Predicting outcome in acute stroke

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The natural history of acute stroke is well defined. Predicting outcome in individuals, however, remains difficult, because prognostic studies examining associations between clinical signs or syndromes and outcome differ in patient selection, timing and choice of neurological assessments and outcome measures. Accuracy has been disappointing. Osler in 1892 stated that the ‘course of the disease ... is dependent on the situation and extent of the lesion’. Until recently, it has not been possible to examine the stroke prognosis, using Osler’s approach, with any great accuracy. The advent of diffusion weighted magnetic resonance imaging (DWI), which is highly sensitive to the pathophysiological changes underlying stroke, offers this possibility as it measures the site and extent of irreversible infarction. This review summarises the results of syndrome or sign-based predictive studies and shows how DWI may explain different outcomes in patients with identical neurological presentations, according to the ‘situation and extent of the lesion’.

One of the most important tasks a doctor can perform for a patient is to give an accurate prognosis in terms of survival and the quality of that survival. Since Rankin published his major study in 1957, doctors have sought a simple, reliable means of predicting outcome in stroke. Predicting outcome might be expected to be simple as we now have a wealth of information on the natural history of stroke from community-based studies in Bristol, Oxford and Copenhagen. There is a relatively rapid phase of recovery in the first 3 weeks, during which time most deaths occur and, in most patients, the majority of recovery occurs in 3 months. Significant recovery occurs in 30% over the next 3 months and, although this is not statistically significant at the group level, it is clinically significant for individuals. Both the Oxford and Copenhagen studies showed that at 6 months about 20% of people with a stroke are dead, 50% are independent and 30% are dependent in self-care. As Osler pointed out, ‘the course of the disease...depends on the situation and extent of the lesion’ and the Oxford and Copenhagen studies provide epidemiological proof of this. The Oxford Community Stroke Project reported 6 month outcome in ischaemic stroke according to a
quasi neuro-anatomical classification (Table 1) of LACI (lacunar anterior circulation infarct), TACI (total), PACI (partial) and POCI (posterior circulation infarct) and the Copenhagen study which classified stroke as ‘mild’, ‘moderate’, ‘severe’ and ‘very severe’, reported that 80% of patients in these groups made their maximum functional recovery at 3, 7, 12 and 13 weeks, respectively.

Predictive models and single clinical variables

It would seem that all researchers need to do is examine a large number of patients with acute stroke, assess their outcomes at 6 months, use statistical techniques to identify significant predictor variables and then assign probabilities of outcome group membership to individual patients according to the presence of these variables. It has not proved as simple in practice and the literature offers a huge variety of predictive models. Some use single signs (e.g. level of consciousness or incontinence)\textsuperscript{1,10-13}, others use combinations of signs (e.g. visual neglect, level of consciousness, hemiplegia)\textsuperscript{14,15}. Some use neurological scales or have investigated neuro-imaging (CT scan, NMR, SPECT, PET)\textsuperscript{16-18}. However, the doctor wishing to advise patients with stroke on the basis of these studies may find them difficult to apply to their clinical practice for a number of reasons.

What a clinician requires of a good prognostic model is that it be based on a representative sample of patients, make clinical sense, be accurate and simple. However, studies often differ in their selection of patients, e.g. community based\textsuperscript{19}, hospital based\textsuperscript{12,15,20}, stroke unit based\textsuperscript{21} or restricted to patients under 75 years\textsuperscript{19}. Timing of the neurological assessment that predicts outcome varies from 24 h\textsuperscript{20}, to 1 month\textsuperscript{12}. Methods of neurological assessment may be part of standard clinical practice or may include new measures, which may or may not have been validated\textsuperscript{22}. Timing of outcome assessment varies from 2 months, to 4 months, to 6 months, or at discharge and may vary within the study. Outcome measures vary between studies from ‘place of discharge’ to ‘independence in self-care’ to Barthel or other ADL score and the means used to classify people as ‘independent’ or ‘dependent’ may vary and may or may not have been standardised\textsuperscript{22}. Outcome groups may be merged, e.g. ‘dead and dependent’, even though they are clinically very different. There may be significant variation within any one outcome group, e.g. ‘dependent in personal ADL’ covers the whole range from doubly incontinent and requiring PEG feeding to being able to do everything except get in and out of the bath unaided. Few studies\textsuperscript{15,19} grade dependency as ‘mild’, ‘moderate’ or ‘severe’, and none have tried to predict specific activities of daily living, such as ‘able to transfer with one’, but it is these categories that may be clinically relevant.
to the difficulty of arranging a discharge home or elsewhere, and resource use thereafter. There is usually significant variation in patient management within individual studies as well as between studies. The Stroke Unit Trialists Collaboration’s systematic review indicates that those managed on a stroke unit\(^2\)\(^3\)\(^23\) or geriatric units\(^23\) may well receive better management and have a better outcome than those managed on general medical wards\(^14\)\(^15\)\(^20\). Stroke is a disease primarily of old age\(^5\), but pre-existing disability\(^23\) and general cognition\(^2\)\(^14\)\(^23\) are rarely taken into account. Presentation of results varies. The most useful, clinically, is recording the sensitivity, specificity, accuracy and likelihood ratio of any one predictor variable or equation. Studies giving statistical correlations between predictor variables and outcome are less immediately useful. Odds ratios are useful in identifying factors, such as fever or hypoglycaemia, that worsen prognosis and whose modification should, therefore, be the focus of a randomised controlled trial, but do not help with individual patient prediction. Some multi-variate models use complicated predictive equations\(^2\)\(^3\)\(^14\)\(^15\). Although not in itself a major criticism, this inconvenience makes it less likely that such models will be used. Finally, most models do not differentiate between patients with haemorrhage and those with an infarct, although there is evidence from the Copenhagen studies that outcome is no different once the level of severity of stroke is adjusted for.

