Letters to the Editor

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Ischemic Stroke and Tissue Hypodensity on Computed Tomography

To the Editor:

Clinical experience and experimental data have shown that early identification of patients with a large ischemic brain edema and subsequent hemicraniectomy can decrease mortality and morbidity.[1,2] I read with great interest the article by Haring and colleagues[3] and appreciate the efforts of the authors to find CT criteria that could early and reliably discriminate acute stroke patients with a malignant course and the potential benefit from craniectomy for those with a more favorable prognosis. I am afraid, however, that the authors did not really meet this goal.

The authors used a case-control design and defined the patients with malignant course by their vascular findings (occlusion of the internal carotid artery or middle cerebral artery [MCA] trunk) and by tentorial herniation caused by brain edema within 24 to 96 hours after admission. The authors did not reveal whether the matched controls had the same type of arterial occlusion or why they chose older patients (median age 71 versus 64 years). They found that an attenuated corticomedullary contrast covering at least the entire MCA territory is the only radiological feature that yields both high specificity and sensitivity for a malignant course compared with other CT findings, such as parenchymal hypodensity and signs of focal brain swelling. They correctly stated that the attenuation of the corticomedullary contrast is caused by cortical hypodensity. In their cohort of 31 patients with malignant course, 27 patients showed a hypodensity of the entire MCA territory cortex. They found, however, only 18 patients with a parenchymal hypodensity in >50% of the MCA territory and only 14 patients with hypodensity >67% of the MCA territory. I cannot imagine patients with hypodensity of the entire MCA cortex—which means a total MCA infarction—but hypodensity in <50% or even 67% of the MCA territory. Unfortunately, the authors did not present an image of one of those 9 patients with parenchymal hypodensity in <50% of MCA territory but with hypodensity of the entire MCA cortex. They showed a patient (Figure A1) *without* compression of the subarachnoid space (according to the legend) and with malignant course, although they stated in Table 3 that *all* these patients had a compressed subarachnoid space.

It is my experience with CT that tissue hypodensity is best depicted in gray matter like the basal ganglia or the cortex. Isolated cortical involvement occurs after cerebral hypoxia. With arterial occlusion, however, almost always the cortex *and* subcortical tissue are affected. Therefore, I think that "attenuated corticomedullary contrast" is not a CT sign after ischemic stroke but an artifact without a pathophysiological meaning. The study confirmed our hypothesis that parenchymal hypodensity exceeding 50% of the MCA territory is a highly specific finding for a malignant course.[4]

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A Standardized MRI Stroke Protocol: Comparison with CT in Hyperacute Intracerebral Hemorrhage

To the Editor:

We read with great interest the article by Schellinger et al[1] regarding the use of MRI for detection of intracranial hemorrhage and applaud the efforts of the authors in performing these difficult studies. We have also observed that MRI is capable of detecting early acute cerebral hemorrhage and find the potential of MRI in this setting extremely promising. However, although we strongly agree that there is growing evidence that MRI is more sensitive than previously believed for the detection of acute intracranial hemorrhage, we also urge caution. It may be somewhat premature to declare that MRI is "as good as CT"[1] for the exclusion of parenchymal hemorrhage in acute stroke patients.

Current evidence supporting the use of MRI alone in this situation is based on only a handful of patients.[1,2] In addition, the hemorrhages detected to date, including the hemorrhages in this series, have been relatively large (>2.0 cm in diameter), which increases the probability of detection. No data have been reported on smaller, less-easily detected hemorrhages, which could still be at risk for worsening if a thrombolytic is administered. In addition, the possibility of MRI overestimating the degree of bleeding in patients with petechial hemorrhage undetectable on CT has not been studied. This could potentially lead to exclusion of patients who might otherwise benefit from thrombolysis. The problem of ruling out subarachnoid hemorrhage is also a concern, as appropriately pointed out by the authors.

We strongly agree that the use of MRI instead of CT for the assessment of acute stroke patients would substantially simplify patient management, and we have advocated the use of MRI, especially diffusion-weighted imaging (DWI), in the assessment of acute stroke patients. DWI is highly accurate in identifying ischemia, and both initial DWI and perfusion-weighted imaging (PWI) volumes are highly correlated with stroke outcome.[3–5] In addition, its clinical utility in this setting appears to be substantial.[6] If MRI is also acceptably accurate at identifying acute cerebral hemorrhage, this would vastly improve our ability to rapidly assess and treat acute stroke patients. However, we also believe that these promising observations need to be further substantiated in larger studies. We and others are currently organizing such investigations.

