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Advances in cerebrovascular disease research in the last year

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Abstract The following review summarizes the progress in cerebrovascular disease research published in the Journal of Neurology in the last year.

Keywords Cerebrovascular disease · Metabolic syndrome · Carotid stenosis

Cerebrovascular disease is the leading cause of disability and the third of death in industrialized countries. At present, the European Medicines Agency and the US Food and Drug Administration have only approved intravenous alteplase for acute ischemic stroke in the 3-h time window after symptom onset. In daily clinical practice it is only used in approximately about 5% of patients because of contraindications. The European Acute Stroke Study III (ECASS III) trial and the Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Registry (SITS-ISTR) provide more than enough evidence of the efficacy and effectiveness of alteplase within 4.5 h after symptoms onset, although every effort should be made to treat patients as early as possible. Improvement in medical treatment requires a better understanding of ischemic pathophysiology, advances in diagnostic techniques and development of secondary prevention strategies. The following review summarizes the progress in cerebrovascular diseases research published in Journal of Neurology during the past year.

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Biomarkers: understanding the pathophysiology of ischemia

Cerebral ischemia triggers the activation of a cascade of events that generate chemical substances which are potentially measurable in peripheral blood.

The MITICO study (inflammation markers and prediction of post-stroke vascular disease recurrence) was a multi-centered prospective observational study in patients with ischemic stroke not receiving anticoagulation, recruited within 1–3 months from stroke onset designed to assess the prognostic value of markers of inflammation in relation to the risk of recurrence of vascular disease. Castillo et al. [1] demonstrated that baseline values of IL-6 >5 pg/mL and VCAM-1 >1,350 ng/mL increase the risk of new vascular events or vascular death in patients with ischemic stroke 21-fold and 4-fold, respectively.

Tsai et al. [2] evaluated the value of leukocyte adhesion molecules in 65 acute ischemic stroke patients and 60 controls, showing that the expression of leukocyte adhesion molecules on admission is significantly increased in patients with acute ischemic stroke. This prospective study found that higher neutrophil PSGL-1 expression on day 1 is associated with a higher risk for early neurologic deterioration (END) and that monocyte Mac-1 expression reflects the severity of ischemic stroke.

Elevated serum levels of C-reactive protein (CRP) are found in up to three quarters of patients with ischemic stroke and may reflect a systemic inflammatory response, the extent of tissue injury, or concurrent infections. den Hertog et al. [3] studied the relation between CRP values and poor outcome (mRS > 2) or death at 3 months in 561 patients within 12 h of ischemic stroke onset that participated in the Paracetamol (Acetaminophen) In Stroke (PAIS) trial. Patients with CRP levels ≥7 mg/L more often

had a poor outcome (57 vs. 42%; $p = 0.006$) or died (23 vs. 13%; $p = 0.0007$) than patients with lower CRP levels. Adjustment for potential confounders did not change these results. They conclude that C-reactive protein in the very early phase of acute ischemic stroke is associated with poor outcome and death.

Oxidative stress is a major contributor to brain damage in patients with ischemic stroke, mediated in part by over expression of matrix metalloproteinase 9 (MMP-9) after cerebral ischemia. Uric acid (UA) is a potent endogenous antioxidant molecule that in experimental ischemia in rats is neuroprotective. Amaro et al. [4] evaluated in a pilot, double-blind, randomized and controlled study of 24 patients with acute stroke treated with rtPA (<3 h) whether treatment with UA decreased the levels of MMP-9. Total matrix metalloproteinase (tMMP)-9 and active (aMMP-9) levels were measured in serum at baseline (<3 h), at the end of study treatment infusion (<5.5 h, T1), and at 48 h. UA treatment was associated with reduced levels of aMMP-9 at T1 ($p < 0.02$) in multivariate models adjusted for age, NIHSS score, and baseline aMMP-9 levels. Lower increments of aMMP-9 were associated with better outcome at 3 months.

A phase III multicentre, interventional, randomized, double-blind and vehicle-controlled efficacy study with parallel assignment (1:1) to determine whether the combined treatment with uric acid and rtPA is superior to rtPA alone in terms of clinical efficacy in acute ischemic stroke patients treated within the first 4.5 h of onset of symptoms is underway.