Kwakkel et al\(^2\) reviewed 78 prognostic studies and set up 10 criteria of internal, external and statistical validity. Only 13 (17%) studies met 8 or more of these criteria and many studies failed to meet some of the most basic, such as the use of reliable and valid outcome measures or predictor variables. Of the 13 studies, Kwakkel chose 8 that met all criteria for internal and statistical validity\(^2\)\(^12\)\(^15\)\(^18\)\(^20\)\(^24\)\(^25\) and selected from those studies only the findings based on valid and reliable predictor variables. Urinary continence, loss of consciousness, disorientation, age, degree of paralysis were common predictors of outcome, with individual studies also identifying social support\(^25\), visual neglect\(^15\), tactile extinction\(^24\) and visual field defects\(^2\). Scrutiny of these studies illustrates the difficulty of applying even these carefully selected findings to groups of stroke patients in general. One study only looked at outcome in those under 75 years\(^19\). Another study only recruited patients who were conscious and able to swallow medication at 48 h\(^20\)\(^24\). Some\(^2\)\(^15\)\(^25\) used measures that are not yet part of standard clinical practice and one\(^18\) depended on PET scanning, which may not be routinely available, particularly in the UK. Some presented results as correlation coefficients rather than giving sensitivity and specificity. Some merged death and dependency into one outcome\(^12\)\(^20\)\(^24\) and most excluded death altogether\(^2\)\(^15\)\(^18\)\(^19\)\(^25\).

Kwakkel et al\(^20\) noted that few studies have been revalidated on a fresh sample of patients. Where this has happened, there may be good
correlation between actual and predicted outcome but not so close as to be clinically useful in individual patients\textsuperscript{21}. Indeed complex multivariate models had little advantage\textsuperscript{1,11,13,26} over simple clinical predictors such as level of consciousness or incontinence. Even the most well validated predictors are not very accurate and there is little to support the use of predictive models in the clinical setting. They are more likely to be useful in stratifying clinical trials or in case mix analysis\textsuperscript{15,20}. Simple predictors, such as level of consciousness\textsuperscript{1,10-12,26}, have a sensitivity for predicting death that varies from 40–78\%, specificity that varies from 72–96\% and overall accuracy of 60–80\%. There is similar variation in the ability of level of consciousness to predict ‘death or dependency’. Incontinence at 1 month predicts ‘death or dependency’ at 6 months\textsuperscript{1,11,12,26}, but sensitivity (57–92\%), specificity (84–90\%) and accuracy (75–89\%) varies. More complex models, such as the Guy’s Index or its modification, the ‘G’ score\textsuperscript{20}, predict ‘death or dependency’ with sensitivity of 34–86\%, specificity of 63–99\% and overall accuracy of 70–86\%\textsuperscript{20,26}. Most models are derived from clinical findings in the acute stage, but none seem able to account for the heterogeneity of stroke and accurately reflect ‘the situation and extent of the lesion’.

Prediction and syndromes

Advice to patients and their relatives might, therefore, be better based on the epidemiological studies carried out in Oxford and Copenhagen, which have used a syndromic approach. Clinical syndromes combine individual signs, not in a mathematically generated fashion, as in a predictive model, but in a way that makes pathophysiological sense. They are used to diagnose stroke, and have, in the Oxford studies in particular, been used to study natural history. It would be reasonable to tell a patient with a LACI, for example, that their chances of survival are good and that two-thirds of patients with LACIs become independent in self-care and that a quarter are dependent to varying degrees (Table 1). The general discussion with them and their family would then include the fact that actual outcome remains uncertain. A similar ‘syndromic’

<table>
<thead>
<tr>
<th>Outcome at 6 months</th>
<th>LACI</th>
<th>TACI</th>
<th>PACI</th>
<th>POCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dead</td>
<td>7%</td>
<td>55%</td>
<td>10%</td>
<td>14%</td>
</tr>
<tr>
<td>Dependent</td>
<td>25%</td>
<td>39%</td>
<td>34%</td>
<td>18%</td>
</tr>
<tr>
<td>Independent</td>
<td>66%</td>
<td>4%</td>
<td>55%</td>
<td>68%</td>
</tr>
</tbody>
</table>

LACI, lacunar anterior circulation infarct, TACI, total circulation infarct, PACI, partial circulation infarct, and POCI posterior circulation infarct
approach, not relying on acute stage signs, but on findings several weeks post-stroke, divides patients into three groups: those with only motor deficits, those with motor and sensory deficits and those with motor deficits, sensory deficits and hemianopia. Studies using this simple scheme, which ignores higher cortical function, appears to identify different recovery patterns. Nearly 90% of ‘motor only’ patients became independently mobile (at a mean of 2.5 months post-stroke), 55% of ‘motor and sensory’ became mobile at a mean of 4.5 months, and 30% of ‘motor, sensory and hemianopia’ became mobile at 5.5 months. More work is required to examine the value of this classification in an unselected population at different times post-stroke.

