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Imaging for Prediction of Functional Outcome and Assessment of Recovery in Ischemic Stroke

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Keywords

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Stroke is a leading cause of long-term adult disability worldwide. Only a small proportion of stroke survivors (approximately 14%) achieve full recovery of activities of daily living (ADLs), while 25%-50% require some assistance, and approximately half experience long-term dependency [1]. Prediction of outcome after ischemic stroke therefore is important for setting realistic and attainable treatment goals, informing patients and their relatives properly, facilitating discharge planning, and anticipating possible consequences for home adjustments and community support[2]. Moreover, knowledge of the expected recovery pattern is necessary to assess the effectiveness of new therapeutic interventions and their contribution to recovery and should be applied to select comparable patients populations for treatment trials[3].

A number of standardized measures assess various aspects of stroke outcome and recovery, including quantification of neurologic deficits, functional outcome measures, and quality of life measures. Activities of daily living, including dressing, mobility, and bathing, are assessed most frequently by the Barthel Index (BI[4]) and by the modified Rankin Scale (mRS[5]), but also by the Glasgow Outcome Scale[6], the Functional Independence Measure[7] or other ADL assessment tools[8]. Frequently used measures of quality of life include the Stroke Impact Scale and European Quality of Life Scale (EQ-5D).[9, 10] A considerable number of prognostic stroke studies used the BI and the mRS as the primary outcome measure reached after 3 – 6 months and found that scores on scales assessing severity of neurologic deficits such as the National Institutes of Healt Stroke Scale (NIHSS)[11-13] and Canadian Neurological Scale[14] in acute stroke (i.e. within 72 h) are strongly associated with outcome beyond 3 months[2, 15].

A systemic review of prognostic studies[8] indicated that age and motor weakness were important predictive variables of outcome in addition to stroke severity; however gender and presence of vascular risk factors were not. Employing simple models, a modestly large percentage of patients could be correctly classified with respect to survival and functional recovery (70.4% and 72.9%[12]) and to the severity of impairment on the BI (severe vs. mild neurologic deficits, AUC 0.789 to 0.808 depending on time of assessment 2 days to 5 days,[16]). The addition of more clinical variables and application of more complex models

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improved prediction accuracy only slightly (83.9%[13]). Treatment with recanalization therapies such as intravenous tissue plasminogen activator (IV tPA) is also an important predictor of improved outcome.

Advanced neuroimaging techniques are now widely available for the assessment of stroke. These studies have the potential to improve accuracy of stroke outcome predictive scales, provide valuable insights into the pathophysiology of stroke injury and recovery, and provide biomarkers to test the efficacy of putative therapies. In this review, we discuss the contributions of various neuroimaging studies in predicting recovery and functional outcomes in ischemic stroke patients, and their role in assessing the efficacy of rehabilitation therapies both in clinical trials and in individual patients.

Structural Imaging

Computed Tomography

The most widely used imaging procedure in acute stroke is noncontrast head CT, which allows differentiation between hemorrhagic and ischemic stroke, localization of the lesion, and assists in decision-making regarding administration of potentially risky stroke therapies including thrombolytics. As a measure for quantifying ischemic changes on CT, the Alberta Stroke Program Early Computed Tomography Score (ASPECTS) was developed to evaluate the extent and location of ischemic changes in 10 regions within the territory of the middle cerebral artery (MCA)[17] and has been found to be a reproducible scale that can help to predict functional outcome on mRS at 3 months post-stroke. In combination with age and the severity of neurologic deficits, a subacute ASPECTS of better than 5 had a significant predictive value of greater functional independence at 3 months (R^2=0.701) and 1 year post-stroke (R^2=0.528)[18]. In another large study, initial lesion volume was found to be a strong and independent predictor of stroke outcome in a statistical regression model that also accounts for age and NIHSS. By including the lesion volume as an additive predictive factor, the fraction of unexplained variability could be reduced by 15%[19]. As a consequence, the inclusion of lesion size in predictive models of outcome has the potential to improve stratification of samples and increase power for effect detection in trials of acute therapies and of rehabilitative strategies in ischemic stroke.

