Reducing post-stroke disability in diabetic patients

Y. Samson

APHP Urgences Cérébro-Vasculaires Salpêtrière, Groupe Hospitalier Pitié-Salpêtrière,
47-83, boulevard de l’Hôpital, 75013 Paris France, and UPMC Paris Universités, France

Abstract

Stroke is the main cause of acquired disability in adults and is particularly frequent in diabetic patients. Recent data have shown that stroke-related disability may be substantially reduced by emergency treatment of acute stroke in dedicated stroke units and by rapid management of transient ischaemic attack (TIA) and minor strokes, which remain too often neglected. Simple clinical scores have been developed to improve pre-hospital diagnosis of acute stroke and risk estimation in patients with TIA or minor stroke. They are simple enough to be adapted in patient education programs and stroke education may reduce stroke-related disability by increasing the number of patients immediately seeking appropriate stroke care. Immediate access to diffusion MRI and intra-cranial MR angiography further improves diagnosis and risk estimation in TIA and minor stroke. Urgent investigations should also include systematic non-invasive and high quality detection of severe carotid stenosis, which requires rapid endarterectomy, and of permanent or paroxysmal atrial fibrillation (AF), which requires oral anticoagulation.

© 2010 Elsevier Masson SAS. All rights reserved.

Keywords: Diabetes; Stroke; TIA; Patient education; Thrombolysis; Endarterectomy; Atrial fibrillation; Review

1. Introduction

Stroke occurs frequently in diabetic patients [1], and stroke patients often have diabetes [2]. In a population-based study with a 20-year follow-up [3], stroke occurred in 27% of the patients with type 2 diabetes mellitus (DM), and 37% of patients had previously known or newly diagnosed DM in a series of 286 consecutive acute stroke patients [2]. Furthermore, stroke is also more severe in diabetic patients and this well-known association has been recently confirmed in the SITS-ISTR registry, which included more than 16,000 thrombolysed patients [4]. The adjusted OR for mortality was 1.31 (1.12-1.53) in patients with history of DM and the adjusted OR for independence was 0.83 (0.73-0.94). Thus an important goal would be to reduce the post-stroke disability in diabetic patients.

The first strategy is pharmacological and will be detailed elsewhere. It relies on tight post-stroke glycaemic control.
There is growing evidence suggesting that even mild hyper- 
glycaemia is toxic in acute stroke and that early and strict 
control of serum glucose levels within the therapeutic window 
may decrease infarct growth [5]. This hypothesis is currently 
being tested in several randomised trials, which may turn out 
to be positive if strict euglycaemia is achieved fast enough 
(within 3-6 hours post-stroke) and hypoglycaemic episodes 
are avoided [6].

We will focus here on a “knowledge-based” strategy. All 
recent advances in stroke care emphasize emergency access 
to dedicated stroke units as the major factor of therapeutic 
efficiency. Unfortunately, many stroke patients do not receive 
augate emergency care. This is partly explained by insufficient 
medical resources, but the number of stroke units is 
rapidly increasing. There is also a lack of public knowledge 
of stroke symptoms and the course of action to take when 
stroke is suspected [7]. There is finally a lack of medical 
knowledge of new methods of triaging transient ischaemic 
attacks (TIA) and mini-strokes according to the subsequent risk 
of stroke [8]. Since diabetic patients are at very high risk of 
stroke and since diabetologists have a long experience in patient 
education, we believe that the “diabetes community” could be 
an excellent target for testing the efficiency of improvement 
in stroke knowledge for reducing stroke disability. We will 
successively consider potential thrombolysis candidates and 
TIA and mini stroke.

2. Thrombolysis candidates

Thrombolysis is an efficient treatment of ischemic stroke 
but remains underused: about 3% of stroke patients in France. 
One of the reasons is the very short therapeutic window [7]. 
The treatment needs to be initiated within 4.5 hours after stroke 
onset. Moreover, the efficiency decreases sharply with time. 
The number of patients needed for treatment in order to have 
one more patient returning to normal life at three months is 
4.5 during the first 90 min, 9 during the 90 min-3 hour period, 
and 14 between 3 and 4.5 hours [9]. Therefore, stroke-related 
disability can be reduced by increasing the number of patients 
treated and even more by reducing treatment delay. In the 
SITS-most registry, 11% of the patients had already been 
treated within 90 minutes [10]. To increase this proportion, 
it is necessary to set a one hour maximum delay between 
stroke onset and admission in a well organized stroke unit. 
Therefore, each minute and each second count.

