Future NEUROLOGY

COMMENTARY

Ischemic stroke subtypes and the implications for stroke management

"The classification in subtypes of ischemic stroke appears therefore to have important pathogenic, clinical and epidemiological implications as well as from a diagnostic and clinical point of view."

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• subtype • stroke • TOAST classification

In their review article entitled "Why identification of stroke syndromes is still important," Kumar and Kaplan affirmed "Within the broad category of brain ischemia, subtypes also vary dramatically in cause: from systemic hypoperfusion to atherosclerotic large artery disease to penetrating artery disease to dissection to emboli arising from the heart valves or atria, to emboli arising from the aorta to paradoxical emboli to occlusion of cerebral and dural sinus veins to hypercoagulability. These subtypes are as different as grapes and watermelons: two substances contained within the large category of fruits" [1].

There is much truth in this picturesque statement since ischemic stroke is far from being a single disease. It combines several clinical syndromes that are sometimes very different, with differing pathophysiology, clinical manifestations, neuroradiological findings and localization. This complexity requires an approach that, despite the limitations of a Linnaean taxonomy approach to biological material, over time has led to various attempts at classification of cerebral ischemia based on clinical and anatomic, and now finally on a pathophysiological basis. The aim of these efforts is likely tied to achieving a classification model that is as close as possible to the phenomenological reality of ischemic stroke in order to improve the diagnostic and therapeutic approach to ischemic stroke, a disease in which these elements are worthy of an implementation of neuroimaging techniques, since the use of systemic and intra-arterial thrombolysis have only partially improved in recent years.

Categorization of subtypes of ischemic stroke has undergone considerable study, and in the past, classifications have been based primarily on risk factor profiles, clinical features of the stroke and the findings of brain imaging studies: computed tomography or MRI, but clinical and brain imaging findings in brain ischemia are not often specific for any particular subtype of ischemic stroke.

In 1993, Adams *et al.* developed a system for the diagnosis of subtype of ischemic stroke that uses components of existing diagnostic schemes for the

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Trial of Org 10172 in Acute Stroke Treatment (TOAST) [2].

The TOAST classification system includes five categories: large-artery atherosclerosis, cardioembolism, small-artery occlusion (lacune), stroke of other determined etiology and stroke of undetermined etiology. Diagnoses are based on clinical features and on data collected by tests such as brain imaging (computed tomography/MRI), cardiac imaging (echocardiography, among others), duplex imaging of extracranial arteries, arteriography and laboratory assessments for a prothrombotic state.

Determining the cause of stroke does influence choices for management and in particular it can have repercussions on epidemiological, pathogenic and therapeutic issues. Anticoagulation therapeutic choice could represent a good example of the importance of precise evaluation of stroke subtypes. The use of adjusted-dose warfarin for stroke patients with atrial fibrillation who do not have significant bleeding risk has been advocated in several professional guidelines [3–6], and the benefit has been demonstrated in clinical practice. However, not all strokes in patients with atrial fibrillation are cardioembolic in origin [7–9], and some evidence suggests that warfarin may not prevent noncardioembolic strokes [10]. It has also been shown that anticoagulation in patients with small-vessel cerebrovascular disease carries a higher risk of intracranial hemorrhage. Thus, it appears very important to consider stroke subtype carefully to avoid starting anticoagulation with antivitamin K drugs.

A recent study by Evans *et al.* including 386 acute stroke patients with atrial fibrillation treated with adjusted-dose warfarin or aspirin had rates of recurrent stroke by subtype and major and minor bleeding complications as main outcome measures [11]. These authors showed that the rate of recurrent stroke was higher but that of major bleeding was lower with aspirin. They also showed that increased stroke rate with aspirin was due predominantly to cardioembolic recurrence in patients presenting initially with cardioembolic stroke. The recurrence rate in aspirin-treated patients who presented with lacunar stroke and atrial fibrillation was similar to that seen in patients receiving warfarin. The findings of this study strongly indicate how determination of stroke subtype may be important in anticoagulation decisions for secondary prevention of stroke.

Stroke subtype may also significantly differ due to the epidemiological relationship with different cerebrovascular factors and some pathophysiological instances such as inflammatory activation degree of the acute phase. Precise classification of stroke also has epidemiologic involvement, and several studies have evaluated the role of cardiovascular risk factors and stroke subtypes.

Our group conducted a study to evaluate cerebrovascular risk factor prevalence in diabetic stroke patients compared with nondiabetics, to analyze whether diabetics have a different prevalence of stroke subtypes as classified by the TOAST classification. We reported that diabetes was associated with lacunar ischemic stroke subtype and with a record of hypertension [12].