Magnetic Resonance Imaging

High resolution structural MRI sequences reproducibly identify even small stroke lesions, but relating the size of lesions to clinical impairment and functional outcome is difficult especially since small lesions of the subcortical white matter or the brainstem can produce disproportionate clinical disturbances[20]. Involvement of the corticospinal tract by the ischemic lesion is a particularly important factor limiting motor recovery[21]. Severe white matter disease may also be an independent predictor of poor functional outcome.[22]

Diffusion-weighted imaging (DWI) provides an early, distinct, and sensitive measure of both the size and location of ischemic brain lesions. DWI is sensitive to the movement of water molecules within the tissue which is reduced in regions of cytotoxic edema during early ischemia. In patients with nonlacunar strokes in the anterior circulation, lesion volume assessed by DWI in addition to age and NIHSS score was an independent predictor of outcome, separating patients with a final BI above or below 85[23]. DWI lesion volume significantly increased power of some, but not all[24], prediction models; however, this effect was not large enough to be clinically important in another analysis[25]. The likelihood of achieving excellent neurological outcome diminished substantially with growth in DWI infarct volume in the first 5 days after ischemic stroke of mild to moderate severity[26]. Some studies have incorporated information on infarct location to predict neurologic deficits.[27, 28]

Diffusion tensor imaging (DTI) permits visualization of white matter pathways in the brain and has been specifically used to demonstrate damage to the corticospinal tract, which is commonly associated with motor impairment in chronic stroke patients[29]. DTI measures may also be used to predict long-term outcome; in one study, the extent of damage to the corticospinal tract following a corona radiata infarct assessed 7 – 30 days after a stroke was related to motor function of the affected hand 6 months later[30, 31]. The damage to the pyramidal tract assessed by fractional anisotropy in DTI progressively decreased in the medulla as well as in proximal portions 1 to 12 weeks after pontine infarction, and these anterograde and retrograde degenerations were accompanied by deterioration in the clinical scales of motor function[32]. The prediction of motor impairment and recovery was improved if not merely the pyramidal tract but also alternative motor fibers were included in the classification of damage[21].

Efficiency of rehabilitative therapy has been related to DTI parameters of individual tracts and tract combinations and may indicate a patient's individual recovery potential and the optimal rehabilitative intervention[33]. Additionally, gains from treatment were related to the degree of injury to specific motor tracts (descending from primary motor cortex, supplementary motor area, dorsal premotor cortex and ventral premotor cortex, respectively), and the damage to these tracts had a greater impact on the therapeutic effect than infarct volume or baseline clinical status[34]. Damage to the posterior limb of the internal capsule within 12 hours of symptom onset correlated well with motor impairment at 30 and 90 days; the sensitivity and specificity of the DTI parameters were superior to lesion volume in the corona radiata or the cortex and to baseline clinical scores[35].

Nonmotor pathways can also be studied by relating their damage to higher brain function, e.g. language performance. Lower fractional anisotropy (FA) values in the superior longitudinal and arcuate fasciculi of the left hemisphere were correlated with decreased ability to repeat spoken language and lower FA values in the arcuate fasciculus were associated with comprehension deficits; these relationships were independent of the degree of damage to cortical areas[36].

All these data stress that the connectivity in networks as assessed by DTI is likely to be more important for outcome and recovery than the extent of the primary structural lesion. However, despite all these promising results, structural neuroimaging neither provides information on the cause of the ischemic lesion and compensatory mechanisms, nor indicates whether or how surviving tissues are working[37]. The functional connectivity between cortical and subcortical components of neural networks determines the capacity for reorganization and recovery. The studies of these measures require modalities for physiologic, molecular, and functional imaging.