There are various modes of organization, but all efficient 
ones have organized direct access to the stroke unit via an 
emergency call system [7]. In Newcastle on Tyne, England, 
the patients who called the emergency medical services arrived 
within one hour at the stroke unit in 27% of cases, compared 
to 3% of those who contacted their general practitioner or went 
directly to the hospital emergency department [11]. We also 
believe that the development of thrombolysis telemedicine 
networks will be indispensable for increasing the number of 
treated patients and reducing treatment delay, not only in remote geographic areas but also large, traffic-congested urban 
centers. This should be given a very high priority in stroke care organization since the safety and efficiency of 
telethrombolysis is now well established [12].

Efficient treatment of acute stroke however requires hat 
the patient or the bystanders recognize the stroke and act in an 
appropriate way. Mass media campaigns are efficient, but they 
are expensive and their effect diminishes after a few months. 
In addition, we still have questions as to what extent public 
education really influences people behaviour [7]. Focusing on 
high-risk populations may be a cost-effective strategy, and we 
believe that, given the high risk of stroke in diabetic patients, 
diabetic education programs should include stroke education.

Simple and repeated messages are likely to be the most 
efficient. They should focus on three issues: 1) Stroke is an 
emergency; 2) In case of stroke, look at your watch, note the 
time of stroke onset, and immediately contact the 
emergency medical services (in France dial 15). This message 
is likely to be efficient since the word “stroke” is already 
one of the most used by patients or bystanders in emergency 
medical service calls [13]; 3) Increase knowledge of stroke 
symptoms. We advocate the use of the “FAST” method, 
which is a simple and efficient method of pre-hospital stroke 
diagnosis [11]. FAST stand for Facial paresis, Arm drift, 
Speech abnormalities, and Time. Systematic use of the FAST 
questions improves stroke detection rate in paramedics and 
ambulance dispatchers. It also improves knowledge of stroke 
symptoms in the public, and is increasingly popularized by 
media campaigns in many countries. Even if FAST sensitivity 
is not perfect, it is well suited for thrombolysis screening since 
FAST-negative strokes are unlikely to reach the minimum 
level of severity required to consider thrombolysis, given the 
risk of symptomatic haemorrhage. In summary, in addition to 
primary prevention in diabetic education programs, teaching 
the concept of stroke emergency, the need for an immediate 
emergency medical service call and the FAST knowledge of 
stroke symptoms may be effective ways for reducing stroke 
disability in this high-risk population.

3. TIA’s and mini strokes

Patients with TIA or mini strokes do not always seek rapid 
medical attention, and even when they do, they often wait 
weeks or months before being investigated and treated. For 
example, in the Oxford population-based study, only three per 
cent of the endarterectomies were performed within 2 weeks 
of the presenting event, and only 43% within the first 12 
weeks [14]. This is worrying since in the randomised trials, 
the number of patients needed to treat in order to prevent one 
stroke in 5 years was 5 for those randomised within 2 weeks 
and 125 for those randomised after 12 weeks [15].

There is a very low level of public knowledge on TIA, 
and the medical community has until recently underestimated 
the risk of early recurrent stroke after a TIA or a mini-stroke, 
as well as the benefit of emergency treatment in specialized
centres [8]. The high risk of early recurrent stroke after TIA and mini stroke was first demonstrated in patients with severe carotid stenosis. In the patients of the Oxford population study with ≥ 50% carotid stenosis, the risk of stroke prior to endarterectomy was 21% at 2 weeks and 32% at 12 weeks [14]; in addition, as already stated, in randomized clinical trials there is a 25-fold decrease in the benefits of endarterectomy when randomisation is done more than 3 months after the index event [15].

3.1. The ABCD² score

Prognosis scores have shown that the risk of recurrent stroke is not only related to the underlying disease but also to very simple clinical characteristics of the TIA or minor stroke. Among these scores, the ABCD² score has become widely used [16]. This 7-point score is based on: Age ≥ 60 years: 1 pt; Blood Pressure ≥ 140/90 at the first measurement after index event occurrence: 1 pt; Clinical Features: unilateral weakness: 2 pts, speech impairment without weakness: 1 pt; duration ≥ 60 min: 2 pts, 10-59 min: 1 pt; and diabetes 1 pt. It was developed and validated in four independent groups of patients (n = 2893) in the USA and UK, and it has been shown to be highly predictive of the risk of recurrent stroke after seeking medical attention for possible TIA. In the original study [16], the risk of stroke at 48 h was 1% in the low-risk group (ABCD² < 4; 34% of patients), 4.1% in the moderate-risk group (ABCD² 4-5; 45% of patients) and 8.1% in the high-risk group (ABCD² ≥ 5; 21% of patients). The risk of stroke at 3 months was 3.1%, 9.8%, and 17.8% in these 3 groups. Another important finding was that the predictive value was similar in patients with a confirmed diagnosis of TIA by a neurologist and those thought not to have had a TIA. The ABCD² score also predicts the risk of very early recurrent stroke. In a recent study [17], the stroke rate at 24 h was 2% with a score < 5 and 10% with a score ≥ 5. Such a high rate suggests that patients with high ABCD² scores should be managed with almost the same degree of emergency attention as the thrombolysis candidates. However, patients with a low ABCD² score still have a high 3% risk of stroke at 3 months, and therefore should also undergo rapid investigation. This is supported by recent data of the Bichat group that found that 20% of the patients with an ABCD² < 4 had an underlying disease requiring immediate admission such as atrial fibrillation (AF) or severe carotid or intracranial arterial stenosis; they recommended EKG and carotid imaging within 24 hours after postponing a complete TIA investigation [18].

