Rehabilitation of the younger adult stroke patient

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Stroke is often seen as an affliction of the elderly, in whom indeed it is the most common single cause of long-term disability. However, stroke in the younger adult age groups is not uncommon and deserves special consideration, as the needs of younger people tend to be different in certain important respects. These include employment, family and childcare responsibilities and driving. The causes, pathology, epidemiology, comorbidities, investigation and acute management of their stroke may also differ. For example, there is more likely to be a hematological, vasculitic or metabolic cause. These differences may have a knock-on effect on rehabilitation. A review of younger stroke rehabilitation therefore does require some attention with regards to the events in the pathway leading to rehabilitation and how they are organized.

This review will be highly selective. As far as rehabilitation is concerned, a comprehensive review of the medical, therapeutic, service organization and social issues would be impossible in the space available herein. It would also tend towards producing an abbreviated set of evidence-based guidelines, resembling those of the Royal Colleges of Physicians in England [1] and Scotland [2] and adding nothing of value to them. Those great pieces of work are being taken as the starting point and bedrock for this review, rather than being reiterated. Since the College guidelines are evidence- and consensus-based, a review extending far beyond that base is likely to embrace extensive areas of ignorance, uncertainty and controversy.

It is now well established that stroke management in a specialized system results in a better outcome (both short- and long-term) than stroke management on the general medical ward [3], does not increase in-patient stay, [4,5] and costs no more [6]. This effectiveness has been quantified as the avoidance of four deaths and two institutional admissions for every 100 patients treated [7]. Avoiding hospital admission ('hospital-at-home') in stroke has not been found to be worthwhile [8]. Conversely, while in-hospital care pathways have not yet been found to be of benefit in acute stroke management [9], multidisciplinary community-based teams may both enable earlier discharge [10] and improve early outcome [11].

However, it remains difficult to ascertain which components of the system are crucial. Much of the clinical practice involved in stroke rehabilitation is not yet evidence-based in the conventional scientific sense. There are reasons for this. Drug treatments, which tend to be standardized and easily subjected to analysis using randomized controlled trial methods, play a relatively small role in stroke rehabilitation. Rehabilitation is largely therapy based, and therapy programs are often designed to meet the individual patient's personal and social needs, rather than being based on their diagnosis. Therefore, standardizing a therapy program may not be appropriate. In addition, designing a convincing placebo control may sometimes be beyond human ingenuity and choosing one intervention for study may remove it from its supporting context [12]. This may, for example, explain why, although it has long been known that an organized stroke rehabilitation service results in a better short- and long-term outcome, it is nevertheless difficult to identify which elements are or are not contributing to benefit.

However, there is a continuing effort to do just that, and to 'unpack the black box of rehabilitation' [13], perhaps to find the 'Russian doll' within [14]. The limitations of application of the results of randomized, controlled trials quickly become apparent when considering rehabilitation. For example, some treatments (such as cognitive rehabilitation for spatial neglect) may improve test performance without necessarily altering functionality [15]; while the effect of other interventions (such as provision of information and education for patients and carers) may be difficult to detect [16], while obviously being desirable. Similarly, evidence for the effectiveness of speech and language therapy (SLT) in improving aphasia following

Keywords: stroke, stroke management, young adult population

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stroke is inadequate [17]; but nevertheless, SLTs play a major role in assessing and treating patients, and educating carers, about their communication problems.

This review will therefore focus on certain areas, in particular, organizational issues, new, emerging and future medical problems and treatments, emerging or controversial therapies and foreseeable prospects for the future. Questions arise from various areas, particularly from the patient and family, because we are all increasingly user-centered. Various answers are needed, including those of a medical, therapeutic, service organizational, financial and social nature. The focus is on the UK system and experience, drawing also on the National Service Framework for Long-Term Conditions [18].

Changing the language – ICIDH to ICF

Classifications of stroke based on underlying pathology are essential when considering prevention and acute treatment, but are of less relevance for rehabilitation. Although the stroke mechanism influences prognosis, it cannot predict practical outcomes, such as independent living, social integration or return-to-work potential.

The first model of disease consequence, the International Classification of Impairments, Disabilities and Handicaps (ICIDH), was released in 1980 by the WHO. The aim was to establish a common framework for coding information on health-related issues to complement the International Classification of Diseases (ICD), a classification of pathology. The model considered associations of disease (abnormality at the level of the organ) with abnormalities at three further levels: impairment (abnormality of the person); disability (alteration in their behavior); and handicap (change in their social position).

The most recent revision, known as The International Classification of Functioning, Disability and Health (ICF), was released in 2001 [19]. Here the language is neutral with respect to etiology, placing emphasis instead on function [20]. The terms 'disability' and 'handicap' have been replaced by 'activity' and 'participation'. Environmental and personal contextual factors, representing facilitators or barriers to function, are made explicit. The ICF is culturally relevant, appropriate across lifespan, and quality of life (QoL) aspects are incorporated [21]. The interactive nature of multiple complex factors is highlighted in place of the progressive, linear model of the 1980 ICIDH.

Why do younger people have strokes & are these reasons changing?

The leading risk factor for both ischemic and hemorrhagic stroke is advancing age. However, younger patients may be predisposed owing to genetic, environmental and pregnancy-related factors (**Box 1**), in addition to the conventional stroke risk factors.

The ethnic mix of a population influences stroke incidence and prevalence of subsequent disability, since risk is higher in black compared with Caucasian groups [22]; while following stroke, black people appear to have a long-term survival advantage [23].