Assessment of Brain Blood Supply and Cerebral Perfusion

Ischemic stroke is directly caused by the reduction of tissue blood flow below a critical threshold for a critical period of time. Usually this shortage in blood supply is due to the occlusion of the feeding vessel and the insufficiency of collateral perfusion. Occlusion of a large intracranial vessel, such as the basilar, internal carotid or middle cerebral artery, is associated with higher mortality and more severe permanent deficits and therefore the pathologic vascular state can be expected to contribute predictive value to models of stroke outcome. Retrospective studies of patients undergoing conventional angiography found that basilar and internal carotid artery occlusions had the highest NIHSS scores[38] whereas normal angiograms predicted a good prognosis. In a prospective study, results from CT angiography (CTA) performed within 24 hours of symptom onset were related to outcome after 6 months[39]. Larger vessel occlusion significantly increased 6-month mortality (4.5-fold

increase) and was negatively correlated to good outcome (mRS ≤ two-threefold reduction). In a multivariate analysis, the presence of basilar and internal carotid occlusions independently predicted outcome in addition to age and NIHSS. Inclusion of information from CT angiography contributed significantly more to outcome prediction than the ASPECTS score[40, 41]. Evidence of large vessel occlusion therefore may be crucial for improving outcome by early endovascular interventions. The STOP Stroke study reported that CTA information improved stroke outcome prediction when combined with the NIHSS.[40] In a pooled analysis from all three of the desmoteplase trials, in patients with a visible occlusion on noninvasive vessel imaging at baseline, the desmoteplase groups had greater rates of good clinical response.[42]

The vascular occlusion and its eventual recanalization are decisive for the evolution of tissue damage and for clinical deficits, but the final size of an infarct is also influenced by the extent and quality of collateral circulation to the affected brain area. The presence of robust collateral flow is best visualized by conventional angiography and has been linked to improved clinical outcomes and reduced infarct volumes; in cases receiving thrombolysis, collateralization was a significant univariate predictor in addition to occlusion type and recanalization[43, 44]. CT angiography as a non-invasive alternative has better spatial resolution than transcranial Doppler or MR angiography and can depict leptomeningeal collaterals. Rapid recruitment of sufficient collaterals was related to favorable outcome, whereas patients with diminished sylvian and leptomeningeal collaterals had a greater risk of worsening[45]. Univariate analysis identified the grade of leptomeningeal vascularity as an independent predictor of good outcome[46].

The validity of perfusion parameters obtained by CT or MRI for prediction of long-term outcome has not been accurately established, but some data indicate a weak relationship of PWI lesion size early after the ictus[47] as well as perfusion CT-mismatch[48] and mRS score 3 months after the stroke, confirming early results of the relationship between cerebral blood flow measured with 133 xenon[49] or with 99m Technetium-labeled hexamethylpropyleneamine[50] and final outcome.

Several studies have suggested that ASPECTS applied to CTP is more accurate in predicting outcome compared to NCCT ASPECTS.[51, 52] Location-weighted CTP analysis may be a valuable tool for predicting motor improvement and language improvement.[5354] For multimodal MRI, addition of both DWI and MTT lesion volumes to NIHSS information is superior to NIHSS alone in predicting outcomes.

Penumbral Imaging and Predicting Outcomes and Response to Reperfusion Therapy

A discussion of the approaches to penumbral imaging and its role in selecting patients for reperfusion therapies is beyond the scope of this review. However, a number of prediction scores have been developed and reported in cohorts undergoing reperfusion therapies.

For patients treated with IV tPA within 3 hours of onset, older age, high blood glucose, NIHSS score, and presence of current infarction on imaging were all related to poor outcome.[55] The DRAGON score includes premorbid mRS, age, glucose, onset-to-treatment time, NIHSS score and imaging signs (dense artery or early infarct signs on CT); in a large validation study of patients treated with IV tPA, the score performed well in predicting poor and good outcome (AUC 0.82 and 0.84 respectively).[56] The tool has been adapted for MRI employing a DWI ASPECTS measure.[57] The DEFUSE investigators developed a 5-item scale (age, NIHSS score, infarct volume, white cell count, hyperglycemia) to predict

outcome in patients undergoing IV tPA treatment. When applied to the DEFUSE cohort, the model achieved 83% sensitivity and 86% specificity.[58]

In several clinical trials of reperfusion therapies including EPITHET, the DEFUSE studies, and a study of intravenous tenecteplase, reperfusion demonstrated on perfusion imaging in treated patients was associated with good clinical outcomes. [59-6162] In MR RESCUE, although treatment with embolectomy with first generation devices did not improve outcome compared to standard care, reperfusion at day 7 demonstrated both on perfusion imaging and non-invasive vessel imaging was associated with improved outcomes.[63] The Houston Intra-arterial Therapy 2 (HIAT2) score combining clinical and imaging variables (age, glucose, ASPECTS NIHSS) predicted poor outcome (regardless of reperfusion) at discharge for scores ≥ 5 in patients undergoing intra-arterial therapy [64].

