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Stroke Rehabilitation
New Insight From Neuroscience - A Focused Review

Howard S. Kirshner, M.D.

Vanderbilt University Medical Center, Nashville TN, USA

ABSTRACT

Stroke is the most common cause of disability and the most frequent indication for inpatient rehabilitation. New information from neuroscience indicates that the cerebral cortex can reorganize or remodel after injury. In animal models, exercise of a paretic limb and restraint of the normal limb increase not only motor power, but also the size of the cortical forelimb area. Similar findings have recently been reported in man. Evidence of cortical reorganization has also been found during recovery of behavioral disorders such as aphasia and neglect. Rehabilitative therapies such as constraint-induced therapy apply these concepts in human stroke rehabilitation. Other promising techniques involve deafferentation procedures, neural transplantation, transcranial magnetic stimulation, and pharmacotherapy for stroke. Considerable evidence exists for the overall benefit of stroke rehabilitation, but the evidence for specific therapies is less compelling, and there is limited evidence favoring inpatient over subacute rehabilitation. Medical complications of stroke are reviewed. In the future, therapy techniques can be tested both for clinical efficacy and for changes in cortical organization by brain imaging.

ÖZET

İnme en sık rastlanan özürlülük nedeni ve yatan hasta rehabilitasyonunda en sık karşılaşılan endikasyondur. Nörolojik bilimler alanındaki yeni bilgiler serebral kortekste hasar sonrasında reorganizasyon veya remodeling oluşabildiğini göstermektedir. Hayvan modellerinde parezi oluşmuş bir ekstremitenin (örneğin kolun) egzersizi ve normal ekstremitenin hareketinin sınırlanması yalnızca motor gücü artırmakla kalmamış aynı zamanda kortikal önkol alanının büyüklüğünü de artırmıştır. Son dönemlerde benzer bulgular insanlarda da rapor edilmiştir. Kortikal reorganizasyona dair kanıtlar afazi ve savsaklama (neglect) gibi davranışsal bozuklukların iyileşmesi sırasında da gözlenmiştir. Sınırlama tedavisi gibi rehabilitasyon tedavileri insandaki inme rehabilitasyonunda bu kavramlara uygulanmaktadır. Umut veren diğer teknikler arasında deafferentasyon prosedürleri, nöral transplantasyon, transkranial manyetik stimulasyon ve inme farmakoterapisi yer almaktadır. İnme rehabilitasyonunun genel faydaları ile ilgili önemli kanıtlar bulunmaktadır ancak spesifik tedaviler konusunda kanıtlar daha az gerekli olduğu yönündedir ve subakut rehabilitasyona kıyasla yatan hasta rehabilitasyonu lehinde sınırlı kanıt mevcuttur. İnmenin tıbbi komplikasyonları gözden geçirilmektedir. Gelecekte tedavi teknikleri hem klinik etkinlik yönünden hem de beyin görüntülemesi yoluyla kortikal organizasyon değişiklikleri yönünden test edilebilir.

Address for correspondence: Howard S. Kirshner, M.D.
362 Vanderbilt Medical Center South 2100 Pierce Avenue Nashville TN 37212.
Telephone. 615-936-1354, Fax. 615-936-1286
e-mail: Howard.Kirshner@vanderbilt.edu

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INTRODUCTION

Every year, nearly 750,000 Americans suffer strokes. Stroke is the third leading cause of death in the U.S., but more importantly the leading cause of disability in adults. Of every 100 stroke survivors, only 10 return to work with no disability, 40 suffer mild disability, 40 have moderate or severe disability, and 10 require care in a long-term nursing facility [1]. Stroke accounts for 31% of the patients in rehabilitation facilities in the U.S.A., and nearly half of the $43 billion annual cost of stroke in the U.S.A. is spent for acute hospital, inpatient rehabilitation, and nursing facility rehabilitation [2].

Rehabilitative therapies, whether carried out in inpatient units, home health services, and outpatient facilities, have the same goals: 1) to facilitate spontaneous recovery of lost functions; 2) to provide compensatory strategies to deal with remaining deficits; 3) to help the patient achieve independence in activities of daily living (ADL's); and 4) if possible, to achieve home discharge and return to work. Where independence is not feasible, family training is important to permit discharge home. For the neurologist, responsibilities include medical measures for secondary stroke prevention, treatment and avoidance of complications of stroke, psychological support, and supervision of rehabilitative therapists and prescription of adaptive equipment.