Arterial dissection

Extracranial internal carotid-artery dissection is a major cause of cerebral infarction in younger patients [24]. Associated factors are shown in **Box 2**. Intracranial internal carotid-artery dissection is rare but when found, is most common in patients aged 20–30 years [25].

Paradoxical embolus

There is increasing interest in patent foramen ovale (PFO), a persistent connection between the right and left atria, in younger patients. The prevalence of PFO is approximately 25% in the general population but case–control studies have documented a higher frequency in young adults with cryptogenic ischemic stroke [26].

Thrombophilia

Underlying thrombophilia should be considered in individuals with venous dural sinus thrombosis, positive family history or those who have stroke recurrence. Of the inherited thrombophilias, Factor V Leiden and the

Box 1. Causes of stroke in younger patients.

Ischemic stroke

- Arterial dissection
- Paradoxical embolus
- Thrombophilia
- Pregnancy
- Drug misuse

Hemorrhagic stroke

- Trauma
- Vascular malformations
- Collagen vascular disease
- Eclampsia
- Drug misuse

Box 2. Factors associated with arterial dissection.

Predisposing risk factors

- Smoking
- Familial tendency
- Oral contraceptives
- Atherosclerosis
- Ehlers–Danlos syndrome Type IV
- Marfan syndrome

Mechanisms of injury

- Manipulations of the neck
- Blunt trauma
- Three-point restraint seat belt during road traffic accident

prothrombin 20210 mutation have an association with stroke, which is statistically significant in patients under the age of 40 years, increased further with exposure to oral contraceptives [27].

High levels of homocysteine are both prothrombotic and atherogenic. An independent and graded relationship between homocysteine level and stroke risk has been demonstrated among middle-aged men [28]. Hyperhomocystinemia is most commonly due to dietary deficiencies in folate and vitamin B12.

Antiphospholipid antibodies, initially found associated with systemic lupus erythematosus, also occur in its absence (primary antiphospholipid antibody syndrome). The two major types, anticardiolipin antibodies and lupus anticoagulant, are associated with a hypercoagulable state characterized by fetal loss, thrombocytopenia, venous and arterial thromboses. Approximately 10% of all patients with ischemic stroke have antiphospholipid antibodies and the figure is higher in younger patients [29], although the asociated risk for stroke recurrence is not clear [30].

Thrombotic thrombocytopenic purpura (TTP) is extremely rare but is most commonly found in 20–40-year old females. It causes microvascular occlusions due to multiple platelet-fibrin thrombi with a clinical syndrome of stroke with associated fever, Coombs-negative microangiopathic hemolytic anemia, thrombocytopenia and renal failure.

Hereditary stroke disorder

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is the most common known form of hereditary stroke disorder [31], and is due to mutations in the *Notch3* gene [32]. Although rare, it may be underdiagnosed. The syndrome presents as recurrent transient ischemic attacks (TIAs) and strokes in those aged 30–50 years; migraine with aura earlier in life; cognitive decline and psychiatric disturbances [33,34]. The diagnosis should be considered in stroke patients with an autosomal-dominant family history of migraine, early-onset stroke or dementia [35].

Pregnancy-related stroke

Women aged 35 years and older are particularly at risk of pregnancy-related stroke, with further risk from concomitant lupus, blood transfusion and migraine [36]. Postpartum cerebral venous thrombosis and preeclampsia are the major causes of cerebral infarction and cerebral hemorrhage, respectively [37].

Drug abuse

Drug abuse is associated with both hemorrhagic and ischemic strokes, the majority of which develop minutes to an hour after administration of the index drug (e.g., cocaine, amphetamines, ecstasy). Acute, severe elevation of blood pressure [38], cardiac dysrhythmia, cerebral vasospasm, vasculitis or embolization due to infective endocarditis, dilated cardiomyopathy or foreign material injected with diluents have been suggested as possible underlying mechanisms. Rupture of aneurysms and arteriovenous malformations have been detected in up to half of the patients with hemorrhagic stroke due to cocaine abuse [39].

Vascular malformations

Cerebral arteriovenous malformations (AVMs) are most commonly discovered in young adults aged 20–40 years and hemorrhage at a rate of 4% per year, with approximately half of these carrying significant morbidity or mortality.

HIV-associated stroke

Effective antiretroviral regimens are now able to prevent the progression of HIV infection and avoid early mortality, but the incidence of vascular complications is increasing. This may be related to metabolic derangements from protease inhibitors accelerating atherosclerosis; also, cerebrovascular hemodynamic function is impaired in otherwise-healthy HIV-infected patients [40].

Previous transient ischemic attack

Identification of individuals at high risk of early stroke following a TIA enables timely investigation and treatment. A six-point risk score,

termed ABCD, has been validated in community and clinic cohorts [41], and may be of use in clinical practice (Table 1). Almost all patients who proceeded to completed stroke within 7 days scored 5 or more on their ABCD.

New, emerging & forthcoming treatments

Thrombotic stroke

Approximately 80% of cerebral strokes are infarctions caused by temporary or permanent loss of local tissue blood flow. There is a major effort to understand how to minimize infarct size. The acute anoxic and metabolic insult, causing death of infarcted tissue, is followed by edema and a process of neuronal and glial cell loss in a surrounding ischemic penumbra, which may occur over a period of days or weeks. Rapid restoration of blood flow to the ischemic penumbra by thrombolysis has been shown in several trials [42] to be effective in reducing infarct size and improving outcome [43], and is now in widespread clinical use [44]. It has been shown that thrombolysis, currently using clotbusters, such as tissue plasminogen activator (tPA), is effective if given within 3 h of the onset of stroke symptoms, although it is much more doubtful whether it is beneficial when given between 3–6 h [45]. However, at the longer and the shorter intervals alike there is a substantially increased risk of hemorrhagic transformation of the infarct when using thrombolysis treatment (~5 vs 1%), and this increased risk has been shown to outweigh any benefit if treatment is delayed beyond 6 h.