In the interim, we believe that MRI alone for the exclusion of hemorrhage should be used with care, particularly in patients being considered for thrombolytic therapy. Hopefully, future studies will confirm the promising results of Schellinger et al and greatly improve our ability to evaluate acute stroke patients.

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Response

We appreciated the letter of Drs Tong, Albers, Yenari, and Marks. There is obvious agreement with several aspects and conclusions of our study.[1] We agree that to date few patients with hyperacute intracerebral hemorrhage have been evaluated with MRI[1,2] and that microhemorrhages and subarachnoid hemorrhages have not yet been a subject of multicenter clinical investigations.[3] On the other hand, animal experimental data on the use of MRI in intracerebral hemorrhage[4–6] and data on the efficiency of MRI in the diagnosis of subarachnoid hemorrhage[7] become more and more available. We firmly believe that the use of stroke MRI with diffusion- and perfusion-weighted MR images, MR angiography, T2-weighted fast spin-echo, and perhaps FLAIR images alone (instead of CT) would optimize patient management. Without doubt, further studies such as large multicenter trials are needed and are now underway in Europe and the United States to obtain sufficient data to allow the broad application of stroke MRI. We also agree that missing tiny hemorrhages could lead to complications if thrombolytic therapy[8] were performed. However, the inexperienced investigator may confuse small basal ganglia calcifications seen on CT with small hemorrhages and therefore withhold thrombolytic therapy.

Despite the generally accepted inability to differentiate intracerebral hemorrhage and ischemia by clinical signs and symptoms,[8] we do not believe that there is a relevant risk of withholding a potentially effective thrombolytic therapy from eligible patients with inconclusive stroke MRI findings. Differentiation between hemorrhagic and ischemic stroke, and therefore candidacy for recanalization therapy, may very well be achieved by stroke MRI findings. Stroke MRI findings of cerebral hemorrhage and ischemia differ significantly, and, in our experience with more than 70 patients (not to speak of those who receive stroke MRI within the clinical routine), cannot be confused. Cerebral ischemia appears on stroke MRI as a hyperintensity on diffusion-weighted MRI, an area of disturbed perfusion on perfusion-weighted MRI equal to or exceeding that of the diffusion-weighted imaging lesion, and a potential vessel occlusion by MRA.[9] Thrombolysis ideally is performed when there is evidence of a large tissue at risk (volume difference between the lesions on diffusion- and perfusion-weighted imaging, respectively) and a vessel occlusion.[9] Petechial hemorrhage is seen in vasculitic lesions, which are no indication for thrombolytic therapy, or in hemorrhagic transformation of ischemic strokes. The latter does not typically occur in the time window accepted for thrombolysis. We agree, however, that those facilities not familiar with stroke MRI should perform an additional CT scan in doubtful cases before applying thrombolysis.

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Secondary Change in the Substantia Nigra Induced by Incomplete Infarct and Minor Hemorrhage in the Basal Ganglia Due to Traumatic Middle Cerebral Arterial Dissection

To the Editor:

