“Computed Tomography–Negative” Intracerebral Hemorrhage

Case Report and Implications for Management

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Background: Noncontrast computed tomographic (CT) scanning of the brain is the main imaging modality recommended for the initial emergency evaluation of acute stroke. The main role of CT in this setting is to rule out intracerebral hemorrhage, especially in subjects who are potential candidates for thrombolytic therapy.

Objectives and Results: We studied a patient who had symptoms suggestive of a transient ischemic attack. Although serial CT scans showed no evidence of hemorrhage, a subacute intracerebral hemorrhage was demonstrated by magnetic resonance imaging.

Conclusions: This case suggests that an alternative to CT scanning should be considered in patients with acute stroke to lower the risk of an undetected intracerebral hemorrhage, especially in patients being considered for thrombolytic or anticoagulant therapy. There is evidence in the literature of other “CT-negative” cases of intracerebral hemorrhage, as well as the availability of alternative imaging techniques such as gradient echo (“susceptibility-weighted”) magnetic resonance imaging sequences, which can enhance the ability of magnetic resonance imaging to detect an acute intracerebral hemorrhage.

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EUROIMAGING is often used as the basis for diagnostic and therapeu tic decisions in neurologic emergencies. This is especially true during the initial examination of patients with acute stroke, in particular regarding their eligibility for thrombolytic treatment. A high level of reliability of early imaging findings is thus essential, since misdiagnosis and deviation from treatment protocols can have serious consequences; for example, recombinant tissue plasminogen activator protocol violations have resulted in rates of intracerebral hemorrhage (ICH) as high as 11%, of which 2% have been fatal.1

Noncontrast computed tomographic (CT) scanning is currently the recommended imaging procedure for both the initial evaluation of suspected stroke and the determination of eligibility for recombinant tissue plasminogen activator treatment as defined by the protocol of the National Institute of Neurological Diseases and Stroke.2,3 In addition to its short acquisition time and relative affordability, CT became the imaging technique of choice in stroke protocols because of its reported high level of sensitivity in the detection of acute ICH.4,5 Although diffusion-weighted magnetic resonance (MR) imaging detects acute ischemic changes with greater sensitivity than CT,6 MR imaging has not been used routinely in this setting because of reports of a lower sensitivity in the detection of acute ICH when compared with CT.2 However, subacute or chronic ICH can be missed by CT as a result of predictable changes in the chemical composition of the ICH over time.7

We describe a patient examined for symptoms of a transient ischemic attack. Although serial CT scans showed no evidence of hemorrhage, the presence of an ICH was clearly demonstrated by MR imaging, a finding that illustrates the pitfalls of relying solely on CT scans for the exclusion of ICH before the use of therapies with potential for causing or increasing intracranial bleeding.

REPORT OF A CASE

A 74-year-old, right-handed woman was admitted to the hospital after reporting 2 episodes of right-hand “numbness.” She had had hypertension for 30 years and had completely recovered from a stroke involving the left frontal lobe 9 years earlier. She had also been diagnosed as having poorly differentiated squamous cell carcinoma of the
lung and concomitant renal cell carcinoma that were treated by surgery, chemotherapy, and radiotherapy (limited to the right lung and right kidney area, without cranial irradiation) more than 10 years previously.

Two days before admission, she noted numbness in her right hand that resolved after 5 minutes. The same pattern of numbness recurred on the day of admission. The patient denied associated headache, weakness, or difficulty speaking or swallowing. Two months before admission, she had fallen and injured her head, but had no loss of consciousness or residual symptoms.

On physical examination, she had regular pulse, and her blood pressure was 144/65 mm Hg. She was alert and oriented and her language and memory were normal. Cranial nerve function was intact. She had no abnormalities of sensation. Motor power, gait, and coordination were normal; the deep tendon reflexes were symmetric; and plantar responses were flexor. Results of laboratory tests, including complete blood cell count, serum electrolytes, liver function tests, and stool guaiac, were normal.

