Comments and Opinions

Incomplete Cerebral Infarction — Focal Incomplete Ischemic Tissue Necrosis Not Leading To Emollision

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UNTIL THE ADVENT OF CT SCANNING, the diagnosis of cerebral infarction was based mainly on clinical criteria with lumbar puncture, angiography, and Tc⁹⁹m scans affording supplementary evidence. Autopsy showed that the diagnosis often was in error. In particular, a clear differentiation between ischemic infarction and a smaller intracerebral hemorrhage was impossible. Today this situation has changed, as completely infarcted tissue is readily seen as hypodense areas on CT scans. True, diagnostic problems still exist with smaller lesions and with special locations, but a positive diagnosis, based on direct visualization of the localization and size of the infarct in vivo, is now available.

This has led to the mental image that the lesion in ischemic stroke is precisely what we see on CT scan: the evolving emollision — the area of complete cerebral infarction. Once more we are, by pragmatic necessity, slaves of the tools available. We tend to forget the well known fact that ischemia may damage the brain and kill many neurones without completely destroying the tissue’s structure. “The well known fact” — these words seem appropriate because classical pathoanatomical descriptions of ischemic infarction abound with comments on incomplete or partial tissue damage around areas of complete necrosis. As will be argued below, it may be important to recognize incomplete cerebral infarction clinically. Sometimes it may dominate over complete infarction, or perhaps even be the only manifestation of the ischemic damage.

The pathoanatomical picture: localized ischemic damage without emollision

The lesion is analogous to that seen more diffusely in the brain after cardiac arrest. A detailed description with many references to the older literature is given in 1957 by Scholtz.¹ The discrete nature of the early stages should be stressed; there are no macroscopic changes, no softening of the tissue, and no obvious edema. Only by staining the tissue can the classical signs of anoxic neuronal death be seen in form, particularly, in changes of the nuclei. No mention is made of early changes of the glial cells. The terminal stage after some months is generally fairly easy to recognize even by the naked eye. The incomplete ischemic infarct consists of a region with narrowed irregular cortical gyri separated by wide sulci, narrowed cortex with subtotal neuronal loss and gliosis, and narrowed subcortical white matter with demyelinization and gliosis. Often the brain also shows many small areas of emollision due to complete ischemic infarction.

The clinical picture: a stroke without abnormalities on X-ray-transmission CT scanning during the first weeks

The clinical description of incomplete ischemic infarction cannot at the time of writing be quite precise. The purpose of this text is to discuss the syndrome and thus to contribute toward its clinical recognition.

CT scanning shows, within 24 to 48 hours, the areas of complete infarction as hypodense lesions. Very often a stage with X-ray contrast enhancement develops at 1 to 2 weeks at which time the hypodensity tends to disappear only to reappear in the same localization subsequently, outlining the final lesion. In incomplete ischemic infarction, one would guess that no tissue hypodensity develops. But a phase of X-ray enhancement, e.g. of cortical gyri might or might not exist.

Let it be assumed, then, that brain areas undergoing incomplete ischemic infarction are CT negative during the first 5 to 10 days. Also that enhancement does, perhaps, not develop. Then the only CT abnormality to be expected would be an area of localized cortical-subcortical atrophy developing over months after the stroke. CT scanning is notoriously not very sensitive for detecting such a lesion.

This clinical picture, “the CT negative stroke,” would long ago have led to clinical recognition of incomplete infarction were it not for complicating factors. First, that a stroke may be caused by a small deep-seated infarct that easily is missed on the CT scans. In other words, one cannot on the basis of the clinical symptoms say, “in this stroke patient, the left posterior parieto-occipital cortex is not functioning; hence, as CT is negative, the patient must have an incomplete infarct of these cortical areas!” The symptoms might have been caused by deeper infarct missed on CT scanning. Secondly, the number of such stroke patients (with repeatedly negative early CT scans) coming to autopsy some months after the ictus, when the lesion has become obvious, is still quite small — early autopsy easily missing the lesion, if it is not looked after deliberately.