Cerebral infarction caused by middle cerebral artery (MCA) occlusion (MCAO) can lead to secondary neuronal damage in discrete-remote brain areas, including the ipsilateral thalamus and substantia nigra.[1–4] These neuronal changes have been considered to develop due to either anterograde or retrograde degeneration or transsynaptic injury after the initial ischemia.[1–4] An early study of MRI showed that the lesion in the substantia nigra persisted for at least several months after the stroke.[4]
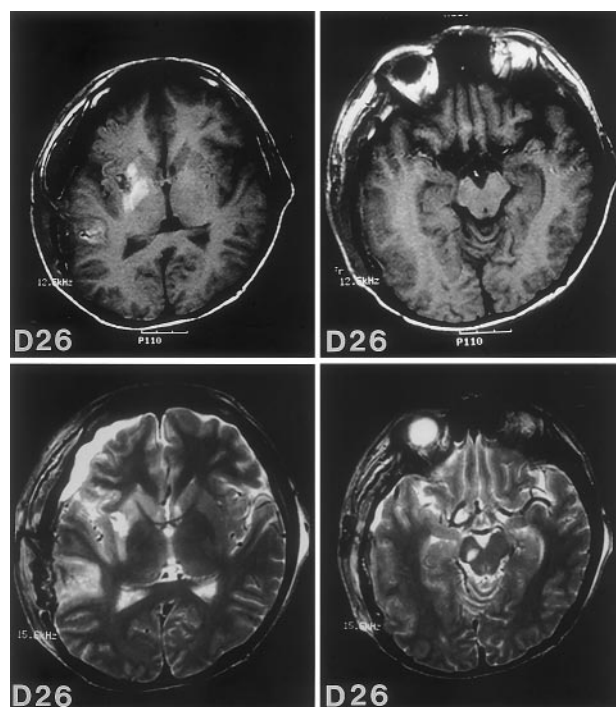
Transient changes in the substantia nigra on MRI have never been reported in patients after basal ganglionic ischemia.

We have investigated basal ganglia injuries after various types of transient brain energy failures in humans and rats using repeated MRI.[5–8] Recently, we showed that a specific change in the caudate putamen of humans and rats on serial MRI represented an incomplete ischemic injury of selective neuronal death and gliosis associated with biochemical changes which affect the magnetic field.[7,8] We present the first MRI study of the temporary change in the ipsilateral substantia nigra in a patient with minor hemorrhage and incomplete infarct in the basal ganglia after traumatic MCA dissection (MCAD).

An 18-year-old man received a head injury in a motorcycle accident on May 29, 1997 (day 0). His neurological state was normal on his admission to a local hospital. CT scans revealed no findings at that time. However, left hemiparesis and dysarthria developed in the patient on day 3. CT scans on day 3 demonstrated a low-density area in the right putamen. He was referred to our hospital for further examination on day 4. On admission, he was conscious and alert but suffered from left hemiparesis and dysarthria. CT scans on day 4 showed low-density lesions in the right putamen and cerebral cortex of the right frontal lobe. Cerebral angiography revealed stenotic change of the right MCA horizontal portion. The initial MRI on day 5 revealed ischemic changes of hyperintensity/hyperintensity on T1-weighted/T2-weighted (T1W/T2W) images, respectively, in the lateral portion of the right putamen (we tentatively designated this area as P1), hypointensity/hyperintensity in another portion of the right putamen (P2), and linear ischemic change of hypointensity/hyperintensity in the right cerebral cortex. The second MRI on day 26 demonstrated lesions of hypointensity/hyperintensity on T1-/T2-WI in the P1, hyperintensity/hyperintensity in the P2, and hyperintensity/hyperintensity in the right cerebral cortex (Figure). Furthermore, the MRI on day 26 revealed delayed ischemic change of hyperintensity on T1W and relative hypointensity on T2W images in the right globus pallidus (Figure). Additionally, in the right substantia nigra, the MRI on day 26 revealed a late-onset change of isointensity/hyperintensity on T1W/T2W images that the first MRI did not reveal (Figure). The third MRI on day 39 showed hypointensity/hyperintensity in the P1, hyperintensity/hyperintensity in the P2, hyperintensity/relative hypointensity in the right globus pallidus, and linear change of hyperintensity/hyperintensity in the right cerebral cortex. In the right substantia nigra, the delayed change on MRI disappeared on day 39. The patient's neurological state improved gradually during hospitalization. The patient could walk without any assistance, although he had a slight left hemiparesis. He could communicate with other persons without any speech disturbance. He left the hospital on day 48 and was admitted to a rehabilitation center for further neurological recovery. He resumed his university studies at the beginning of October 1997.

The neuroradiological data in our patient can be interpreted as follows. First, cerebral angiography demonstrated right MCA stenosis, which led to delayed neurological deficits after a mild head injury, suggesting traumatic dissection of the MCA. Second, repeated MRI revealed hemorrhagic infarction with subsequent cavitation in the right putamen P1. Third, MRI also showed evidence of a minor hemorrhage that was not evident on CT scans in the right putamen P2.[5] Fourth, MRI depicted a delayed lesion of persistent hyperintensity/relative hypointensity on T1W/T2W images, respectively, in the right globus pallidus, suggestive of the presence of the incomplete ischemic injury, which had been reported previously in our clinical and experimental studies.[7,8] Last, MRI exhibited a transient delayed change of isointensity on T1W and hyperintensity on T2W images in the right substantia nigra.