Assessment of Hemorrhagic Transformation

Hemorrhagic transformation (HT), visualized on noncontrast CT or T2*-weighted MRI sequences is a biomarker of potentially poor outcome. GRE is significantly more sensitive to HT than CT or other MRI sequences.[65] Rating scales incorporating the extent of hemorrhage along with measures of neurologic deterioration have shown that the presence of HT, particularly when considered “symptomatic ICH”, is predictive of poor functional outcome. However, compared to other predictive factors, the contribution of symptomatic ICH may be smaller.[66] Of interest, even “asymptomatic HT” appears to be a predictor of poor outcome.[67] A number of baseline imaging biomarkers that are predictive of HT have been reported, including the volume and severity of ischemic injury (measured on DWI, ADC, CBV, or Tmax), [68-73] as well as biomarkers of blood brain permeability.[70, 74]

Role of Functional Imaging in Stroke Patients

Since destroyed tissue usually cannot be replaced or regenerated in the adult human brain, improvement or recovery of neurological deficits can be achieved only by reactivation of functionally disturbed but morphologically preserved areas or by recruitment of alternative pathways within the functional network. These compensatory mechanisms are expressed in altered patterns of blood flow or metabolism at rest and during activation within the functional network involved in a special task, and therefore functional imaging tools can be applied successfully to study the physiological correlates of neuroplasticity and recovery noninvasively after localized brain damage. Neuroimaging studies focused on brain injury and recovery following stroke can include measurements at rest, comparing location and extent to deficit and outcome, and measurement during activation tasks, comparing changes in activation patterns to functional performance. Longitudinal assessments at rest and during activation tasks during the early and later periods following a stroke can demonstrate recruitment and compensatory mechanisms in the functional network responsible for complete or partial recovery of disturbed functions. [75-81].

Motor and Somatosensory Deficits

The degree of motor impairment and the potential for motor recovery depends on the site of the lesion, the combination of lesions in cortical areas and fiber tracts, and the involvement of deep gray structures, e.g. the basal ganglia, thalamus and brainstem. The patterns of altered metabolism and blood flow and the patterns of activation after stimuli or during motor tasks are manifold and reflect the site and extent of the lesion, but they are also dependent on the paradigm of stimulus or task.

While there is a lack of a clear concept of “neuronal plasticity” applicable to recovery from motor stroke due to varying experimental study designs, one recent review concluded that

"motor recovery after stroke depends on a variety of mechanisms including perilesional motor reorganization, use of motor pathways in subcortical structures, use of collateral pathways in the ipsilateral hemisphere, use of collateral pathways in the contralateral hemisphere, or possibly the development of entirely new motor networks"[76]. In most fMRI or PET studies involving active or passive movements, a widespread network of neurons was activated in both hemispheres. While changes in both the damaged and the undamaged hemisphere can be observed, ipsilateral activation of motor cortex is consistently found to be stronger for movement of the paretic fingers after recovery from stroke. In contrast, movements of the unaffected hand (as in normal subjects) are accompanied mainly by activation of the contralateral cerebral cortex. In addition to stronger intensity, the spatial extent of activation in motor cortex is enlarged, and activation on the ipsilateral side is also seen in premotor and insular cortex. These results indicate that recruitment of ipsilateral cortices plays a role in recovery; in one study, the higher the activation in the ipsilesional motor cortex, supplementary motor cortex and insula, the better the recovery 1 year after stroke [82].