For vertebrobasilar strokes, reported numbers are smaller, but again there is evidence that tPA treatment may improve outcome, in spite of increasing the risk of hemorrhage [46]. Here, the available time window may perhaps extend to 12 h.

Although the clinical evidence-base for stroke thrombolysis is still significantly controversial [47], and applicable to only a small minority of patients, it has revolutionized the organizational side of the acute treatment of stroke for everybody. It is a real challenge to service organization to get the patient to a specialist center, assessed, scanned (to exclude tumor or hemorrhage) and ready for thrombolysis within 3 h from the onset of symptoms. It has required the development and installation of an organized team-based and protocol-driven system for acute stroke management, akin to acute coronary care services. Even so, in most services only a small minority of patients (perhaps 2%) currently qualify for, and get, thrombolysis.

Delivering thrombolysis by arterial catheter directed towards the occlusion has also been successfully trialled (often where intravenous thrombolysis has failed), although it may result in an even higher rate of hemorrhagic transformation [48]. There are also a number of mechanical endovascular devices that have been developed for the purpose of dispersing or withdrawing thrombus from cerebral arteries (by laser, ultrasound microbubble, catheter suction, agitation or corkscrew impalement and withdrawal); but none as yet have reached routine clinical practice [49].

Cells in the core of the infarct die rapidly owing to necrosis, but cells in the penumbra die later, largely by apoptosis (programmed cell death), which is a complex cascade process, potentially reversible at various stages. This process has been modified at different points in experimental animal models of stroke using excitotoxin blockers, (such as glutamate receptor antagonists), antioxidants, calcium-influx blockers, membrane sealants, caspase inhibitors, dietary restriction, estrogens and several neurotrophic factors and cytokines (e.g., brain-derived neurotrophic factor, glial cell-derived neurotrophic factor, transforming growth factor-β and basic fibroblast growth factor). None of these interventions have yet reached clinical use and trials of excitotoxin blockers have been disappointing thus far. Steroids, too, have been shown to be of no benefit in reducing infarct size in stroke. Nonapoptopic programmed cell death using a reversible mechanism initiated by autophagy ('necroptosis') is now becoming recognized. It is possible that small-molecule inhibitors of the process could lead to another means of limiting the infarct penumbra [50]. When, and if, effective blockers of apoptosis, necroptosis or other methods of secondary neuroprotection become clinically available, it

Table 1. 7-day 'ABCD' stroke risk factors following transient ischemic attack.

Risk factor	Score
Age ≥ 60 years	1
Blood pressure > 140/90 mmHg	1
Unilateral weakness	2
Speech disturbance without weakness	1
Other focal features	0
Duration > 60 min	2
Duration 10–59 min	1
Duration < 10 min	0

would be expected that they will be incorporated into acute stroke management protocols without requiring too much further service reorganization. The reason for this is that, for the reasons mentioned above (programmed cell death vs necrosis), the time window for effectiveness will be likely to be less stringent than for thrombolysis.

Embolic stroke

Management of younger stroke patients with paradoxical emboli and PFO is controversial owing to the lack of randomized evidence. Antiplatelet therapy is often advocated initially. Warfarin is recommended empirically if stroke recurs during antiplatelet therapy or if predisposition to recurrent deep-venous thrombosis is identified [51]. The role of approaches such as transthoracic or percutaneous closure, is not yet clear [52].

Hemorrhagic stroke

Intracranial hemorrhage, which accounts for approximately 10–15% of all strokes, is associated with the highest mortality rate and degree of disability among survivors. Surgery has typically been undertaken in younger patients with low or deteriorating Glasgow Coma Scores (GCSs) and larger hemorrhages [53], but the lack of efficacy found in the International Surgical Trial in Intracerebral Hemorrhage (STICH) [54] has seen a shift of interest to minimally invasive and catheter/thrombolytic approaches for clot evacuation [55].

Computerized tomography-based studies have demonstrated that the initial hematoma expands following onset of stroke, and progressive bleeding of this type has been associated with poor outcome after early (within 4 h) surgical clot evacuation [56]. Recombinant factor VIIa given soon after the onset of symptoms may be useful to control hematoma growth [57], through acceleration of thrombosis within ruptured small penetrating arteries or arterioles. Trials of recombinant factor VII in hemorrhagic stroke are currently underway.

Three modalities of treatment for AVMs are currently available: endovascular introduction of agents which occlude part or all of the AVM; standard microneurosurgical techniques to remove AVM; or radiosurgery [58].

Subarachnoid hemorrhage

A Cochrane review identified one randomized, controlled trial assessing surgery timing following aneurysmal subarachnoid hemorrhage (SAH) [59]. Late surgery was found to be associated with a greater incidence of rebleed and delayed ischemia, although not apparent with concomitant adminsitration of the calcium channel blocker, nimodipine.

Interventional radiology is an alternative to surgery, using coil embolization to pack the aneurysm. In 2002, the International Subarachnoid Aneurysm Trial (ISAT) was stopped prematurely when it was shown that coiling was more likely to result in survival without disability at 1 year when compared with neurosurgical clipping [60]. This independent survival benefit has been found to continue for at least 7 years, with late risk of rebleeding low, although more common after endovascular coiling than after neurosurgical clipping [61].