Focal brain ischemia produces a severe ischemic core with the surrounding area of milder ischemia and a nonischemic region.[9]

Changes in the basal ganglia, cerebral cortex, and substantia nigra on MRI (day 26). (T1W/T2W images; upper/lower images). MRI demonstrated lesions of hypointensity/hyperintensity on T1W/T2W images, respectively, in the lateral portion of the right putamen, hyperintensity/hyperintensity in another portion of the right putamen, and hyperintensity/hyperintensity in the right cerebral cortex. The right globus pallidus appeared hyperintense on T1W images and relatively hypointense on T2W images. The T2 hyperintensity of the substantia nigra observed at day 26 cleared by day 39.

In this case, we believe that MCAD led to severe ischemia (hemorrhagic infarction followed by cavitation) in the P1, relatively moderate ischemia (minor hemorrhage that could not be detected on CT scans)[5] in the P2, and mild ischemia producing "delayed ischemic hyperintensity on T1W MRI" (DIH)[7,8] in the globus pallidus. We showed that this DIH corresponded to selective neuronal death and gliosis without infarct or hemorrhage.[8]

An interesting finding in our patient is the late-onset change of isointensity/hyperintensity on T1W/T2W MRI, respectively, in the ipsilateral substantia nigra after the primary ischemic lesion in the basal ganglia. The consciousness level of our patient remained clear throughout his hospital stay. The MRI change in the substantia nigra could be detected on T2W images obtained on day 26 but not on day 5. Therefore, this MRI abnormality of delayed onset in the substantia nigra seemed to result from a remote effect of the ischemic lesion in the basal ganglia (secondary change through the striatonigral and/or nigrostriatal pathways) but not a direct effect of the initial head trauma.

Interestingly, the T2 hyperintensity of the substantia nigra observed at day 26 cleared by day 39. Although remote effects of central nervous system injuries have been seen on various MRI sequences,[4,10] this is the first observation of a remote effect leading to transient MRI change within the substantia nigra of humans. This distant effect from the basal ganglia might cause the edematous change on MRI in the substantia nigra. Based on an early experimental study,[3] Nakane et al[4] suggested that the remote neuronal degeneration in the ipsilateral substantia nigra of their patients were caused by a transsynaptic, neurotransmitter-mediated disinhibition due to

the loss of striatal neurons of the striatonigral pathway. The loss of an inhibitory γ-aminobutyric acidergic output from the striatum to substantia nigra is considered to result in excessive excitation sufficient to cause the neuronal damage in the substantia nigra.[3]

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Monitoring the Effectiveness of Anticoagulative Therapy in Left Atrial Spontaneous Echo Contrast by Cerebral Microemboli Detection

To the Editor:

We observed high-intensive transient signals (HITS) in continuous transcranial Doppler (TCD) sonography in a patient with stroke and massive spontaneous echo contrast in the left atrium. These HITS occurred only when insufficient anticoagulation was present.

HITS detected in continuous transcranial Doppler spectral curves are correlated with embolic conditions and stroke.[1] Fulfilling several criteria, they are accepted as cerebral microembolic events. Until now, no influence of anticoagulation on the presence of HITS has been proved.[2] Only one case examines the influence of intravenous heparin on the rate of HITS in a patient with stroke, but in this patient no embolic source was found.[2] In another published case,[3] remitting cerebral ischemia is correlated with the rate of microembolic signals, but there is no relation to anticoagulation with intravenously applied heparin.