It has also been demonstrated that task-oriented arm training increased activation bilaterally in the inferior parietal area, in premotor areas and in the contralateral sensorimotor cortex, suggesting bilateral functional brain reorganization[83]. In summary, newly learned movements after focal cortical injury are represented over larger cortical territories, an effect which appears to be dependent on the intensity of rehabilitative training. It has also been shown that the unaffected hemisphere actually inhibits the generation of a voluntary movement by the paretic hand,[84] and this effect of transcallosal inhibition can be reduced by repetitive transcranial magnetic stimulation (rTMS)[85, 86]. Recovery from infarction is also accompanied by substantial changes in the activity of the proprioceptive systems of the paretic and non-paretic limb, reflecting an interhemispheric shift of attention to proprioceptive stimuli associated with recovery[87].

Post-stroke aphasia

In right-handed individuals with language dominance in the left hemisphere, the left temporo-parietal region is most frequently impaired, and the degree of impairment is related to the severity of aphasia. The functional disturbance as measured by regional cerebral metabolic rate of glucose (rCMRGlc) in speech-relevant brain regions early after stroke has been shown to be predictive of the eventual outcome of aphasia; moreover, the metabolism in the hemisphere outside the infarct was also significantly related to outcome of post-stroke aphasia [88].

Additionally, the functionality of the bihemispheric network has a significant impact on outcome; although the brain recruits right-hemispheric regions for speech-processing when the left-hemispheric centers are impaired, outcome studies have revealed that this strategy is significantly less effective than repair of the speech-relevant network in adults[89]. Patients with subcortical and frontal lesions improved substantially and regained regional left supramarginal temporal gyrus activation at follow-up. Patients with temporal lesions improved only in word comprehension and could not reactivate the left supramarginal temporal gyrus[90-92]. One study demonstrated improved aphasia recovery post-stroke by use of inhibitory repetitive magnetic stimulation (rTMS) on the right which favored recruitment of left-hemispheric language networks [93].

The activation studies in the course of recovery of post-stroke aphasia suggest various mechanisms for the compensation of the lesion within the functional network.

A hierarchy for effective recovery might be deduced:

- Optimal recovery can only be achieved by restoration of the original activation pattern after small brain lesions outside primary centers.
- If primary functional centers are damaged, reduction of collateral inhibition leads to activation of areas around the lesion (intrahemispheric compensation).
- If the ipsilateral network is severely damaged, reduction of transcallosal inhibition causes activation of contralateral homotopic areas, which is usually not as efficient as intrahemispheric compensation. In most instances, the disinhibition of homotopic areas contralateral to the lesion impairs the capacity for recovery – a mechanism, which might be counteracted by rTMS of these contralateral active areas. This approach might open a new therapeutic strategy for post-stroke aphasia.

Conclusions

Prediction measures of recovery and outcome after stroke perform with only modest levels of accuracy if based only on clinical data. Prediction scores can be improved by including morphologic imaging data, where size, location and development of the ischemic lesion is best documented by MRI. In addition to the primary lesion, the involvement of fiber tracts contributes to prognosis and consequently the use of DTI to assess primary and secondary pathways improves prediction of outcome and of therapeutic effects. The recovery of ischemic tissue and the progression of damage are dependent on the quality of blood supply. Therefore, the status of the supplying arteries as well as of collateral flow is not only crucial for determining eligibility for acute interventions, but has also an impact on the potential to integrate areas surrounding the lesion that are not typically part of a functional network into the recovery process. The changes in these functional networks after a localized lesion are assessed by functional imaging methods, which additionally show altered pathways and activated secondary centers related to residual functions and demonstrate changes in activation patterns within these networks with improved performance. These strategies in some instances record activation in secondary centers of a network, e.g. also in homolog contralateral areas, which might be inhibitory to recovery of primary centers. Such findings might have therapeutic consequences e.g. image guided inhibitory stimulation of these areas. In the future, a combination of morphological imaging including DTI of fiber tracts and activation studies during specific tasks might yield the best information on residual function, reserve capacity and prospects for recovery after ischemic stroke.

Prediction of long-term functional outcomes following ischemic stroke is complex; imaging approaches in both the hyperacute and subacute stages provide added value over clinical and treatment prediction variables. In the future, this information, combined with clinical data may be used to guide both acute and recovery therapies and provide valuable prognostic information. Large databases including both clinical and imaging data may be developed to allow prognostic and therapeutic decision-making to be individualized based on specific clinical factors and individual pathophysiology.

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