Following aneurysmal obliteration, the risk of cerebral vasospasm remains. Ischemic symptoms from vasospasm occur in approximately a third of all patients with subarachnoid hemorrhage. 'Triple H' therapy reduces stroke due to vasospasm through: elevation of the blood pressure (induced hypertension), hemodilution to improve cerebral blood flow and maintenance of high normal circulating blood volume (hypervolemia) [62].

Secondary prevention of stroke

Stroke recurrence

The WHO multinational monitoring of trends and determinants in cardiovascular disease (MONICA) project repeated population surveys of cardiovascular risk factors (**Box 3**) and monitored stroke events over a 7–13-year period. A recurrence rate of stroke of 20% was found in the study population aged 35–64 years [63]. However, a recent study found that after a mean of 6 years, the frequencies of later vascular events in ischemic stroke patients younger than 50 years, with 0–5 of the traditional stroke risk factors, were 2.1, 6, 19, 26, 30 and 67%, respectively [64]. Patient evaluation should be directed towards identification of the stroke mechanism, in order that appropriate secondary preventative measures can be implemented.

Box 3. Major cardiovascular risk factors: WHO MONICA project [65].

- Systolic blood pressure
- Daily cigarette smoking
- Mean level of serum cholesterol
- Body mass index
- Diabetes

MONICA: Multinational monitoring of trends and determinants in cardiovascular disease.

Blood-pressure control

Results from the 2001 Perindopril Protection Against Recurrent Stroke Study (PROGRESS) trial implied that it may be worth lowering blood pressure in people who have had a stroke even if they are not defined as hypertensive, and that blood pressure should be lowered as much as tolerated. Combination therapy may be more effective, since it lowers blood pressure to a greater extent than monotherapy. An exception is in patients with bilateral carotid stenosis of 70% or greater, where aggressive blood-pressure lowering is not advisable [66].

Antiplatelet agents

The Antithrombotic Trialists' Collaboration found that doses of 75–150 mg aspirin daily are at least as effective as higher daily doses [69]. The addition of dipyridamole to aspirin produced no significant further reduction in vascular events compared with aspirin alone. Clopidogrel reduced serious vascular events by 10% compared with aspirin, but is considerably more expensive. Combination therapy with clopidogrel and aspirin may have a role in those with recurrence on aspirin alone. However in high-risk patients, the combination has not been found to significantly reduce major vascular events when compared with clopidogrel alone, and is associated with an increased risk of major or life-threatening bleeding [70].

Statin therapy

Statin therapy reduces the incidence of ischemic strokes by approximately a quarter with no apparent effect on cerebral hemorrhage, even among individuals who do not have high cholesterol concentrations. This benefit holds for people with preexisting cerebrovascular disease, even if they do not already have manifest coronary disease [71].

Diabetes

Attempts should be made to normalize blood-glucose concentrations. Optimization of diabetic control often improves an abnormal lipid profile in patients with Type 1 diabetes and sometimes those with Type 2 diabetes [72].

Anticoagulation

Following stroke, warfarin is indicated for atrial fibrillation [73], recent myocardial infarction and in the presence of valvular heart disease. Although warfarin has commonly been used in preference to aspirin for atherosclerotic intracranial arterial stenosis, it has been shown to be associated with a significantly higher rate of adverse events, with no benefit over aspirin [74].

New models for international normalized ratio monitoring are emerging, including use of computerized support software to regulate warfarin dosing [75] and patient self-management [76]. Ximelagatran, an orally administered direct thrombin inhibitor, has received interest since it does not require monitoring of coagulation parameters and is not restricted by drug interactions. However to date, it is not considered likely to be cost-effective in patients with embolic stroke risk [77] and long-term clinical utility appears limited by liver enzyme elevation [78].

Carotid endarterectomy

Identification of significant carotid artery stenosis is important owing to a high risk of early ischemic event recurrence. Carotid endarterectomy is advisable for European Carotid Surgery Trial-measured stenosis greater than 70%, in surgically fit patients [79]. In addition to the degree of arterial stenosis, additional factors of age, sex and time since last symptomatic event must be considered when advising patients on endarterectomy. The number needed to treat with carotid endarterectomy to avoid one ipsilateral stroke is 18 among those younger than 65 years of age, compared with five among patients older than 75 years [63]. Benefits from surgery seem greatest in males and those who have surgery within 2 weeks of their last ischemic event. Surgical risk is inversely proportional to surgical volume, implying that patients should be referred to busy carotid endarterectomy centers.

The role of endovascular treatment as an alternative to endarterectomy is not yet clear. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) found that at 1 year after endovascular treatment, more patients had 70% or greater stenosis of the ipsilateral carotid artery than after endarterectomy [80]. The majority of patients were treated by angioplasty without stenting and results from further randomized studies, such as Carotid Revascularization Endarterectomy versus Stent Trial (CREST), are awaited. At present, carotid stenting is available in only a few specialist surgical centers, although good results are reported particularly in high-risk patients [81].

Unruptured aneurysms

Coexisting aneurysms of all sizes in patients post-SAH due to another, treated aneurysm carry a higher risk for future hemorrhage than

do similar-sized aneurysms without a prior SAH history, and warrant consideration for treatment [82].

Lifestyle issues

Smoking

As an ischemic stroke secondary prevention measure, smoking cessation carries a relative risk reduction of 33% [83]. Cigarette smoking is also the most important modifiable risk factor for SAH; giving up smoking decreases but does not eliminate the excess risk [84].

Exercise

Leisure-time physical activity has been shown to significantly reduce the risk of stroke among men and women; young and old; across races; with dose–response relationships for both intensity and duration [85].

