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Review article

Stroke and Age-Brain barrier : how many bricks in the wall ?

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Abstract

Although older people contribute more and more to the increasing social burden of stroke, they are often excluded from potentially effective treatments in clinical practice. With the aim to separate myth from reality, we have examined the barriers preventing such therapies (with reference to atrial fibrillation, thrombolysis, carotid stenosis and patent foramen ovale) in the elderly. We conclude that elevated age alone should not be considered an exclusion criterion and both stroke physicians and researchers should make efforts to greatly improve management of these patients.

Key words : Stroke ; atrial fibrillation ; thrombolysis ; carotid stenosis ; patent foramen ovale.

In Western Countries stroke is the leading cause of disability and the third of mortality. Stroke prevalence and incidence rise with age, and aging of the population is estimated to double stroke mortality by 2020 (Warlow *et al.*, 2003) ; the social burden of the increasing stroke-related disabilty in the elderly is also a major health problem. Thus prevention and management of stroke in elderly patients are among the most challenging issues for stroke experts and health authorities in the next years. The bulk of evidence supporting safe and efficacious treatments for "stroke", however, is at present not easily translated into clinical practice for "elderly stroke patients" (in particular, patients > 80 years old). As a matter of fact, their exclusion from, or limited inclusion in most clinical trials and the higher risk perceived by some physicians (due to the impact of comorbidity on outcome or just because "senectus ipsa morbus est" – as written by Publius Terentius Afer in 161 a.C.n.), have created an "age-brain barrier" which may exclude them from optimal treatment. With the aim to separate myth from reality, we like to focus on some relevant, recently debated age-watershed topics : atrial fibrillation, thrombolysis, carotid stenosis and patent foramen ovale.

Prevalence of *atrial fibrillation* increases with age, affecting approximately 10% of patients over the age of 80 years. Although the use of warfarin in the elderly has been increasing, fewer than half of eligible patients take warfarin and elevated age represents one of the main barriers to anticoagulation (Lane *et al.*, 2008). Because of the higher thrombotic risk in untreated patients and the higher haemorrhagic risk in the treated ones, the question is : to treat or not to treat ? It is necessary to "tailor" therapy for each patient individually comparing the risk of ischaemic stroke with that of bleeding (Strong *et al.*, 2007). The CHADS2 risk-stratification scheme, based on a clinical history of heart failure, hypertension, age > 75, diabetes, or prior stroke, is a useful clinical tool to identify patients likely to benefit from warfarin, distinguishing these patients from patients at lower risk for whom aspirin is sufficient. On the other hand, risk factors for systemic bleeding (such as ulcerative gastrointestinal disease, certain neoplasms and coagulopathies – due to haematologic causes or severe liver disease) and intracerebral hemorrhage (anticoagulation intensity, hypertension, age, and previous stroke or cerebrovascular disease) are not rare in elderly patients and should be considered with caution. Moreover, high-resolution brain imaging techniques allow to identify further risk factors for intracerebral haemorrhage (both spontaneous and associated with antiplatelet/anticoagulant drugs) such as cerebral amyloid angiopathy and leukoaraiosis. The absolute number of cases of intracerebral haemorrhage is expected to increase in the future because the proportion of cases occurring at 75 years of age or over increases, partly due to the rising number of elderly patients with antithrombotic and anticoagulant drugs-induced haemorrhagic stroke (Flaherty *et al.*, 2007). This, however, should not discourage physicians a priori : prevention of

ischaemic stroke with these treatments remains a key-goal for the future (Kjellström *et al.*, 2007).

Thrombolysis with alteplase (rt-PA), which is the most effective acute ischaemic stroke treatment (Hacke *et al.*, 2004), cannot be delivered to patients aged > 80 years in clinical routine practice according to the SITS-MOST selection criteria (Wahlgren *et al.*, 2007) because of a "perceived" higher risk of symptomatic haemorragic transformation of the ischemic lesion. However, despite the restrictions rising from this huge European observational study (6483 patients), it is worth underlining that the criteria proposed in the most recent American guidelines (Adams *et al.*, 2007) define no upper age limit. They are based on the results of a randomized trial (National Institute of Neurological Disorders and Stroke - NINDS rt-PA Stroke Trial), which in a post-hoc subgroup analysis showed no significant difference in the benefit from rt-PA among subgroups of patients categorized according to age (The NINDS t-PA Stroke Study Group, 1997). Unfortunately, the low number of patients older than 80 years of age included in randomized trials of intravenous thrombolysis has not allowed definitive conclusions, and only off-label studies (Sylaja *et al.*, 2006 ; Zeevi *et al.*, 2006) were able to show that early treatment with rtPA in carefully selected elderly patients (with ischemic stroke from any cause) is actually both as safe and efficacious as in younger patients. In conclusion, age alone should not be perceived as an exclusion criteria for thrombolysis but a dedicated randomized trial seems highly desirable in order to define more precisely its implementation in routine clinical practice.

As for *carotid stenosis*, which accounts for about one third of ischaemic strokes, the potential management strategies are multiple (carotid endarterectomy, CEA ; carotid stenting, CAS ; medical therapy) and raise the same question : what is the best option in the elderly ? In particular, is endarterectomy at higher risk than other less invasive options ? In the review by Narins et al. (Narins *et al.*, 2006) advanced age alone should not be a criterion for favouring CAS instead of CEA, in the absence of other comorbid or specific conditions (high carotid bifurcation, prior neck radiation therapy, recurrent stenosis, prior radical neck surgery, neck immobility, tracheostomy stoma, significant cardiac or pulmonary disease, contralateral recurrent laryngeal nerve dysfunction). In fact, although no direct comparative trials of CAS vs CEA have been undertaken in the elderly, retrospective data suggest that CEA may be preferable to CAS among octogenarians requiring carotid revascularization. Periprocedural complications among elderly patients undergoing CAS can occur despite the use of embolic protection and their etiology is not completely understood. It has been noted that aortic arch tortuosity and calcification become more common with advanced age, thus increasing the likelihood of carotid atheroemboli from the aorta during catheter manipulation (Hobson *et al.*, 2004). The elderly also seem to be at higher risk for clinically significant problems related to baroreceptor-mediated bradycardia and hypotension, commonly seen with distention of the carotid bulb during stent deployment (Mlekusch *et al.*, 2003). Moreover, special caution is advisable for the subgroup of the very old : because of the restricted life expectancy, the risks and benefits of undertaking any form of carotid revascularization need to be weighed with care, especially if the patient is asymptomatic, considering the low (2%-3%) annual risk of stroke with conservative nonoperative treatment (Alamowitch *et al.*, 2001).

Finally, Handke *et al.* (Handke *et al.*, 2007) have recently underscored that the association between a *patent foramen ovale* and cryptogenic stroke may also occur in "older patients" and not only in young patients as previously shown by others (Overell *et al.,* 2000). However, the diagnostic criteria, which are essential to define the association, are not used homogeneously and in this study the "older patients" group (mean age, 68+/-7 years) to which the conclusions apply, does not represent the huge number of "elderly" stroke patients managed in routine clinical practice. The barrier against a possible closure of a PFO in the elderly is thus represented by the fundamental necessity to prove its pathogenetic role in these patients via large, rigorous studies. If the causal relationship can be proven, it would offer several new therapeutic options for the secondary prevention of stroke in older patients, both medical and surgical.

Taken together, the above-mentioned data underlines that elevated age alone should not be an absolute barrier for efficacious stroke treatments to be delivered, and we are convinced that future research will help to definitely destroy all the bricks of this wall.

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