question: Contrast enhancement where the blood–brain barrier (BBB) is intact leads to hemorrhage in 20–30%, whereas contrast extravasation where the BBB is broken leads to hemorrhage in almost 100% [50].

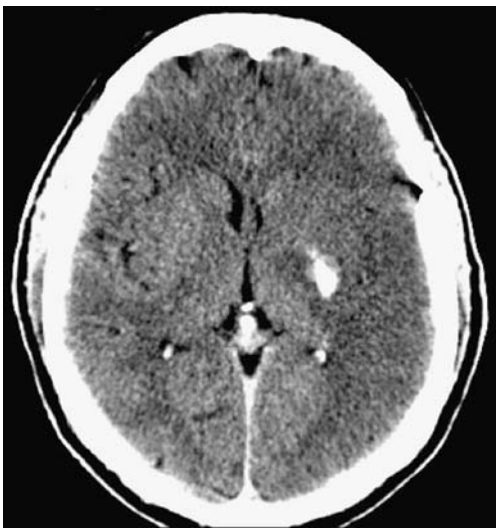

Fig. 17 Patient having undergone intra-arterial thrombolysis for a left-hemispheric stroke. The CT shows hyperdensity in the left basal ganglia corresponding to contrast

Table 1 Overview of studies comparing CT and MR in acute stroke.

Lansberg et al. (2000): DWI + in all cases, CT not
Barber et al.: DW (1999)I 100%, CT 75%
Mullins et al.: DWI: sensitivity: 97.3%, CT: 61.9%
Fiebach et al. (2002).: DWI: accuracy: 91%, CT: 61%
Fiebach et al. (2001): DWI: 100%, CT 71%
Chalela et al. (2007): MRI: 46%; CT: 10%; at 3 hours: MRI: 46%; CT: 7%

Conclusions

Computed tomography still has an important role to play in the investigation of patients with signs suggestive of acute cerebral ischemia. It still is more easy to use for the detection of hemorrhage since most radiologists will not be acquainted with the early MR appearance of hemorrhage. The problem most clinicians are nowadays confronted with when dealing with radiology, and this is especially true when dealing with a disease such as stroke, is to quickly provide a precise answer to a difficult question by using a challenging technology. Computed tomography has remained at the forefront of imaging in acute stroke because it is slightly faster than for example MR, and patient handling is simpler and more secure because there are no concerns regarding claustrophobia and magnetic fields (the patients must not be metal-free as they should be in MRI). This is why it is the method that has been used up until now within the scope of the major defining drug studies for thrombolysis (ECASS) and is the method recommended by most guidelines [51, 52]. While CT is the gold standard for the clear-cut exclusion of hemorrhage, the use of the remaining acute ischemic signs is lightly more open to debate. Indeed, while most are known to be of negative prognosis, they cannot be used alone to prevent a patient from undergoing thrombolysis. The really established CT criteria for thrombolysis are on the one hand the presence or absence of hemorrhage and on the other hand the presence of a large tissular hypodensity: Both these signs have been demonstrated to be of use to exclude patients from potential harmful effects of therapy. This is of course true for the treatment that we are currently using now with tissue plasminogen activator. However, the potential emergence of new drugs or even the switch toward mechanical

thrombectomy and vessel recanalization therapies may render some of these signs (hypodensity) of less use for the future.

Also, there has been great progress in scanner hardware, and these new CT units now allow scanning the whole brain in a few seconds. Perfusion coverage is also improved, and while a few prototypes allow whole brain coverage, unfortunately, most scanners can only cover a few slices. In many centers, CT has remained the standard for all acute stroke investigations. However, there is a shift of paradigm in some centers due to some specific advantages of MRI. Indeed, MRI will detect better small cortical or lacunar infarctions. This certainly explains why in most studies (Table 1), MR with diffusion imaging is seen as a clearly superior method [53–57]. Whatever method is chosen, it is important that certain standards be followed that are being established at the moment [58]. However, many of the early signs that are known can be seen on very close inspection of scans by experienced readers. While more difficult to interpret than the light bulb effect we see on diffusion-weighted imaging (DWI) [59], these signs are often seen and can help in the workup. Also, despite the fact that from known literature MRI should be equivalent in the detection of hemorrhage, CT is still the gold standard for the exclusion of hemorrhage in the acute phase, which is the main aim of radiology. For more complicated studies about the behavior of the ischemic lesion related to ischemia or neuroprotective drugs, CT will not be as useful as MRI due to the less clear delineation of the acute lesions. Also, whenever follow-ups are required, in order to avoid excessive radiation doses being applied to the patient, one might switch over to MRI which also helps in improving final lesion volume assessment. Also, while not yet playing a role in acute stroke management, hybrid technologies such as PET-CT have a role for the workup of patients with stroke who have a carotid stenosis as the underlying cause. CT itself is in a constant flux of development, and even more advanced methods such as 320 row detector CT units [60] or the advent of plat panel-derived CT [61] will allow us to go faster, acquire more tissular parameters and rendering acquisition, and evaluate more easily without slowing down the pre-therapeutic process.

Conflict of interest statement We declare that we have no conflict of interest.

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