Advice should include permanent reduction in dietary saturated fat and partial replacement by unsaturates [86], in addition to alcohol moderation, sodium restriction [87], an emphasis on fruits and vegetables [88] and avoidance of excess weight. In younger stroke patients, raised homocysteine levels can be lowered through vitamin supplementation (folate and pyridoxine).

Do younger people require their own acute stroke services?

Acute stroke management should not be age-based. Patients over the age of 77 years may benefit from tPA treatment, although medical contraindications are more often present. The same time constraints and similar investigation protocols will therefore apply, so it is rational to use the same organisation in the acute management of adult strokes of all ages.

How do we measure what we do?

Rehabilitation medicine is unusual in that neither death nor cure is relevant as an indicator of what we do, or our success in doing it. For this reason, the development and validation of appropriate outcome indicators, and their appropriate use in the right circumstances, has during the last 20 years been prominent in the rehabilitation literature [89]. There are measures of impairment, disability (activity), handicap (participation) and quality of life (QoL). Some cover particular aspects, such as mobility or hand function, while others attempt to cover a wide range of common daily activities. All of the measures in clinical use have been developed for use in all adult age groups, rather than specifically for the younger adult. In the postacute rehabilitation process, global measures of disability are foremost, as they can predict the probability of being able to return home and the amount of care assistance that may be needed. The long-established Barthel score does this, while focusing only on aspects of disability that predict physical independence within the home, and says nothing about cognitive or communicative disabilities [90]. There are well marked floor and ceiling effects, with the score being insensitive to changes in mild or severe disability [91]. Attempts have been made to develop the Barthel, to increase the discrimination between levels of dependency [92], but this development has been criticized as not adding significantly to its sensitivity to change [93].

The Functional Independence Measure (FIM) score, which adds a number of extra domains and further subdivides the level of independence achieved in each domain, builds on the Barthel in this way, and is applicable in stroke [94,95]. It has superseded the use of Barthel in many UK rehabilitation units, even though it takes longer to score. The test can be scored by telephone interview [96], but the inter-rater reliability depends somewhat on the setting [97,98]. Often it is supplemented with the Functional Assessment Measure (FAM), which adds a number of extra cognitive and communication domains, complementary to FIM. However, FAM is not universally accepted, as there are a number of associated problems with validity and scaling [99].

Measures of disability may not be sensitive to many of the issues that arise in life following a stroke, which affect satisfaction and QoL. Global QoL measures may also be insensitive to changes in the specific features of stroke experience. There has been some interest in the development of a combined score for physical and social outcome in stroke, which should correlate with observable variables, such as social contact, employment, mobility and sex life [100]. These measures would not be applicable to in-patients.

Do younger people benefit from more intensive rehabilitation?

In most National Health Service (NHS) in-patient stroke rehabilitation units in the UK, daily face-to-face therapy does not exceed 2 h, and is often less. It is natural to suppose that more intensive therapy might lead to a better outcome. However, this is not necessarily the case. A meta-analysis of trials of additional exercise therapy for arm function in stroke suggested

that more exercise therapy may be better than less [101], if they can be tolerated. Younger patients are more likely to be able to cope with a more intensive therapy program, as they are likely to have fewer comorbidities and to be more resistant to fatigue than their elders. There is an increasing recognition that acute illnesses result in a sharp loss of physical (neuromuscular and cardiopulmonary) fitness. When combined with physical disability, as after stroke, this unfitness could limit functional recovery. Explicit physical fitness training seems likely to be more acceptable to younger stroke patients, although so far the data to show an improved functional outcome following a targeted exercise regime, remain limited [102].

Should younger stroke patients be rehabilitated in a neuro- or stroke rehabiliation unit?

There is no scientific evidence base on which to design this aspect of stroke rehabilitation services. However, there are organizational considerations. Stroke is relatively uncommon in younger age groups, and many of the rehabilitation issues will resemble those faced by patients with other causes of neurological disability, such as traumatic brain injury or multiple sclerosis. Younger adults with stroke may find they have more in common with their contemporaries, than they find with older adults with the same diagnosis. Peer-group support is important in a rehabilitation unit, where patients may be dealing with similar problems over a matter of weeks or months in hospital. Conversely, in many parts of the UK, the local stroke unit may be much more local to the patient's home than the regional neurorehabilitation unit. The recommended staffing and procedural standards [103] can be met in a range of different settings, with appropriate controls being exerted through a relevant system of clinical governance [104].

Does the physiotherapy approach matter?

Evidence suggests that early physiotherapy intervention improves outcome after a stroke compared with spontaneous recovery [105]. What treatment approach is followed by the therapist, and how that influences recovery, has been under scrutiny and discussion for many years. Therapists use a wide variety of approaches. In the UK, the two most recognized and widely used approaches are first, the Bobath concept, an approach based on neurodevelopmental therapy and focused on promoting normal movement by facilitating movement sequences [106] and second, the movement science approach, which is aimed at task-specific repetition of movement based on the principles of motor learning [107]. In practice, most therapists tend to use a combination of approaches and research has demonstrated variable effectiveness when comparing the two.

Langhammer and Stanghelle originally found that for patients treated with the movement science approach, length of hospital stay was shorter and physical outcome better when compared with the Bobath approach [108]. However, in a later study, the same authors did not demonstrate any differences between the two approaches at 1- and 4-year follow-up [109]. Recently, a single-blind, randomized, controlled trial compared the outcome for 120 patients in a stroke rehabilitation unit receiving physiotherapy based on either one of these approaches. The study did not show greater effectiveness of one approach with regards to measures of movement ability and functional independence over the other [110]. Marsden and Greenwood recently emphasized the confusion caused by the number of variables that are present in therapy intervention and the need for further research to achieve conclusive evidence [111].