Urgent assessment and treatment markedly reduce the risk of subsequent stroke. In the EXPRESS study [19], the 90-day risk of stroke fell from 10.3% to 2.1%, while the median delay for assessment fell from 3 days to less than 1 day and treatment initiation from 20 to 1 day. In the SOS-TIA report [20], the 90-day stroke rate was 1.2%, whereas the predicted rate from the ABCD² score was 6%. A systematic review found that the lower risk of recurrent stroke was seen in studies of emergency treatment in specialist stroke services (0.9%) and the highest in population-based studies without urgent treatment (11%) [21].

In summary, the ABCD³ score may be considered as “the FAST score of TIA and mini stroke”. Patients with ABCD² scores ≥ 4 should be admitted as soon as possible in a stroke unit and considered as potential thrombolysis candidates in case of early recurrent stroke during the first 24-48 hours. Patients with lower scores should ideally have access to MRI, carotid imaging and EKG within 24 hours. The diabetic community should generalize the use of the ABCD² score, and diabetic education programs may consider the fact that any hypertensive diabetic patient ≥ 60 years with transient unilateral weakness or speech impairment will likely have an ABCD² score ≥ 4 and should be admitted as soon as possible in a stroke unit.

3.2. MRI

The recent American Heart Association/American Stroke Association (AHA/ASA) guidelines stated among the Class 1 recommendations that “patients with suspected TIA should be evaluated as soon as possible after an event” and that “MRI, including DWI (diffusion weighted imaging) is the preferred brain diagnostic imaging modality” and should be performed within 24 hours of symptom onset [22]. The DWI sequence is often but not always abnormal in recent TIA. A DWI abnormality proves the diagnosis of acute ischemic event and its localization. Conversely, a normal DWI does not rule out the diagnosis of TIA. It is however associated with a very low risk of recurrent stroke, even in patients with high ABCD² scores. For example, in a multi-hospital study of 944 TIA patients, disabling stroke occurred at 90 days in 0% of DWI-negative patients with low ABCD² scores, and in only 0.6% of those with high ABCD² scores [23]. In another collaborative study [24], the rate of stroke at 7 day was 9 of 2322 (0.4%) in DWI-negative patients. A hypothesis is that many DWI-negative patients have TIA mimics, since it is increasingly clear that focal ischemia is not the only cause of transient neurological symptoms [25].

On the other hand, patients with DWI abnormalities have a high or very high risk of recurrent stroke. In the former study [23], disabling stroke occurred at 90 days in 6% of DWI-positive patients with 0-3 ABCD² scores, and in 15% of those with 4-6 ABCD² scores; in the latter study [24], the rate of stroke at Day 7 was 63 of 884 (7.1%). This study also showed the improved predictive power of the ABCD²-I score, which added 3 points to the ABCD² score for brain infarction at DWI or CT.

Intracranial arterial occlusion is associated with an even higher risk of recurrent ischemic stroke. In a study of 120 patients with TIA or minor stroke and MRI within 24 hours [26], recurrent stroke occurred at 90 days in 10.8% of patients with DWI lesions and no vessel occlusion at MR angiography, and
in 32.6% of patients with DWI lesions and vessel occlusion. The percentage of patients who were functionally dependent at 90 days were 1.9% in patients without DWI abnormalities, 6.2% in patients with DWI lesions and 21% in patients with DWI lesions and vessel occlusion. In the SOS-TIA clinic, 8.8% of 1823 patients had intracranial artery narrowing or occlusion on transcranial Doppler (TCD) [27]. This finding was independently associated with age, hypertension and diabetes. The incidence of recurrent vascular event at one year was 7% in patients with positive TCD and 2.4% in patients with normal TCD. The hazard ratio was 2.29 after adjustment for age, diabetes and hypertension, and 2.5 after adjustment for an ABCD² score ≥ 4. Intracranial artery obstructions are frequently associated with misery perfusion [28], indicating exhausted cerebrovascular autoregulation and a high risk of subsequent stroke [29]. We believe that treating hypertension may be dangerous in this situation although the issue remains controversial.