The well-known condition of spontaneous echo contrast, shown by transthoracic (TTE) or transesophageal echocardiography (TEE), occurs mainly in the left atrium in cardiac embolic cases. It is explained by aggregations of erythrocytes, indicates a hypercoagulative state, and is associated with a high incidence of left atrial thrombus as well as a higher stroke risk in these patients.[4]

Our 62-year-old male patient developed persisting atrial flutter for the first time with an embolic occlusion of the left internal carotid artery (ICA) and a consecutive territorial infarction in the area of the left middle cerebral artery (MCA). TEE demonstrated massive spontaneous echo contrast in the left atrium, due to atrial flutter and enlargement of the left atrium. The patient received intravenously heparin with a partial thromboplastin time of about 55 seconds. Three continuous TCDs were performed over the following days, the second without anticoagulation because, unnoticed by nurses and physicians, the patient disconnected the IV line with heparin nearly 1 hour before examination. Only in this examination were significant HITS found in the right MCA. The left MCA showed artifacts in all examinations because of bad bone window and turbulent cross flow over the circle of Willis.

We concluded that the patient's symptoms were due to the occlusion of the left ICA but that the microembolic events which registered in the right MCA only in a situation without any anticoagulation were the consequence of the embolic cardiac condition visualized as spontaneous echo contrast in the TEE. To our knowledge, this is the first time that an effect of anticoagulation in the treatment of cardiogenic embolic disease has been directly demonstrated through detection of cerebral microembolic signals.

We conclude that the effectiveness of anticoagulant therapy in spontaneous echo contrast can be monitored through detection of microembolic signals. The as-yet unproved influence of anticoagulation in cardiac embolic disease on the occurrence of microembolic signals may result from a too-low detection level for emboli by this method in some cases. However, it might be effective in the special situation of spontaneous echo contrast, which indicates a massive tendency for coagulation and embolic events.

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Response

Doppler monitoring of blood flow velocity patterns in the intracranial arteries has been used for several years to detect HITS, which have been prematurely accepted as synonymous

with microembolism despite warning hints that this may not always be so.[1]

First, the majority of HITS are clinically silent, and reports of associated transient ischemic attacks or strokes are extremely rare (eg, in patients with prosthetic heart valves as many as 1 million HITS per month may be extrapolated without neurological or neuropsychological problems). These HITS have recently been identified as resulting from gaseous artifacts (so-called microcavitations).[2] Others that are less frequently observed in patients with cerebral ischemia are more likely to represent features of ongoing microembolism,[3] eg, in the presence of symptomatic carotid disease; however, neither the constituency of these microembolic particles nor the risk of stroke or transient ischemic attacks associated herewith has been identified so far. Second, the information from the Doppler signal is insufficient for interpretation of the size and composition of microembolic particles because of several physical and physiological problems, as observed in experimental conditions: signals from identical emboli may vary enormously due to the nonuniformity of the ultrasound field inside the skull, only small differences between Doppler signals from surrounding blood versus those from microembolic particles, and unpredictable trajectories of a particular embolus passing the vessel and the ultrasound beam volume.[2] Thus, many attempts to distinguish gaseous from solid microemboli, and in particular to separate different composition and size from patterns of HITS, will always involve a large degree of uncertainty, which supports the caveat against a terminology using HITS and microembolic particles as synonyms.

Several anecdotal observations of patients with identified sources of cerebral embolism, repeated clinical attacks, and HITS detected during TCD monitoring represent an interesting approach to identify the composition of microembolic particles at least in individual subjects by different reactions to agents interfering with their generation and to use this information for a refined and personally stratified therapeutic regimen.

In our article published in *Stroke* in 1996,[3] the therapeutic regimen at the time of investigation was analyzed to establish its effect on incidence of HITS. Among 148 patients with identified sources of embolism, those without a specific treatment (anticoagulation/platelet inhibition) showed a nonsignificant trend for a higher incidence of HITS than those who were on anticoagulation (eg, 20.9% versus 10.8% in patients with vascular sources of embolism and 8.6% versus 3.6% in patients with cardiac sources of thrombembolism). In a case similar to those reported by Siebler et al[4] and by Eggers et al in their letter, we recently described[5] a patient with recurrent ischemic attacks in the posterior circulation due to proximal vertebral artery stenosis, who exhibited both HITS and acute embolic lesion patterns demonstrated by MRI. Clinical events occurred despite standard antiplatelet therapy and oral anticoagulation, but they, as well as HITS, stopped when effective intravenous anticoagulation (partial thromboplastin time of 83 seconds) or a combination of anticoagulants (INR of 1.5 to 3.5) and aspirin (50 mg) was administered.

