The CADASIL Scale: A Screening Tool to Select Patients for NOTCH3 Gene Analysis

Cerebral autosomal dominant arteriopathy with subcortical infaracts and leukoencephalopathy (CADASIL) is characterized by migraine, frequently with aura, transient ischemic attacks and strokes, mood disorders, and cognitive decline leading progressively to dementia and disability in the setting of suggestive neuroimaging. Given the variable expression of these parameters among individuals, definitive diagnosis is established by sequencing the whole NOTCH3 gene from a blood sample. The less expensive approach to assess for mutations in small- and medium-sized arteries skin biopsy sample is specific but with variable sensitivity. Pescini and colleagues sought to develop a clinical screen to predict the genetic diagnosis of CADASIL to select patients with a high probability to be affected by the disease and the need for genetic testing. First, they performed a pooled analysis of 15 published CADASIL series to derive a preliminary CADASIL scale. Second, they applied this preliminary scale to patients with genetically established CADASIL (n=61) and NOTCH3-negative patients with a phenotype similar to CADASIL (n=54) that were followed in the authors’ centers. Notably, only data available at the time of disease suspicion, that is, when genetic testing would be considered, were used. Receiver operating characteristic analysis was then performed to identify a cut-off point able to predict the presence of the disease. Third, logistic regression analyses including a third group of patients with small vessel disease (and the variable age at first transient ischemic attack or stroke) were performed to develop the definitive CADASIL scale that included weighted scores for clinical, neuroimaging, and family history parameters. Finally, ad-hoc optimization of the cut-off point was developed. On the basis of this scale (score ranging from 0 to 25), patients scoring ≥15 points should undergo genetic analysis. As the authors point out, this scale will require confirmation and potential further optimization. Despite its limitations, this scale represents a simple screening tool that may aid the nonexpert in his decision making by asking the right questions. See p 2871.

Risk Factors for Intracranial Hemorrhage in Acute Ischemic Stroke Patients Treated With Recombinant Tissue Plasminogen Activator

Intracranial hemorrhage related to the use of tissue plasminogen activator (tPA) remains an important issue in the treatment of acute ischemic stroke. Whiteley and colleagues report a literature review and meta-analysis on studies regarding associations among variables available before treatment with clinically important post-tPA intracerebral hemorrhage (ICH). They identified 55 studies (11 randomized trials and 44 prospective studies) that met their inclusion criteria with a total of 3953 ICHs in 65,264 acute ischemic stroke patients. The analysis examined 43 baseline variables, for each of which there were a median of 136 hemorrhages and a median of 3215 stroke patients treated with tPA. The considered variables included demographic parameters, prestroke medication, stroke severity, imaging characteristics, and laboratory markers. They found moderate and positive associations between post-tPA ICH and older age, renal impairment, congestive heart failure, ischemic heart disease, atrial fibrillation, diabetes mellitus, higher blood glucose, hypertension, antiplatelet use, statin use, higher National Institutes of Health Stroke Scale, higher Alberta Stroke Program Early CT Score, visible lesion on computed tomography, and presence of leukoaraiosis. Smoking was inversely associated with the occurrence of tPA-associated ICH. The presence of microbleeds, use of anticoagulants, and time to treatment were not associated with hemorrhage risk. These results uphold the validity of many previously described risk factors for post-tPA ICH. As the authors point out, these data highlight that no single variable allows for making definite individualized risk predictions—a knowledge that may aid balancing risk versus benefit and aid in the communication with patients and family members. See p 2904.

What Causes Disability After Transient Ischemic Attack and Minor Stroke? Results From the CATCH Study

Mild or rapidly improving symptoms are frequently cited reasons to withhold fibrinolysis in acute stroke. Yet, this practice has been questioned by the worse than expected outcome in these patients. Potential reasons for this discrepancy are manifold but remain to be elucidated. Coutts and colleagues sought to assess predictors of disability in 499 patients with minor stroke and transient ischemic attack (median National Institutes of Health Stroke Scale of 1 at presentation) that were prospectively and consecutively included in the CT And MRI in the Triage of TIA and minor Cerebrovascular events to identify High risk patients (CATCH) study. Patients were excluded if they had a premorbid modified Rankin scale ≥2, received a thrombolytic drug, or had a comorbidity with life expectancy <3 months. At 90 days, patients were reevaluated to assess recurrent vascular events (categorized according to recurrence versus progression of the initial symptom). At 90 days, 15% of patients had a modified Rankin scale of ≥2. Poor outcomes were not related to carotid revascularization complications, anticoagulation, hemorrhagic transformation, or stroke pathogenesis. One patient died of a primary intracerebral hemorrhage. The authors developed 2 multivariate models, which both did not consider recurrent symptoms as a potential predictor. Model 1 included all patients and National Institutes of Health Stroke Scale; model 2 excluded patients with recurrent events and included ongoing symptoms in the ED. The predictors of disability were similar in both models: diabetes mellitus, female sex, baseline National Institutes of Health Stroke Scale, computed tomography/computed tomography angiography metric (model 1) versus diabetes mellitus, female sex, ongoing symptoms in ED, computed tomography/computed tomography angiography metric (model 2). As one would expect, patients with recurrent symptoms had a very high likelihood of a poor outcome. However, most patients (74%) with disability did not have recurrent events, indicating that recurrent events are a very important surrogate for disability, but numerically not the major factor in predicting a disabled outcome. This study highlights the need to elucidate what exactly causes disability in patients without recurrent vascular events. This will be critical for clinical trial design and to provide guidance as to whether fibrinolysis for patients with minor symptoms might be helpful. See p 3018.