FLAIR and T2* sequences should also be done since they detect previous silent infarcts and signs of microvessel disease such as leucomalacia, lacunar infarcts, and microbleeds. In summary, in less than 10 minutes of imaging time, a standardized MRI procedure including diffusion, FLAIR, time of flight MR intracranial angiography and T2* provides without any contrast injection very accurate diagnostic and prognostic indices immediately after a TIA or a minor stroke. An important unsolved issue concerns the best magnetic field (1.5 T vs. 3 T), since we recently found that 1.5 T has a much higher diagnostic accuracy than the 3 T MRI unit in thrombolysis candidates [30]. Whether this is also true in minor strokes and TIAs imaged within 24 hours remains to be established.

3.3. Carotid artery imaging

Imaging of the carotid bifurcation is mandatory in all patients with TIA and minor stroke because of the demonstrated benefits of endarterectomy in recently symptomatic patients with severe (> 70%) and moderate (> 50%) North American Surgery Carotid Endarterectomy Trial (NASCET) method of measurement of stenosis. Furthermore, there is growing evidence that endarterectomy should be performed as soon as possible after the index event since the time-window for effective stroke prevention is short. Therefore, carotid imaging should ideally be performed within 24 hours of the index event.

Non-invasive imaging methods have replaced digital subtraction angiography (DSA), which is an invasive, time-intensive and expensive technique, and has a small but real risk of permanent neurological deficit. Doppler-ultrasound (DUS), contrast enhanced magnetic resonance angiography (CE-MRA) and CT angiography (CTA) are the most used non- or minimally-invasive imaging methods. Each of these techniques has advantages and disadvantages, but all remain operator-dependent during image acquisition and/or post-processing of the data [31]. Compared to DSA, a meta-analysis concluded that CE-MRA was more sensitive (0.94) and specific (0.93) for > 70% stenosis than DUS (sensitivity: 0.89, specificity: 0.84) and CTA (0.76; 0.94) [32]. However, DSA is at best an imperfect gold standard, and the meta-analysis was done on relatively old data published between 1980 and 2004, whereas non-invasive imaging technologies are rapidly improving. Even with high quality imaging methods however, the accuracy of grading the degree of ICA stenosis remains an important issue. In practice, we consider, as in many other centres, that two non-invasive techniques are required to make the decision for medical or surgical treatment. The results of the two methods are not always concordant, but in our experience, the most severe grading is the most reliable evaluation and discordances are often resolved by reviewing the original image files.

3.4. Atrial fibrillation

Atrial fibrillation (AF) is a major and treatable cause of recurrent stroke and is especially frequent in DM [33]. AF was reported in 30.1% of patients with DM history and in 24.8% of patients without DM history (p < 0.001) in the thrombolysis SITS-MOST registry [4]. AF also occurs in TIA and minor strokes. In the TIA-SOS registry, AF was found in 10.7% of cases with ABCD² scores ≥ 4 and in 5.9% of patients with ABCD² scores < 4 [18]. About one-third of patients will have a recurrent stroke in 5 years without oral anticoagulation. This treatment, although burdensome, is extremely efficient: 3 warfarin treatments prevent one case of recurrent stroke in 5 years [34]. By comparison, it is necessary to perform 6 endarterectomies in recently symptomatic severe carotid stenosis to prevent one stroke in 5 years.

Therefore it is important to assess all stroke patients for AF, including those with cervical or intracranial artery stenosis, since atherosclerosis does not offer protection from AF. An important issue is the diagnosis of paroxysmal AF (PAF), which carries the same stroke risk as permanent AF in randomised trials [35]. A systematic review reported that routine Holter monitoring can identify PAF in approximately 1 in 20 patients, and that extended duration of monitoring may improve detection rate [35]. Event loop recording and implantable devices may further improve detection rates, but the significance of very short AF bursts remains to be established [36]. An alternative approach is transtelephonic EKG in which patients frequently self-record short EKGs for 1 month and then transmit the result by phone to a cardiology centre. In a study of 98 stroke or TIA patients with normal 24 h Holter results, we found PAF in 9.2% of cases [37]. The estimated duration of PAF episodes ranged from 4 to 72 hours. The rate of PAF reaches 42.6% in patients with non-lacunar anterior circulation diffusion abnormalities and more than 100 premature atrial ectopic beats in routine 24 h Holter monitoring.
New anticoagulants will facilitate treatment and further decrease the risk of recurrent stroke. In the RE-LY study [38], the overall risk of stroke (ischaemic and haemorrhagic) was 1.4% per year in the warfarin group, 1% in the dabigatran (110 mg) group and 0.7% in the dabigatran (150 mg) group. The risk of brain haemorrhage was particularly low in the dabigatran groups (0.10 and 0.12% per year).

The emergence of low risk anticoagulants suggests that systematic screening for AF and PAF may become in the few next years one of the most efficient methods for decreasing the incidence of disabling stroke in diabetic patients.

4. Conflict of interest

None related to the content of this article.

References