Because the spontaneous course of patients with cerebrovascular diseases varies, anecdotal reports like these cannot be taken for evidence-based therapy. However, these cases challenge the question of whether modification of HITS to individual treatment strategies may become a useful instrument for more efficient secondary stroke prevention, which unfortunately still fails in two thirds of all patients treated according to the results from large clinical trials.

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Hemiosteoporosis Following Stroke: Importance of Pathophysiologic Understanding and Histologic Evidence

To the Editor:

We read with interest the article by Ramnemark et al[1] reporting that patients developed hemiosteoporosis during the first year after severe stroke. These authors concluded that hemiosteoporosis occurred independently of any weight change after stroke. Other reports have indicated that bone mass or bone mineral density (BMD) is reduced in stroke patients on the hemiplegic side, reflecting both degree of paralysis and vitamin D deficiency.[2–4] In these investigations, bone changes were determined by bone mass or BMD with x-ray radiodensitometry[2,3] or dual-energy x-ray absorptiometry,[4] without histologic assessment. However, the diagnosis of osteoporosis requires histological demonstration that both bone matrix and bone mineral area are lost. Ramnemark's report[1] does not mention quantitative assessment of bone biopsy specimens. To our knowledge, histologically proved osteoporosis in patients after stroke has not been reported, although a well-established relationship exists between prolonged immobilization and osteoporosis in spinal cord injury.[5]

Our previous findings[3] have shown lower serum 25-hydroxyvitamin (25-OHD) concentrations in patients following stroke (9.1 ± 4.9 ng/mL for 42 outpatients, 5.9 ± 4.1 ng/mL for 45 inpatients) than in control subjects (21.6 ± 3.1 ng/mL), which correlates well with decreased bone mass as measured by radiodensity. Among the patients, 7 of the outpatients (17%) and 21 of the inpatients (47%) had 25-OHD concentrations below 5 ng/mL, which are considered osteomalacic levels. These deficiencies were caused by malnutrition and sunlight deprivation. In vitamin D deficiency, bone mineralization is impaired, which leads to accumulation of unmineralized matrix or osteoid in the skeleton. Reduction in bone formation occurs with prolonged immobilization from spinal cord injury, as evidenced by diminished osteoid thickness and mineralization rates observed in biopsy specimens.[6] Accordingly, a combination of disuse and hypovitaminosis D may act on bone on the paretic sides of immobilized stroke patients.

As stated by Ramnemark et al,[1] hip fractures are a serious complication after stroke; between 4% and 15% of hip fractures occur as a late complication of cerebrovascular disease.[7,8] The article postulated that hip fractures after stroke reflect both a high incidence of accidental falls and progressive hemiosteoporosis on the paretic side. However, osteoporosis on the paretic side must be distinguished from bone loss on that side caused by a combination of disuse and hypovitaminosis D, because clear identification of the process has important therapeutic implications for the prevention of hip fractures. If only disuse osteoporosis is acting on the paretic side, agents that inhibit bone resorption, such as bisphosphonate[9] or calcitonin,[10] are needed to prevent further bone loss.[11] On the other hand, if the bone changes on the paretic side are caused by disuse and by

hypovitaminosis D, vitamin D supplementation is needed to prevent hip fractures. A recent study has found that daily supplementation with vitamin D (800 IU) and calcium (1200 mg) can reduce hip fracture by 43% in postmenopausal women.[12] The incidence of hip fracture in hemiplegic stroke patients may be similarly reduced by routine use of active vitamin D supplements.[13]

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Response

We thank Dr Sato and his colleagues for their valuable comments on our article.

Bone loss after stroke occurs exclusively on the paretic side, is most pronounced the first year after stroke, and continues significantly the first year after the acute onset of stroke.[1–2] Preliminary data indicate that stroke patients continue to lose bone mass between 1 and 3 years after stroke onset (Ramnemark et al, unpublished data, 1999). A main reason for development of hemiosteoporosis is likely to be the paresis itself (ie, disuse). Vitamin D deficiency cannot be excluded as an additional cause, because stroke patients may be malnourished[3] and stay indoors most of the time. However, in our study we saw only the normal rate of bone loss over the total body during the first year after stroke. This argues against hypovitaminosis D and general immobilization being the main cause of hemiosteoporosis.