Do strengthening exercises have negative side effects?

In contrast to previously held beliefs, studies now suggest that following CNS damage, the resultant muscle weakness is more disabling than the spasticity caused by the lesion [112]. The evidence suggests that resistance exercises do not increase spasticity, but rather decrease it [113,114], and that strength training of the lower and upper limb significantly improves functional outcomes and increases independence [115,116]. Therefore, increased emphasis is now put on strength training and group exercise aimed at achieving gym attendance, maximizing function, exercise tolerance and increasing social participation [117]. The patient is also encouraged to take on the responsibility of managing his/her own condition, attaining a person-centered approach and achieving greater patient autonomy. Increased cardiovascular fitness has the additional important benefit of decreasing the possibility of recurrence of cardiovascular events [118].

Constraint-induced movement therapy

Taub and colleagues developed the forced-use intervention, constraint-induced movement therapy (CIMT) to increase the use of the

affected upper extremity in chronic stroke. The idea behind the therapy is that a part of the disability observed following stroke can be attributed to a learned disuse. Therapy aims to reverse this by performing intensive training (6 h+/day) with the paretic hand, while the nonaffected hand is restrained for 90% of the waking day [119,120]. Studies using positron emission tomography and functional magnetic resonance imaging have demonstrated that the cortical area of hand representation can be increased by constraint-induced therapy [121–123]. No conclusive evidence has established whether the gains observed after CIMT are due to the extensive amount of treatment or to the forced-use of the upper limb caused by constraining the unaffected upper limb.

There are limitations to CIMT. First, it cannot be used in severe weakness of the upper limb, as a significant level of motor activity needs to be preserved in order to carry out task-specific activities. Also, the time constraints of rehabilitation often do not allow a strict adherence to the treatment regime proposed. However, effectiveness has now been demonstrated using a more realistic intensity of therapy [124].

Central pattern generators (CPGs) can be elicited in cats, by gait re-education on a treadmill, with partial body weight support (PBWS) [125]. Currently, there is no conclusive evidence to establish if CPGs are present in humans. In clinically used treadmill gait training, a support harness takes between 20–40% of the patient's weight. Gait speed is set at 0.8–1.2 m/sec to promote automatic stepping [126]. However, reviews of results have found little evidence to support the effectiveness of PBWS treadmill training in improving gait parameters in comparison with conventional physiotherapy [127,128]. There is little evidence to suggest that treadmill training is more effective than conventional overground gait training, although there is a small but significant effect of increased walking speed for independently mobilizing patients [129,130]. The added safety and security of the harness can also play a role in the choice of this intervention [131].

Therapeutic electrical stimulation

Therapeutic electrical stimulation (TES) is used for a variety of reasons, including muscle strengthening and improved activation of movement. Electrical stimulation is aimed to increase the afferent feedback from muscles and joints to achieve long-term potentiation [132], facilitate learning, thereby optimizing motor recovery [133]. De Kroon and colleagues found, in a review of the literature of upper-limb electrical stimulation, that very varied stimulation parameters are being used and these are determined mainly by muscle contraction achieved and patient comfort, rather than physiological principles. The main deduction drawn from the review was that there was greater improvement with movement-triggered stimulation rather than with repetitive, applied stimulations [134]. This emphasises the fact that intent adds a cognitive element to therapy and this achieves more appropriate reorganization in the primary motor area as demonstrated by previous studies [135].

Novel & experimental interventions

Robot therapy

Unlike constraint therapy, this intervention can be used to treat the severely weak upper limb. Treatment can be selected among passive, active-assisted and bimanual mirror-image movements [136]. A recent study has also demonstrated greater effectiveness of this intervention in comparison with therapeutic electrical stimulation [137].

Visual imagery

Visual imagery is a well known and successful concept in sport training and recent literature promotes its use in neurological rehabilitation [138]. Treatment consists of imagined movements and mental simulations of functional activity, dexterity or manipulation of objects. The beneficial effects are thought to be linked to activation of the motor system by cognitive processes. This concept is not at present a part of the mainstream treatment approach and may be of limited value for patients with cognitive impairments.

Functional electrical stimulation

Persisting foot-drop on the hemiplegic side is common and is treated conventionally using an ankle–foot orthosis (AFO). This prevents the forefoot from catching the floor and avoids the need for special movements (hip-hitching, circumduction). Some patients find the AFO uncomfortable or gait-limiting, as it prevents push-off plantarflexion. For some, functional electrical stimulation (FES) of the ankle dorsiflexors can reduce effort and give a more functional gait [139]. The stimulation is triggered by a switch in the heel of the shoe, so that it occurs only during the swing phase. Care, and therefore good cognition, is needed in the electrode placement and skin care. At present, this is the

only FES device in routine use in stroke rehabilitation, although there have been trials of systems providing hand grasp and release.

Stem cell treatments

Stem cell treatments are not yet in clinical use, although patients often inquire about them and it is explained that, at present, they are therapeutically in the unforeseeable future and that the potential benefit, if any, is unknown.

Spasticity management

Spasticity is undesirable tone, and may develop early or later in the affected limbs, often in an 'antigravity' distribution. Pain commonly occurs as a result of spasticity and may require multidisciplinary management in its own right [140]. Good positioning in the bed and chair, removal of sources of discomfort, early active and passive exercise and sometimes splinting, are the core management of poststroke spasticity. If spasticity is limiting functional recovery and medical treatment is also needed, antispastic medication should not be withheld.