A head CT scan showed the cavity of an old left frontal infarct that appeared unchanged from an MR image obtained 2 years previously (Figure, A-C). A new, subtle focus of hypodensity involving the left frontal lobe was observed (Figure, D). No midline shift or intra-axial or extra-axial hemorrhages were observed. She was admitted with a diagnosis of probable transient ischemic attack and was given a continuous intravenous heparin sodium infusion.

An MR image obtained 3 hours after the CT scan demonstrated a subacute hemorrhage in the left frontal lobe (Figure, E-H). The heparin infusion was stopped, and the patient remained asymptomatic. A follow-up CT scan demonstrated no interval change when compared with the previous one; in particular, the area of T1 and T2 hyperintensity on the MR image could not be identified on the CT scan (Figure, I), suggesting the existence of a CT “isodense” hematoma. An electroencephalogram showed a spike focus in the left frontal lobe, suggesting that the episodes of right-hand numbness may have represented seizure activity. She was started on a regimen of phenytoin sodium and was discharged home.

A follow-up MR image obtained 1 month later demonstrated interval evolution of the left frontal hemorrhage, without evidence to suggest underlying metastatic tumor (Figure, J, K). One day after the follow-up MR image, the patient had the sudden onset of aphasia and dense right hemiplegia. A noncontrast CT showed the cavity of an old left frontal infarct that appeared unchanged from an MR image obtained 2 years previously (Figure, L). A craniotomy for evacuation of the large hyperdense hematoma in the left frontoparietal region (Figure, L). A craniotomy for evacuation of the hematoma was consistent with hypertensive brain tissue obtained at the time of the surgical evacuation.

On initial hyperdensity of approximately 40 to 50 Hounsfield units to CT isodensity with the brain tissue, and ultimately to hypodensity.20 In contrast to the relatively large size of the lobar hemorrhage detected in our case, previously reported hemorrhages were relatively small and involved the basal ganglia. Of the 3 CT-negative ICHs reported, 2 were related to previous traumatic brain injury and 1 to chronic hypertension. The mechanism of the recurrent ICHs in our patient remains uncertain. The lack of evidence of intracranial vascular lesions with bleeding potential, history of cranial irradiation, or cerebral metastases suggested cerebral amyloid angiopathy as their underlying mechanism, possibly precipitated by the head trauma that preceded her first ICH. However, that diagnosis was not confirmed by histologic examination of tissue obtained at the time of the surgical drainage of her second ICH. In the absence of an autopsy study, however, we cannot rule out cerebral amyloid angiopathy as the underlying cause of her ICHs.

Computed tomography–negative microhemorrhages, detectable by MR imaging as T2 hypointensities of up to 5 mm, are of particular interest, since their prevalence in the general population appears to be far from negligible. They have been documented in 5% to 10% of healthy elderly individuals,11-13 and in a recent report from the Framingham Study their prevalence increased after age 75 years to 16.3%.14 Furthermore, 68% of patients with multiple lacunar strokes15 and 54% of patients with symptomatic ICH16 show evidence of multiple chronic microhemorrhages on brain MR images.

This high rate of coexistence of ischemic and hemorrhagic lesions is not surprising, since small-vessel vasculopathies can cause, depending on the circumstances, either ischemic lesions or ICH. Microhemorrhages can be viewed as markers for vessel-wall disorders, since their detection by MR imaging strongly correlates with the histologic demonstration of various types of small-vessel disease, such as hypertensive lipohyalinosis and cerebral amyloid angiopathy.17 The risk of spontaneous bleeding and bleeding after anticoagulation or fibrinolytic therapy could therefore be inferred by the detection of microhemorrhages.18,19 This idea is supported by an association of amyloid angiopathy with the development of ICH after intravenous fibrinolysis or anticoagulation.20,22 In addition, ICH associated with oral anticoagulation may also develop from microhemorrhages, and it has been postulated that oral anticoagulants may cause enlargement of subclinical microhemorrhages into symptomatic ICH.23