Metabolic syndrome: a risk factor for ischemic and hemorrhagic stroke

The metabolic syndrome (MetS) is a constellation of interrelated metabolic abnormalities. According to the updated ATP III criteria, MetS requires the presence of at least three of the following symptoms: (1) blood pressure of at least 130/85 mmHg or treated hypertension; (2) serum triglyceride ≥150 mg/dL (1.7 mmol/L); (3) HDL cholesterol of <40 mg/dL (1.03 mmol/L) in men and <50 mg/dL (1.29 mmol/L) in women; (4) fasting glucose of ≥100 mg/dL (5.6 mmol/L) or previously diagnosed with type 2 diabetes; and (5) central obesity, waist circumference greater than 102 cm in men and 88 cm in women (90 cm and 80 cm according to the ethnic criteria for Asians, respectively). American Stroke Association guidelines for primary prevention of stroke categorize MetS as a less well-documented risk factor to increase all cause cardiovascular morbidity and mortality.

Zhang et al. [5] analyzed the prevalence of MetS and incidental stroke in 2,173 Chinese patients aged over 45 years, without a history of stroke, followed for 5 years. Women had a higher prevalence rate of metabolic syndrome than men (26 vs. 19%). As the number of MetS components increased, HRs for stroke increased significantly, up to 5.1 (95% CI: 1.9–7.4) for ischemic stroke and 3.3 (95% CI: 1.7–5.7) for hemorrhagic stroke. Abdominal obesity had the highest HR (2.12, $p < 0.001$) for ischemic stroke and high blood pressure for hemorrhagic stroke (2.17, $p < 0.001$). After 5-year follow-up survival rates of stroke events were 94.2% among those with MetS and 96.9% among those without. As the number of MetS components increased, survival rates decreased progressively, from 99.6% for individuals with none of the components to 90.1% for those with 4–5 components. The results showed that MetS is highly prevalent among the Chinese adult population and is associated with an increased risk for both ischemic and hemorrhagic stroke.

Kwon et al. [6] evaluated association of MetS with silent brain infarction (SBI) in 1,254 neurologically healthy people older than 65 years. SBI on MR images were found in 15.7% patients, 50.3% had a single SBI and most infarcts (70.5%) were located in the white matter (corona radiata, internal capsule, centrum semiovale, and subcortical white matter). Age was significantly related to the prevalence of SBI, with an OR of 1.09 per year of age. The prevalence of MetS was significantly higher in the SBI group (57.9%) than in subjects without SBI (45.2%). After adjusting for potential confounders the OR of MetS was 1.68 (95% CI: 1.15–2.44). The component of MetS that showed the strongest effect was elevated blood pressure (OR 1.89, 95% CI: 1.23–2.91). Compared with people without MetS components, people with a much higher number of MetS components had a trend towards more SBIs after adjustment for other risk factors (one component: OR 0.87; two components: OR 1.20; three components: OR 1.58; four components: OR 1.89; five components: OR 2.33, $p = 0.03$). This study demonstrates that MetS is associated with SBI independently of traditional cardiovascular risk factors in elderly people. The positive trend between the number of MetS components and SBI could be used as a diagnostic tool to predict and prevent future strokes.

Carotid artery disease: difference between symptomatic and asymptomatic

Carotid stenosis is an increasingly common pathology in clinical practice because of the availability of noninvasive imaging studies. Differentiation between symptomatic and asymptomatic disease is critical for treatment because the natural history differs between them. Class I evidence

shows that carotid endarterectomy (CEA) is effective in preventing ipsilateral ischemic events in patients with symptomatic moderate and high-grade stenosis but in patients with asymptomatic stenosis the benefit is marginal. Patients with carotid artery stenosis are considered symptomatic if they have transient or permanent focal neurologic symptoms related to the ipsilateral retina or the cerebral hemisphere, but cognition and neuropsychological status are not commonly considered or evaluated.