Baclofen and tizanidine offer roughly equal value for money as oral antispastic drugs [141] and may be chosen on the basis of individual effectiveness and toleration. The dose is titrated upward until either adequate benefit or intolerable side effects are encountered. If oral drugs are ineffective or poorly tolerated, and if spasticity is focal (as it usually is, following stroke), then botulinum toxin A injection in the affected muscles is now considered an important adjunct to physical therapy. It has been shown to improve gait [142] and upper limb comfort, posture, cosmesis, strength and range, although benefit to function in the poststroke upper limb has been harder to prove [143]. Injection may have to be repeated after 4–6 months.

Hemiplegic shoulder pain

Shoulder pain is a common complication of stroke and can occur both in the flaccid and the spastic arm, probably by way of slightly different mechanisms [144]. The normal shoulder needs to be anatomically unstable, in order to allow for its huge range of movement. It is maintained in functional stability by active coordinated neuromuscular means. In the flaccid stroke shoulder, gravitational inferior subluxation (downward slippage of the humerus) causing capsular stretch may be clinically or radiologically apparent. When associated with pain, the temptation is to support the weight of the arm by means of a sling or some more elaborate means. Unfortunately, there is little published evidence that this will prevent or relieve pain, and it may discourage functional recovery by forcing disuse. Shoulder taping does not discourage use, but it is not very effective in achieving reduction. Electrical stimulation of the paretic deltoid has shown encouraging results [145,146].

Often, the initially flaccid stroke arm later develops spasticity in at least some muscle groups. In the spastic shoulder, spasm of the internal rotator and pectoral groups may cause the head of the humerus to ride up, causing impingement of the acromion on the supraspinatus tendon or the long head of biceps, and consequently pain, and even a secondary inflammation of the rotator cuff. Impingement may be aggravated by failure or delay of scapular rotation on the chest wall, or of humeral rotation about its axis. Rotator-cuff inflammation results in a loss of range, which may resemble an adhesive capsulitis ('frozen shoulder'), and is often treated with intra-articular steroid injection, although there is no evidence that steroids are beneficial in these circumstances.

Care in handling the unstable paretic shoulder is crucial, particularly in the acute stages following stroke. Stroke patients often feel that their shoulder pain has been provoked or aggravated by mishandling, for example, during transfers [147]. Perhaps not surprisingly, this is not an area where there is randomized, controlled-trial evidence; but it seems likely that the aggrieved patients are often right.

Neuropathic pain

Pain is common following stroke, with both physical and psychological causes. Spasticity and shoulder instability represent two of more common physical causes, but there are many others, such as constipation, urinary retention or infection, and pressure sores. Musculoskeletal pains are best dealt with by a combination of good positioning, physical therapy, simple analgesics (often under the patient's control) and nonsteroidal anti-inflammatory drugs. Central poststroke neuropathic pain is often a treatment problem and may perhaps occur more frequently in younger stroke patients. It may be associated with sensory alterations, such as allodynia, hyperalgesia, hyperpathia, hyperesthesia and paresthesiae. It was originally described in association with lesions involving the thalamus ('thalamic pain') [148], but it is now recognized that it can follow lesions anywhere in the spinothalamic system or its thalamocortical projection.

The development of pain may occur early after stroke, when it is envisaged as a 'disconnection' or 'disinhibition' phenomenon. Alternatively, it may develop weeks or months later, when it is seen as a 'neural plasticity' or 'denervation supersensitivity' phenomenon. In either case, drug treatment usually involves a tricyclic antidepressant, such as amitriptyline, building to a moderate dose, or an antihyperalgesic anticonvulsant, such as gabapentin or carbamazepine, or a combination of the two classes [149]. Often an opioid analgesic, such as tramadol or codeine, is also needed, in spite of the constipation it causes. Transcutaneous electrical nerve stimulation may be helpful [150] and is free of drug side effects [151]. A multifaceted approach has been advised, involving attention to posture, relaxation, regular review of medication, psychological assessment and advice, and a progressive return to activities of daily living [152].

Depression

Depression following stroke is common [153] and is often multifactorial: there is sudden loss of health, continuity and control; altered brain function; there may be pain, persisting disability, a disrupted life, worries about family, work, money and status. Unrecognized or untreated depression may impede the rehabilitation process and degrade the outcome. The onset of depression may be difficult for the patient to express (for example, by reason of aphasia) and it may be difficult for the clinical team to recognize (for example, by reason of altered emotional expression). Routine screening of poststroke in-patients for depression has been recommended [154], using a small basket of measures (for example, one behavioral, one questionnaire-based, one nonverbal visual analog). Patients are triaged into those not requiring treatment for depression; those whose symptoms can be managed by the ward team; and those requiring specialist psychiatric help. For those triaged into ward-team treatment, a rapidly acting selective serotonin-reuptake inhibitor antidepressant, such as citalopram or sertraline, is recommended, with formal review at 6–8 weeks. There is no strong evidence that drug treatment to prevent depression following stroke is effective [155].

Do drugs impede functional recovery?

There is a tendency in neurorehabilitation practice to try to minimize the use of drugs that could add to drowsiness or fatigue. These will include most anticonvulsants, narcotic painkillers, tranquilizers, sedatives, neuroleptics, antispastics and hypnotics. The obvious reason for this is that reduced alertness and impaired cognition may abbreviate or prevent cooperation in therapy sessions, and hence reduce the effectiveness of the therapy program. It is not acceptable for patients to be merely comfortably in bed.

There is also a subtext to this, which is that there is a suspicion (for which there is admittedly little evidence) that these classes of drugs may impair neural plasticity. Neural plasticity is thought to be one of the mechanisms of recovery following stroke, with adjacent uninjured areas (or corresponding areas of the uninjured other hemisphere) envisioned as taking over functions. There is some functional imaging and neurophysiological evidence that this does take place, both in skills development and following stroke. Some rehabilitation techniques (such as task repetition, constraint therapy or TES) are thought of as encouraging neural plasticity, even if the benefit they bring is sometimes poorly sustained.