Our group also conducted a study to evaluate immune-inflammatory activation in the acute phase of stroke in relation to time of symptom onset, diabetic state and diagnostic subtype. We reported significantly higher plasma levels of cytokines, selectins, adhesion molecules and PAI-1 and diabetic stroke patients exhibited higher plasma levels of PAI-1 compared with nondiabetic patients [13]. Lacunar strokes exhibited significantly lower levels of TNF-α and IL1-β P-selectin and ICAM-1 compared with nonlacunar strokes. Moreover, diabetic patients with lacunar strokes exhibited a minor grade of immune-inflammatory activation of the acute phase at 24–72 h and 7–10 days after stroke onset. The minor grade of immune-inflammatory activation of patients with lacunar strokes, particularly diabetics, could be related to the minor extension of the infarct size, owing to the typical microvascular disease of diabetic subjects which could also explain the better outcome of this subtype of ischemic stroke reported.

In another recent study our group showed that among patients with acute ischemic stroke, patients with cardio-embolic subtype showed significantly higher plasma levels of TNF-α, IL-6 and IL1-β, whereas lacunar subtype showed significantly lower plasma levels of these cytokines [14].

Our study further supports the hypothesis that inflammation may have an important role in the pathogenesis of ischemic strokes, but our findings also suggest a peculiar immune-inflammatory pattern in each subtype of acute ischemic stroke. Patients with cardio-embolic strokes, compared with other subtypes, showed a higher degree of acute neurological deficit

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on admission evaluated by SSS and a higher degree of immune-inflammatory activation of the acute phase. On the other hand in patients with lacunar stroke, compared with other subtypes, we observed a lower degree of acute neurological deficit on admission evaluated by SSS and a lower degree of immune-inflammatory activation of the acute phase. Nevertheless, patients with large artery atherosclerotic stroke (LAAS) subtype showed higher median plasma levels of some immune-inflammatory markers (TNF-α, IL-6 and IL1-β) compared with lacunar subtype, but lower median plasma levels of these biomarkers compared with the cardioembolic-infarct subtype.

Although several intervention trials with ACE-inhibitors, angiotensin receptor blockers, other antihypertensives or statins have been shown, sometimes in primary prevention and mostly in a secondary prevention setting, a significant reduction of stroke incidence, yet few studies, with the exception of some such as SPARCL study [15], used a TOAST subtype oriented analysis. Therefore it is difficult to extrapolate the real benefit of pharmacological prevention strategies against atherothrombotic subtype that is represented by the LAAS and also with regard to lacunar subtype as an expression of lipohyalinosis process which is a further aspect of atherosclerosis. More frequently stroke classification in clinical trials concerns prognosis with terms such as fatal or nonfatal that are less likely to reveal thrombotic or embolic type.

The classification in subtypes of ischemic stroke appears therefore to have important pathogenic, clinical and epidemiological implications as well as from a diagnostic and clinical point of view. Correctly classifying the TOAST subtype in the light of some recent studies also leads to a number of epidemiological and clinical considerations that take on a very important role in diagnostics and therapeutics. Proper assessment of initial stroke subtype in a clinical setting allows physicians to optimize secondary prevention through the appropriate selection of drug (anticoagulant or antiplatelet). The same approach could relate to the decision to use high doses of atorvastatin as indicated by the SPARCL study in the secondary prevention of ischemic stroke. Neither the SPARCL study nor other studies that have evaluated the effectiveness of statins in primary prevention of ischemic stroke have in fact opted for an assessment of the type that could be oriented to identify the subtype likely to show greater efficacy of the therapeutic estimate with high-dose atorvastatin in reducing the recurrence of atherosclerotic strokes (LAAS), unlike the other two types of ischemic stroke identified by the TOAST classification subtype as lacunar and cardioembolic that in the light of the epidemiological studies available so far do not seem to have a background of atherosclerosis. Ischemic stroke is a common multifactorial disease, which is affected by a number of genetic mutations and environmental factors. In a recent study we reported a relationship between pro-inflammatory/anti-inflammatory (1/1 IL-1 variable number tandem repeat of 86 bp) and thrombotic-/fibrinolytic-gene single-nucleotide polymorphisms (CC TPA genotype) and lacunar ischemic stroke that may contribute to delineate a possible stroke risk profile in subjects with cerebrovascular risk factors [16]. Future studies will be addressed to better tailor preventive strategies according to clinical subtypes of stroke to optimize drugs adapted to real thrombotic ischemic events. Each ischemic stroke subtype as reported by some studies is related to inflammation and arterial stiffness in a peculiar way, and to date no study has addressed the effects of secondary prevention with cardiovascular active drugs on these markers in relationship to TOAST subtype, so this topic could represent a possible field of study [17–20].

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