We agree with Sato and his colleagues that bone histopathology studies in hemiplegic patients would be of value, although this is rarely performed in clinical praxis. One previous study[4] analysed histopathological changes in bone biopsies in stroke patients who had suffered femoral neck fracture. However, biopsies were not strictly from the paretic side, and the sample size was too small to draw any conclusions. The diagnosis of osteoporosis in our study was set, according to WHO, as a BMD value (in grams per square centimeter) ≤2.5 SDs below the young adult mean value of BMD (T score),[5] and 84% of patients in our study fulfilled the criteria for osteoporosis in paretic hip at the 12-month follow-up.

Further intervention studies with the aim of reducing fracture risk in stroke patients are of major interest. Sato et al have been instrumental in this area by demonstrating the effects of very interesting treatments on osteoporosis by vitamin D and calcium in this patient group.[6]

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Perimesencephalic Hemorrhage

To the Editor:

The article by Velthuis et al[1] in the May 1999 issue of *Stroke* was an interesting case series, but I feel that their results do not logically lead to their conclusions. A small series of 16 patients with perimesencephalic hemorrhage with no aneurysm detected on CT angiography or digital subtraction angiography (DSA) does not prove that CT angiography alone is adequate for the detection of cerebral aneurysms in patient with perimesencephalic subarachnoid hemorrhage.

Velthuis et al[1] are proposing that CT angiography is an adequate screening examination for cerebral aneurysms in patients with perimesencephalic hemorrhage. The most important

issue in a screening study is sensitivity, not specificity. In their discussion, Velthuis et al point out that the specificity of CT angiography for the detection of cerebral aneurysms is 89% to 100%, according to a number of references.[2–9] They do not discuss the fact that the sensitivity of CT angiography in these studies ranged from 67% to 96%.[2–9] In fact, Velthuis et al reported in a study[5] that CT angiography at their institution depicted 90% of aneurysms confirmed with DSA. One must assume that this 90% sensitivity of CT angiography at their institution also applies to vertebrobasilar aneurysms in patients with perimesencephalic hemorrhage. If one fails to detect 10% of aneurysms that present with the perimesencephalic hemorrhage pattern, and 5% of patients with this pattern actually have an aneurysm,[1] a ruptured aneurysm will not be detected in about 0.5% of cases. The risk of rebleeding from a ruptured aneurysm without surgery or endovascular treatment is between 20% and 30% for the first month after hemorrhage.[10] Patients who rebleed from ruptured aneurysms have an 80% mortality rate.[11] The risk of CT angiography in patients with perimesencephalic subarachnoid hemorrhage can be summarized as follows: (1) because there is an approximately 5% risk that the patient has a ruptured aneurysm, there is a 0.5% risk that a ruptured aneurysm will not be detected by the CT angiogram; (2) this translates into a 0.13% risk that such an undetected ruptured aneurysm will rebleed; and (3) there is an approximately 0.1% risk that the patient will die from rebleeding of the undetected aneurysm within 1 month. The risk of permanent neurological complication associated with cerebral angiography in patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation is known to be extremely low (0.07%) from a meta-analysis of recent, prospective studies.[12] The neurological deficits complicating angiography tend to be much less severe than the morbidity and mortality caused by rebleeding of a ruptured aneurysm.

If the diagnostic value of CT angiography is less than that of DSA, and the risk of missing an aneurysm by performing CT angiography is higher than the risk of DSA, how can one contend that CT angiography is preferable in patients with perimesencephalic hemorrhages? CT angiography has been touted as being useful for patients who are too critically ill to undergo the delay necessary for angiography prior to surgery. However, based on the definition of the clinical syndrome associated with perimesencephalic hemorrhage, these patients are not critically ill. One might argue that CT angiography is less expensive than DSA and therefore more cost effective, but this would have to be evaluated with a cost-effectiveness study. In this select group of patients with perimesencephalic hemorrhage, the rate of aneurysm detection on a second angiogram may, in fact, be too low to warrant a second angiogram if no aneurysm is detected on an initial DSA.[13] But the diagnostic value of performing an initial study with DSA rather than CT angiography in patients with perimesencephalic subarachnoid hemorrhage is quite clear at the present time.