The third and perhaps the most important complicating factor, is that areas of incomplete infarction often coexist in the same brain with areas of complete infarction. This is well described by Jones and coworkers in their comments on the pathoanatomical lesions in experimental ischemic injury in awake monkeys.² Clearly, in order to recognize the full extent of incomplete ischemic tissue damage, one cannot simply rely on...
clinical evidence such as "gross symptoms with small CT lesion," because the clinical judgement of the extent of the tissue dysfunction is, as noted above, too difficult. Hence one must have positive non-clinical diagnostic evidence of the integrity or lack of integrity of "CT-negative" cortical areas in a clinical case where often one or more "CT-positive" lesions are seen. Tomographic imaging of blood flow or metabolism, as commented on below, may afford such evidence.

The pathophysiology of incomplete ischemic infarction

Total ischemia of 15 to 30 minutes duration may well cause such partial tissue necrosis. In patients with ischemic stroke, however, it is probably rare that regional blood flow drops to zero following an acute arterial occlusion, as collateral flow of some magnitude, albeit insufficient to sustain normal tissue functions, is more likely. The experimental studies of Jones et al. 2 illustrate this point in their realistic stroke model using non-anesthetized monkeys. Permanent occlusion of the middle cerebral artery was found to produce infarction below a collateral flow threshold of approximately 17–18 ml/100g/min with diffuse neuronal loss seen in particular surrounding smaller infarcts. Their study suggests, consequently, that incomplete infarction may develop with prolonged (many hours lasting) ischemia in a fairly narrow range of residual flow, perhaps a range as narrow as between 15 and 18 ml/100g/min, as higher flow levels apparently leave the tissue structurally intact. Note, then, that when one expresses the thresholds of ischemia in terms of milliliters of blood, one presupposes that the blood is normal, in particular with respect to oxygen carrying capacity and oxygenation.

These comments have relation to the possibility of avoiding incomplete infarction by medical or surgical therapy: It is possible that even a quite moderate improvement of collateral flow (say from 16 to 20 ml/100g/min) may, if instituted early and sustained, decide if an ischemic area undergoes partial necrosis or remains fully intact (the same holds in principle for avoiding complete infarction).

It should be mentioned that focal incomplete ischemic infarction need not in all cases be due to an acute arterial occlusion. Chronic arterial occlusions complicated by a fall in systemic blood pressure ("hemodynamic crisis") might reduce flow to the critical range for sufficient time to produce it. But more importantly, tissue compression due to a space occupying intracranial mass may reduce the local perfusion pressure in such a manner. To recognize areas of ischemia produced impending or manifest partial tissue necrosis may be very important, as in cases of traumatic brain injury, brain tumors, or intracerebral hematomas, because therapeutic measures may be aimed (and is indeed being aimed) at avoiding such secondary complications.

Concluding remarks

Both the acute phase and the end stage of focal ischemic brain damage without emolllsion are well known to neuropathologists. It is the clinician who has failed to take it into consideration. Focal neurological symptoms, presumed to be caused by ischemia, arise not infrequently from persistently CT negative brain regions. Yet it is widely held, that the functional defect is rather due to a fully reversible hypoxic insult as described by Symon and coworkers, who coined the term "the ischemic penumbra" to liken the phenomenon to the half-shadow characteristic of a partial solar eclipse and who concluded from their studies with rather short lasting arterial occlusion (approx. 2 h) that the cellular dysfunction was reversible.

The difficulties in defining areas of incomplete infarction, clinically, may be partly overcome in the near future. It is possible that tomographic measurement of regional cerebral blood flow or metabolism could be of help: consider, for example, a "CT negative stroke" with essentially normal angiography at the time of study and a much reduced flow or metabolism in the clinically appropriate area days after the onset (preferably to values below 60% of that of the contralateral side — because such low values would appear to exclude simple deafferentiation due to a small deep-seated lesion not found on CT scanning, cf. the data of Phelps et al.) 4 The tomographic images afforded by nuclear magnetic resonance NMR may also, due to superior resolution of grey from white matter, help in visualizing the end stage of localized tissue atrophy. It is clear, however, that most of all one needs to correlate the clinical picture and all the various supplementary investigations to the pathoanatomical findings that so readily define the condition. Meanwhile it is worthwhile for neurologists and neurosurgeons, in particular, to bear in mind that X-ray tomography is "but the shadow of the truth" or, more precisely expressed: with regard to irreversible ischemic tissue damage one must clearly recognize in every case with the possibility that the CT lesion (the area of emolllsion), if present, outlines only part of the irreversible damage.

References

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