Pathophysiologically based prediction

Until recently it has not been possible to examine the prognosis of stroke using Osler’s approach, that the outcome depends upon the site and extent of the lesion, because at least 30% of patients have a normal CT. The future direction of prognostic studies may be dictated by developments in neuro-imaging (see Jäger in this issue). Diffusion and perfusion weighted imaging MRI (DWI and PWI) and MRI angiography allow the arterial territory of cerebral infarction to be accurately identified, whereas clinical examination (and hence the use of syndromic classification) is inaccurate. Furthermore, studies beginning in the first few hours after stroke may show significant pathophysiological differences in the state of the ischaemic insult present in patients with identical stroke syndromes. DWI lesions in patients who have undergone spontaneous recannalisation do not increase in size, whereas in patients with a persisting arterial occlusion and an ischaemic penumbra (DWI–PWI mismatch) further increases in the volume of infarction may occur. This might explain some of the variability in outcome even within groups of patients with infarction in the same arterial territory. We are not alone in believing that such MRI studies have the potential to help clinicians make the most accurate prediction of prognosis for individual patients. Pritchard and Grossmann commented that MRI techniques are ‘unique among all imaging methods in their sensitivity to the pathophysiological changes underlying acute stroke’ and are likely to become the investigations of choice in the acute management of stroke.

To give examples of the way in which the accurate localisation of the lesion obtained by these techniques might be used to predict outcome we present three cases. Figures 1–3 show the DWI images taken within 24 h of stroke, of 3 patients with identical TACI-type syndromes presenting with hemiparesis, the PWI and MRA images were normal in each case.
implying spontaneous recanalization so there was no risk of developing further ischaemic damage. The white areas represent acute infarction. The contrast that can be seen between damaged and normal tissue is very easy to see, and this demonstrates how precisely these images can localise cerebral infarction. In case 1 (Fig. 1), the primary motor cortex was involved (thin arrows). Although the subcortical section of the pyramidal tracts was intact (thick arrows), the patient made little motor

Fig. 1 The DWI lesion reveals extensive cortical infarction which involves the primary motor cortex

Fig. 2 The DWI lesion shows extensive subcortical infarction, importantly the posterior limb of the internal capsule, hence motor tract, is involved in the lesion.
FIG. 3 The DWI lesion shows extensive cortical and subcortical infarction, however both the motor cortex and internal capsule are spared.

recovery (Barthel 20 out of 100). In case 2 (Fig. 2), the primary motor cortex was spared (thin arrows), but the subcortical corticospinal tract was damaged (thick arrows), and the patient made little motor recovery (Barthel 15). In case 3 (Fig. 3), with a similar volume infarct to case 1, the primary cortex and the subcortical region carrying the pyramidal tracts were spared (arrows) and the patient made considerable motor recovery (Barthel 80). This patient had some sub-cortical damage, but the rim of non-infarcted tissue indicated by the thick arrow, which is supplied by the anterior choroidal artery, is not infarcted. This type of region can only be identified by techniques with this degree of resolution. Conventional CT scanning can not distinguish between patients with persisting occlusion and spontaneous recanalization and the resolution of infarction of DWI is far beyond that of conventional CT scan imaging; this may explain the relatively small contribution made by CT to prediction of outcome. Thus, although all three patients were clinically indistinguishable, only one of them (case 3) had an intact cortico-spinal tract and this was the patient who made a motor recovery. We suspect that further work using this technique will enable, for the first time, the stroke syndrome to be classified into coherent physiological categories, and that having done so, the logical and expected relationship between damage and outcome will be revealed. Further studies will determine whether this is so, and whether such imaging can reliably predict death, dependency, recovery of individual deficits (e.g. dysphasia and neglect), or even specific activities of daily living, such as walking or transfers.
Until these techniques become widely available, perhaps the information we give patients should be based on the large scale epidemiological studies and the most valid prognostic studies. This means defining the stroke syndrome and routinely measuring the single clinical variables identified as important by previous prognostic studies, such as consciousness, paralysis, continence and neglect. An experienced clinician can then tailor his or her prediction, and refine it as the patient's clinical course is revealed. Even experienced clinicians will be wise to admit that their predictions are fallible. Uncertainty should worry us as clinicians, because if we can not predict the outcome of a disease, then we almost certainly do not know enough about it. The recent developments in neuro-imaging may remedy this by providing adequate information about 'the situation and extent' of the cerebral lesion to enable prognostication to take place along the lines Osler first suggested.

Acknowledgement

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