It should be borne in mind that neural plasticity is not always beneficial. It seems quite likely that spasticity, when it develops after a delay of some weeks and in the absence of sources of discomfort, may also be occurring as a result of neural plasticity, with intrinsic neurons sprouting to innervate motor dendrites denuded by upstream cell or fiber damage. Preventing these connections from becoming dominant, by the prompt and judicious use of antispastic drugs, may perhaps be a method of avoiding long-term problems.

A number of drugs, such as amphetamines, are thought to increase neural plasticity. In some rehabilitation centers, they have been used in a selective manner prior to therapy sessions. However, there is not yet evidence that they do more good than harm when used in this way following stroke [156]. If benefit were demonstrated, it would still be difficult to tell whether this was attributable to increased neural plasticity or to improved alertness during the therapy session.

Incontinence following stroke

Incontinence at 3 days after stroke in the 'younger' (<75 years) stroke patient has been found to be one of the most reliable predictors (along with coma, paralysis and speech/swallowing problems) of a poor functional recovery at 3 and 12 months [157]. Incontinence at 1 week is an even better predictor of death than initial coma in the first 6 months [158]. Persisting incontinence is usually associated with loss of

the ability to inhibit the pontine voiding reflex, and with frontal or basal ganglia lesions. Sometimes there is initially a period of retention following cerebral stroke. The expectation that more prolonged retention or dyssynergic voiding would be associated with strokes involving the pontine tegmentum, does not need to be clearly documented [159]. Fecal incontinence is common in acute stroke and is often associated with constipation in the early hospital stage. Constipation is undoubtedly multifactorial, with immobility, fatigue, dietary change and medications all being significant. In the longer term, persisting fecal incontinence with good bowel management is much less common and is strongly associated with persisting urinary incontinence [160].

Return to work

Many younger people of working age and previously employed fail to get back to work following recovery from a stroke, and failure to return to work is associated with a higher number of perceived unmet needs [161]. It has been apparent that support systems and methods of interagency working that would be required to improve their experience and facilitate a properly managed return to work (as also for younger adults recovering from traumatic brain injury) were not adequately in place. Attempts have been made to rectify this [162,163]. Specific vocational rehabilitation service centers, of which there are currently 36 in the UK [164], draw together the necessary professional expertise. They are reliant on funding from a range of sources, so national coverage is patchy.

Sexual function & role in the family

Stroke is usually unexpected and often instills fear as well as bringing disability, unemployment, loss of income and a change in social role. The partner and family are involved in and affected by these unexpected changes. Sexual relationships are typically damaged more by the social consequences triggered by stroke, than by the physical disabilities or side effects of medication [165]. Patients and partners may require counseling, reassurance and psychological support during the rehabilitation phase, in order to overcome this cluster of consequences. There may be major difficulties in opening a trialog with patient and partner, about a relationship that has not previously been discussed with professional outsiders. Methods for doing so have been described in the nonstroke literature [166].

Expert commentary

Stroke management has been revolutionized over the last 20 years. The revolution has been triggered by developments at both ends of the stroke journey. There was the recognition that an organized system of stroke management and rehabilitation resulted in better long-term survival and independence. In addition, the introduction of effective acute-phase treatments, such as thrombolysis, has enhanced therapy. Each of these advances has required an organizational revolution in secondary hospital-based healthcare systems in order for it to be effective.

There has also been increased effectiveness of medical treatment for stroke prophylaxis. Stroke prevention (both primary and secondary) has been able to progress as part of the general improvements in primary and secondary healthcare provision, usually without requiring major organizational changes of and for itself. The development of emergency clinics for patients who have suffered TIAs would be an exception to this.

There are still many problems in knowing what to do, and how effective our intervention might be. In acute stroke management, we can use survival as a measure, and acute-phase interventions are usually well-defined single events. However, the rehabilitation process is complex and protracted, involving multiple interventions delivered through a multidisciplinary team; it is hard to disentangle the impact of each component of the process. Nevertheless, we know that the process as a whole is effective in improving outcome. Outcome may be measured in terms of activity and functional independence or in terms of discharge destination. These may be fair enough, but they do not cover many important aspects of life quality. The problem is that global measures of QoL tend to be relatively insensitive to changes made to a specific rehabilitation intervention.

Outlook

Stroke is common, and services are organized on a local (district) basis. Stroke thrombolysis requires a highly organized system with a number of facilities in place, 24 h a day. Currently, coverage in the UK is far from complete. The continuing spread of this provision will continue and will continue to provoke an associated growth of inpatient stroke rehabilitation services.

However, there are still some perverse financial incentives in the system. For example, a longer, more effective but more expensive rehabilitation process (increased NHS costs) may be rewarded

with increased independence (reduced social care costs). Prompt rehousing in appropriate accommodation (increased housing capital costs) may reduce care requirements (reduced social care costs). Some form of common accounting system may help remove barriers to progress.

Highlights

- The burden of stroke will increase with the aging population.
- Dedicated stroke services are effective at improving survival and functional outcome.
- Optimal management of stroke in the acute and rehabilitation phases is expensive but cost–effective.
- There are important gaps in understanding the effectiveness of individual therapeutic interventions.
- Acute stroke-management protocols can cover all ages.
- Stroke rehabilitation is largely age-encompassing, but there are some issues, such as employment and family responsibilities, which are specific to younger stroke rehabilitation.

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