Landgraff et al. [7] evaluated cognitive and physical performance in 79 patients with asymptomatic carotid artery stenosis of moderate and severe degrees or occlusion. Cognition was assessed via the repeatable battery for the assessment of neuropsychological status (RBANS) and the executive interview (EXIT). Physical performance was assessed via the physical performance test (PPT) and the Lawton instrumental activities of daily living (IADL). Analysis revealed that 90% of the patients were deficient in the visuospatial/constructional domain. In particular, patients in the severe stenosis group were deficient in all of the cognitive domains assessed, with the exception of language, and patients with occlusion showed deficits in all domains except immediate memory. This observational study indicates that asymptomatic patients may not be truly asymptomatic and suggests that neuropsychological assessment of high level cognitive skills and measure of physical abilities should be included in the clinical examination of patients with asymptomatic carotid artery disease.

The prognosis and management of patients with bilateral occlusion of the ICA is limited by the small numbers of patients and short follow up in the majority of studies; therefore, the optimal treatment is unknown. Persoon et al. [8] prospectively studied 57 consecutive patients (46 men; mean age 60 $\pm$ 9 years) with bilateral ICA occlusion that had unilateral transient or moderately disabling (mRS$\leq$3) cerebral or retinal ischemic symptoms and followed-up for a mean of 5.9 years. Four patients had a recurrent ischemic stroke (two ipsilateral and two fatal stroke) resulting in an annual stroke rate of 1.2% (95% CI: 0.3–3.1); risk factors could not be identified. Eighteen patients suffered a stroke, myocardial infarction or vascular death with an annual rate for major vascular events of 5.3% (95% CI: 3.1–8.3). Age and a history of ischemic heart disease were significant risk factors for future vascular events. This study shows that patients with transient or moderately disabling cerebral or retinal ischemic symptoms associated with bilateral ICA occlusion have a relatively low risk of recurrent ischemic stroke and a risk of any major vascular event that is comparable to this risk in patients with TIA or stroke in general, and suggests that only medical treatment and control of risk factors are justified in these patients.

Neuroradiology to quantify ischemia, its causes and prevent recurrences

The Alberta Stroke Program Early CT Score (ASPECTS) was developed to offer the reliability and utility of a standard CT examination with a reproducible grading system to assess early ischemic changes (<3 h from symptom onset) on pre-thrombolysis CT in patients with anterior circulation acute ischemic stroke. Tei et al. [9] evaluated the usefulness of newly developed posterior circulation (pc-ASPECTS) on DWI in predicting functional outcome. In this scoring system 1 point was subtracting for each high-intensity lesion observed in DWI in the left or right thalamus, cerebellum or posterior cerebral artery, and 2 points for each high-intensity lesion observed in any part of the midbrain or pons. A pc-ASPECTS score of 10 indicates the absence of visible posterior circulation ischemia. In 132 patients with acute posterior circulation ischemic stroke 12–36 h after onset (isolated medullary infarction were excluded), they found that according to the ROC analysis, the optimal cutoff score of predicting favorable outcome (mSR 0–2) at 3 months for pc-ASPECTS was >7 (sensitivity 0.74, specificity 0.82, positive predictive value 0.41, negative predictive value 0.95) and for NIHSS was <5 (sensitivity 0.53, specificity 0.94, positive predictive value 0.85, negative predictive value 0.73).

The main purpose of etiologic subtype classification of stroke is to apply the appropriate treatment and determine prognostic factors. On certain occasions some patients have clinical or radiological features of embolic stroke, but there is no evidence of a cardioembolic source. Ko et al. [10] compared the prevalence of high-risk aortic atherosclerotic disease (AAD), detected by a 64-multidetector row computed tomography study (ECG-gated MDCT), in patients who were clinically or radiologically assumed to have had an embolic stroke but had no evident cardioembolic source (possibly embolic stroke or PES) and in those with acute ischemic stroke attributed to non-embolic cause (NES) who underwent MDCT to screen for coronary heart disease. High-risk AAD was defined if aortic plaque met at least one of the following: (1) at least 4 mm thick adjacent to the aortic wall with transverse projection, (2) ulcerated plaque, or (3) vulnerable plaque (soft plaque). The prevalence of high-risk AAD in this study was 38.0% in the PES group (55 patients) and 13.2% in the NES (106 patients) group ($p < 0.01$). Multivariate logistic regression revealed that each component of high-risk AAD was an independent risk factor for embolic stroke. Furthermore, the risk increased with the increase in plaque thickness; the adjusted OR of plaque thickness of 1–3.9 mm was 2.42 and that of more than 4 mm was 5.98 compared to a plaque thickness of less than 1 mm. Thirty-five patients underwent

both MDCT and TEE. Compared to TEE, MDCT seems to be much more useful in measuring the thickness of plaque, discovering ulceration, and examining its components. These findings suggest that the under diagnosis of AAD may explain much of the undetermined etiology in the TOAST classification, and MDCT may be useful to improve stroke subtype classification.