Intravenous tissue plasminogen activator is an established therapy for acute ischemic stroke, based on evidence from a controlled clinical trial.24 The same type of evidence is lacking for the use of intravenous heparin in patients with transient ischemic attacks or acute ische-
mic stroke. However, intravenous heparin continues to be commonly used, especially in patients with transient ischemic attacks and with acute nonhemorrhagic stroke of presumed embolic mechanism. The controversy about this issue is illustrated by current opinions in favor or against its use. It is likely that the controversy will not be resolved until the completion of the ongoing Rapid Anticoagulation Prevents Ischemic Damage trial. In this multicenter European trial, patients with nonlacunar ischemic stroke are being randomized to either continuous intravenous heparin or placebo, to test the efficacy and safety of heparin in this setting. Depending on the results of this trial, use of intravenous heparin may or may not be a therapeutic consideration in the future, thus making the issue of excluding hemorrhagic lesions either essential or moot. However, the issue will remain a critical one for patients who are candidates for thrombolysis, as well as for those who may be treated with aspirin, a treatment found to be of value in 2 randomized clinical trials.

Successive case brain images. A-C, Magnetic resonance (MR) image obtained 2 years before admission. Sagittal T1 (A), axial T1 (B), and axial fluid-attenuated inversion recovery (FLAIR) (C) images were obtained without intravenous contrast. A well-circumscribed area of decreased signal is seen in the left frontal vertex region (A), consistent with an old infarct with associated gliosis and pericentric changes (B). Diffuse areas of increased signal are seen in the periventricular white matter consistent with chronic microvascular ischemic changes (C). D, Computed tomogram (CT) without contrast obtained on the day of admission. Area of hypodensity is seen in the left frontal lobe. The ventricles and sulci are diffusely prominent, consistent with cortical volume loss. There is no midline shift or intra-axial or extra-axial hemorrhage. E-H, Magnetic resonance images obtained 3 hours after the initial CT. Sagittal T1 (E) and axial T2 (F, G) images were obtained without intravenous contrast. In comparison with image A, a new, well-circumscribed area of increased T1 signal is seen in the left frontal lobe with areas of decreased signal in the center and a rim of decreased signal around it (E). There is mass effect, as evidenced by sulcal effacement (E-G). In T2 images, both new (F) and old (G) left frontal lobe lesions appear as areas of increased T2 signal. The new lesion is hyperintense on the FLAIR images (H). I, The second CT scan obtained 24 hours after the MR image shows no evidence of interval hemorrhage. J and K, MR images with (J) and without (K) contrast obtained 1 month later. The focus of subacute hemorrhage in the left frontal pole has undergone interval evolution and is now smaller, with persistent central T1 (J) and T2 hyperintensity. A ring of FLAIR hyperintensity surrounds the zone of hemorrhage (K). No evidence of an underlying enhancing lesion was found. L, A CT scan obtained 1 day later shows a large hyperdense hematoma measuring 5 cm at its greatest diameter and extending from the left posterior temporal lobe to the parietal and posterior frontal regions, with associated mass effect and midline shift.
What imaging modalities should be substituted for CT scanning in stroke protocols? Concerns that MR imaging cannot detect acute ICH have resulted in reluctance to use it as the only imaging method before initiation of anticoagulation or thrombolytic therapy. Recent studies, however, have demonstrated that T2-weighted and susceptibility-weighted (also known as gradient echo) MR imaging sequences can reliably detect ICH between 2.5 and 6 hours \(^{32,33}\) and even as early as 30 to 120 minutes \(^{34}\) from the onset of symptoms. Furthermore, specific patterns of hypointense, isointense, and hyperintense signal in these MR imaging sequences (progressing from the periphery of the hematoma to the center) allow the determination of hemorrhage evolution over time. \(^{34}\) Finally, the demonstration of chronic microhemorrhages, as discussed earlier, could be of value in the assessment of a patient’s risk of ICH after anticoagulant or thrombolytic treatment. Since the scan time required to complete a basic stroke protocol with multiple MR imaging sequences does not exceed 15 minutes, \(^{34}\) MR imaging is a useful alternative to CT imaging in screening stroke patients before the institution of thrombolytic or anticoagulation therapy.

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