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Response

We thank Dr Cloft for his interest in our article.[1] He is concerned about the risk of missing a vertebrobasilar aneurysm with CT angiography in the assessment of patients with perimesencephalic pattern of hemorrhage. Based on our numbers of patients, he maintains that intra-arterial DSA is still warranted in patients with a perimesencephalic pattern of hemorrhage and a normal CT angiogram. We believe that several assumptions are incorrect in his line of reasoning.

First, Dr Cloft feels that sensitivity (ie, the chance of finding an aneurysm by CT angiography given that an aneurysm is present) is the most important test characteristic. We think that the negative predictive value (ie, the chance that no aneurysm is present in patients with a negative CT angiography) is more important for clinicians. In our study we had 16 patients with vertebrobasilar aneurysms and 24 patients with no aneurysm.[1]

Second, the sensitivity (90%) we found in a previous study,[2] which was based on patients with subarachnoid hemorrhage from all aneurysm locations, including aneurysms of the carotid circulation, cannot be directly applied to the subset of patients who are at risk for ruptured vertebrobasilar aneurysms. The 90% sensitivity refers to detection of both symptomatic and asymptomatic additional aneurysms and includes 24% of CT angiography examinations of suboptimal quality. The majority of missed aneurysms are additional aneurysms located on the carotid circulation. The sensitivity for symptomatic aneurysms in this study was 95%. In patients with perimesencephalic pattern of hemorrhage, we want to exclude a symptomatic vertebrobasilar aneurysm on a CT angiography of good quality. CT angiograms of inadequate quality are either repeated or intra-arterial angiography is performed. The actual sensitivity in our present series is 100%; the true sensitivity will of course be less than 100%, but we feel it is realistic to expect that it is higher than 95% (probably around 97%).

Third, the 0.07% risk of intra-arterial angiography found in the recent review cannot directly be applied to patients with perimesencephalic hemorrhage.[3] These patients need bilateral vertebral angiography, which probably carries greater risk than carotid or 3-vessel angiography. A subset of patients with bilateral vertebral angiography can not be extracted from the review. Moreover, the 0.07% risk for permanent neurological complication with intra-arterial cerebral angiography is combined for patients with subarachnoid hemorrhage and patients with cerebral aneurysms or arteriovenous malformations but without subarachnoid hemorrhage. The permanent neurological risk for patients with subarachnoid hemorrhage in this analysis is higher (0.3%). The case fatality rate of 80% after a rebleed is based on data from another era.[4] In those days, patients with a rebleed were left untreated for 12 days after the rebleed, thereby inducing time for further rebleed. Nowadays, patients who rebleed are treated as soon as possible after the rebleed. The fact that more aneurysms are found on digital subtraction angiography than on CT angiography does not necessarily imply that digital subtraction angiography has a better diagnostic value. In our clinical practice CT angiography is performed immediately after admission and before digital subtraction angiography. This means that the results of CT angiography are at hand when intra-arterial angiography is performed, and therefore the intra-arterial angiography is guided by the results of CT angiography. We have observed several patients in whom the standard projections of intra-arterial angiography did not reveal the aneurysm, and only after additional projections guided by the CT angiography was the aneurysm found on intra-arterial angiography. It is well known that the sensitivity of intra-arterial angiography is not optimal. Combined data of 7 studies regarding patients with subarachnoid hemorrhage and negative intra-arterial angiograms revealed 22 aneurysms in 145 repeat angiograms.[5] Even if we follow the calculation done by Dr Cloft but incorporate a sensitivity of at least 95% (which is presumably too low), the chance of missing an aneurysm in patients with a perimesencephalic pattern of hemorrhage is, at the highest, 0.25%.

The chance of having an aneurysm for patients with a perimesencephalic pattern of hemorrhage and a negative CT angiography can be calculated by means of the likelihood ratio. Assuming a 5% risk of an aneurysm in patients with a perimesencephalic pattern of hemorrhage and a sensitivity and specificity of 97% (in our study both were 100%), the likelihood ratio is 0.03 and the chance of an aneurysm after a negative CT angiographic scan of good quality is 0.1% (1 per 1000).

We feel that these chances of having an aneurysm in patients with a perimesencephalic pattern of hemorrhage and a negative CT angiogram are too small to warrant bilateral vertebral angiography.

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