

Reperfusion therapy in stroke cases with unknown onset

Reperfusion is effective therapy for acute ischaemic stroke, but is only recommended when the time of onset is known. For a large percentage of stroke patients, the onset time is unknown. There is a need for studies to determine the efficaciousness and safety of reperfusion for these patients as well.

Thrombolysis and thrombectomy, also called reperfusion therapies, are effective for treating acute ischaemic stroke. The therapy reduces the risk of permanent neurological deficit, and there is a greater chance that patients will not be dependent on assistance afterwards (1, 2). However, it is time-dependent. The shorter the time from symptom onset to treatment start, the greater the chances of a good result. The proportion of ischaemic stroke patients in Norway who receive thrombolysis is only 15 % (3). The main reasons for this treatment not being administered are delayed hospitalisation and unknown time of onset (4, 5).

Unknown time of stroke onset may be due either to the patient being alone and incapable of stating when the stroke occurred or to the patient waking with the symptoms. Most strokes with known onset occur in the morning (6). If the majority of strokes during sleep also occur in the morning just before the patient wakes up, this would mean that many patients who do not receive thrombolysis at present, might benefit from doing so.

In the cases of patients who wake up with stroke symptoms (WUS) and have a CT scan within three hours of waking up, there are seldom early infarction changes on the CT images. In observation studies of WUS patients, the effectiveness of thrombolysis as reflected in a normal standard CT has been the same as in known onset patients (7).

Viable cerebral tissue?

In cases of ischaemic stroke with unknown time of onset where the appropriateness of offering reperfusion therapy is in doubt, there are in principle two kinds of imaging for determining whether there is an established infarction or not: DWI-FLAIR mismatch and core/penumbra mismatch. With a DWI-FLAIR mismatch, the infarction can be seen on diffusion-weighted MRI, but not on FLAIR.

Both CT and MRI scans can be used to examine core/penumbra mismatch. Ischaemic brain tissue that is believed not to have become an established infarction is called the penumbra of the infarction. A core/penumbra mismatch means that there is an area around an infarction core that can be saved if it correlates with the neurological deficits.

It is still open to question whether WUS patients can have thrombolysis based on a

normal standard CT, or whether they ought first to be treated after scans that show DWI-FLAIR mismatch and/or core/penumbra mismatch. As a means of distinguishing between infarctions with symptom onset before and after 4.5 hours, DWI-FLAIR mismatch has proven to be of uncertain sensitivity and specificity (8). There are also quite large individual differences

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in the conclusions drawn from the findings (8). It is conceivable that selection based on mismatch studies entails a risk of patients who wake up with stroke symptoms, and who should have received thrombolysis, not receiving it because of overly stringent image selection criteria. The importance of scans therefore remains unclarified.

Ongoing studies

In their case report in this edition of the *Journal of the Norwegian Medical Association*, Kvistad et al. show a patient with a very severe ischaemic stroke who benefited considerably from reperfusion therapy, even though the time of onset was unknown (9). The patient received intravenous thrombolysis. CT angiography revealed a proximal thrombus in the middle cerebral artery. Thrombolysis has often not been sufficiently effective in cases of occlusion of one of the large intracranial vessels. Brain circulation was re-established with the aid of thrombectomy, and the patient avoided a major ischaemic stroke.

As a consequence of the unanswered questions regarding efficacy and safety in cases of unknown onset, the American Stroke Association has recommended that thrombolysis should not be administered other than in clinical studies. This recommendation also includes attempts at selection based on imaging (10). The authors of

a systematic review of literature on wake-up stroke also conclude that there is a need for studies to determine efficacy and safety (11).

There are no completed controlled studies, but several ongoing studies are attempting to investigate the efficacy of and risk associated with thrombolysis when the time of stroke onset is unknown. The results of these studies may shed more light on the question of which image- and patient-related criteria are associated with the efficacy of thrombolysis in cases of unknown stroke onset.

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COMMENTS AND DEBATE

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