Limitations of clinical diagnosis in acute stroke

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Trials in acute stroke have recruited on the basis of clinical diagnosis. Using MRI we have shown that clinical diagnosis is more limited than previously appreciated, thus trials may have been underpowered or confounded.

Finding widely applicable and effective treatments for acute stroke has proved elusive. Despite promising preclinical data, all the published studies of neuroprotective drugs have been negative.[1] Angiographic studies have shown that thrombolysis can be an effective treatment for middle cerebral artery occlusion, but large studies of the thrombolytic agent alteplase given to patients on the basis of a clinical diagnosis of acute stroke have been equivocal.[2] By relying on clinical diagnosis these trials may have missed meaningful treatment effects because large numbers of patients were misdiagnosed. The proportion of appropriate patients recruited by using clinical diagnosis is not known. Drug treatments are specifically designed to salvage the ischaemic penumbra; significant treatment effects can only be expected if trials contain high proportions of such patients. Developments in magnetic resonance imaging (MRI), MR angiography (MRA), diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) can now be used to define the pathological processes causing the acute stroke syndrome, and patients with a penumbra can be identified.[3] We have applied these techniques to patients whose clinical syndrome and time of presentation would have made them eligible for inclusion in previous drug trials, to define the pathological heterogeneity of acute stroke.

Consecutive patients with anterior circulation stroke syndromes were recruited and examined within 6 h of stroke onset. Patients were scanned as soon as possible with a protocol of DWI, PWI, and MRA and followed for 7 days (methods available on request). At day 7, a final clinical diagnosis was made from all clinical investigations and imaging data. These diagnoses were classified as: misdiagnosis: completely normal diffusion and perfusion-weighted imaging, MR angiography, and an alternative clinical diagnosis; mis-classified: patients had strokes not due to anterior circulation occlusion such as haemorrhage, small vessel occlusion (lacune), or posterior cerebral artery occlusion; and anterior circulation ischaemia. The last group was further sub-classified into: transient ischaemic attacks—clinical syndromes that completely resolved within 24 h, even if small areas of infarction were seen on the DWI; recanalised cerebral infarction—clinical signs that persisted beyond 24 h, acute cerebral infarction in the anterior circulation territory on DWI, and normal angiography and PWI; acute infarction and persisting arterial occlusion. The latter subgroup was sub-divided into those with no mismatch between the DWI and PWI and those with a greater perfusion than diffusion deficit (a penumbra).

Final diagnosis	No	Time to scan (h)	Mean NIHSS
Misdiagnosis	6	11·6	14·3
Misclassification	15	12·6	12·2
TIA	7	13·4	14·8
Recanalised stroke	16	11·6	14·6
Occlusion with mismatch	15	9·9	16·8
Occlusion with no mismatch	11	10·9	21·0

Diagnosis of patients following imaging

70 patients were entered into the study. The mean time to imaging was 11·4 h. The mean NIH stroke score was 15 (table). 49 (70%) patients were correctly classified as having anterior circulation large-vessel ischaemia. Of the six patients who were misdiagnosed, three had metabolic upset; one had hemiplegic migraine, in one the symptoms were thought to be hysterical, and in one alcohol withdrawal was the final diagnosis. Of the 15 patients who were misclassified, seven had haemorrhage, five had small vessel occlusion (4 in the brain stem, 1 internal capsule), and three had posterior cerebral artery occlusion. Of the 49 patients with anterior circulation large vessel ischaemia, seven patients had a transient ischaemic attack (TIA), 16 had early recanalization, and 26 had a persisting occlusion, of whom 15 had a mismatch of DWI-PWI, despite a mean time to scan of 10 h (range 4–18 h).

This study shows the heterogeneity of clinically defined acute anterior circulation stroke. Using clinical criteria, 9% of patients were misdiagnosed and 21% misclassified. Though the majority (70%) were correctly classified, this group was also heterogeneous, and included patients with TIAs (10%), recanalized stroke (23%), and persisting occlusion (37%). These findings are consistent with previous work[4,5] and have implications for the interpretation of treatment trials that recruited patients using clinical entry criteria. Patients with the wrong diagnosis, transient ischaemia, cerebral haemorrhage, small vessel disease, and patients with infarction but spontaneous recanalisaton formed 63% of this population and none of these were rational targets for treatment. These results suggest that using clinical recruitment criteria, which assume a more homogenous study population than really exists, may have confounded previous treatment trials in acute stroke.

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