Patients who suffer an initial ischemic stroke or transient ischemic attack are at risk for recurrent strokes. The risk of a recurrent cerebrovascular event is highest in the first month (4%) and year (12%) after a stroke; therefore, the recognition of risk factors for early recurrence is important to help patient management. Roquer et al. [11] in a retrospective review of BASICMAR (stroke register designed as a tool to study epidemiological data of stroke in a hospital based population of a single centre in Barcelona, with a population of approximately 300,000 inhabitants) analyzed the association between different brain MRI–DWI patterns and higher risk of stroke recurrence in 253 patients with mild-moderate stroke (NIHSS 1–7). In long-term follow-up of 6–36 months, 38 patients (15.0%) suffered a stroke recurrence. Patients with multiple lesions had greater risk of recurrence than those with single lesions (28.2 vs. 9.9%), patients with single cortical lesions had higher risk than those with deep lesions (14.3 vs. 6.7%), and patients with multiple DWI in different territories or different age had the highest recurrence rate (30.6%) compared to patients with single lesions. Cox regression analysis adjusted by possible confounders, showed that for pattern 1 the OR for recurrence was 2.49 (95% CI: 1.27–4.89); for pattern 2, OR: 1.99 (95% CI: 0.74–5.37); and for pattern 3, OR: 2.85 (95% CI: 1.31–6.15). These findings suggest that brain MRI–DWI patterns assessed in the acute phase of mild-moderate stroke are useful to identify those patients at high risk of recurrence mainly during the first 6 months after stroke.

Quality of life and rehabilitation

Malignant middle cerebral artery (MMCA) infarctions are still one of the most devastating forms of ischemic stroke, with a mortality of up to 80% under medical treatment. Over the last few years, results from randomized controlled trials and their pooled analyses have provided evidence that an early decompressive hemicraniectomy (DH) leads to a substantial decrease in mortality and improves functional outcome. The number needed to treat (NNT) for survival was 2, and for a mRS score of $\leq$3, it was 4. However, there are still important ethical concerns about functional outcome in surviving patients.

Benejam et al. [12] examine quality of life (QoL) and neurobehavioral deficits in 19 (14 right) patients with MMCA and DH at 6 months after stroke. The Sickness Impact Profile (SIP) was used to assess QoL, behavioral changes were evaluated with the Frontal Behavioral Inventory and the Beck Depression Inventory. Patients and relatives were asked if, knowing the present outcome, they would agree again to a DH. Depressive symptoms were present in 50% of the patients. No significant differences in QoL or functional outcome were found between patients with right- or left-sided infarctions. The most frequent neurobehavioral symptoms were decreased speech output, apathy, reduced spontaneity, and irritability. One of the most important conclusions is that 79% of surviving patients and 95% of caregivers would again give consent to hemicraniectomy.

It has been suggested that serotonergic agents may improve motor recovery, independently of their antidepressant action, by modulating cerebral sensory-motor activation. Transcranial magnetic stimulation (TMS) permits evaluation in vivo of the motor impairment of pyramidal tracts and motor excitability in central nervous system lesions. Acler et al. [13] investigated the effect of citalopram, a selective serotonergic action drug, in motor excitability during motor recovery in patients with stroke. Twenty consecutive patients after unilateral ischemic stroke in the territory of the middle cerebral artery were randomly assigned to citalopram 10 mg/day or placebo before rehabilitation. Antidepressive treatment lasted at least 4 months, TMS recording was tested before and 1 month after beginning drug treatment. Patients treated by the serotonergic drug exhibited a decrease of excitability over unaffected hemisphere and better clinical improvement (measured by NIHSS) without notable side effects. No differences were observed between the affected hemispheres. The possibility of acting on the disinhibition of the unaffected hemisphere motor areas represents a new clinical possibility in the rehabilitation of stroke patients.

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