SCIENTIFIC BASIS OF REHABILITATION

For years, rehabilitation therapists have developed exercise and training methods to enhance the recovery of neurological deficits. Most approaches are empirical, with limited scientific evidence. Recent neuroscientific evidence has supported the concept of brain plasticity as the foundation of neurorehabilitation. Rehabilitative therapiess can aid in cortical reorganization or remodeling after brain injury. Early recovery after stroke is likely mediated by revival of non-necrotic ischemic cells, reduction of edema, and reversal of diaschisis, a depression of blood flow and metabolism in functionally connected but structurally undamaged areas of the brain. These processes take place even without active rehabilitative efforts. Later recovery, however, requires reorganization or remodeling of functional brain anatomy.

Bach-Y-Rita [3], a pioneer in the study of plasticity as a basis of rehabilitation, defined plasticity as "the adaptive capacities of the central nervous system ...to modify its own organization and function". Plasticity, like excitability, is a key function of the nervous system. Functions "lost" after stroke can be regained via cortical reorganization, in association with rehabilitation [3]. Reorganization after a stroke has some similarity to ontological events in the development of specialized cortex; in early life a pleuripotential cortical area becomes specialized for one function, but this specialization can change again during recovery from brain injury [4]. Growth factors and other biochemical mediators during development likely also play a role in cortical remodeling.

The best-studied example of brain plasticity is the motor cortex. Nudo and colleagues [5,6] developed a model of stroke in squirrel monkeys by electrocauterizing the motor cortex, producing small cortical infarcts. They mapped the motor cortex by electrical stimulation before and at intervals after the stroke. After injury, the areas from which stimulation elicited forepaw movement (the motor cortex) decreased in size. Active training of the affected limb in an exercise program, however, enlarged the cortical forelimb area almost to pre-stroke level. In addition, restraint of the unaffected limb produced even greater increases in the cortical forelimb area, as well as in the function of the paralyzed limb. Most importantly for rehabilitation research, restraint of the unaffected upper limb without exercise training did not enlarge the forelimb area. At least in monkeys, rehabilitative exercise can facilitate the remodeling of the motor cortex.

In human stroke patients, functional neuroimaging with PET permits the study of the motor cortex during exercise of the paretic limb. After stroke, attempts at exercise produce less activation of the motor cortex than in normal people, just as in the monkey experiments, but other, adjacent cortical areas such as the parietal and dorsal prefrontal cortex show activation not seen in normal subjects. After a stroke, the cortical hand representation spreads to areas not normally part of the motor cortex [7]. Similar findings have been reported with passive elbow movement as the activation condition, with reorganization of the motor system occurring within six weeks of a stroke with major hemiplegia [8]. Others have documented similar changes in the motor cortex after stroke [9,10]. Considerable controversy exists regarding whether motor recovery involves the ipsilateral, contralateral, or bilateral cortices. One recent study [11] suggested that, in patients who recover well, the ipsilateral motor cortex enlarges, whereas in patients with incomplete recovery, the contralateral cortex plays a larger role. This suggests that contralateral cortical reorganization may not be as successful as ipsilateral

reorganization in mediating recovery. These functional imaging studies suggest that cortical remodeling of the motor system in response to exercise occurs in human stroke patients, as well as in experimental animals.

Taub and colleagues [12,13] applied the technique of restraint of the unaffected upper limb to human stroke patients. Like Bach Y Rita, they believe that the lack of use of the affected limb is a "learned disuse" of movement, rather than irreversible paralysis. Liepert and colleagues [13] utilized transcranial magnetic stimulation (TMS) to map the motor cortex of 13 stroke patients, all more than 6 months post-stroke. 10/13 patients had lacunar infarctions in the internal capsule, 3 had cortical infarcts. Patients had $>20^{O}$ of extension of the wrist, $>10^{O}$ of extension at the fingers, and ability to walk with the unaffected arm restrained. Intensive therapy for the weak arm and restraint of the good arm ("constraint-induced therapy" or "CIT") facilitated increased use of the arm, documented by patient diaries, and appeared to increase the area from which contractions of the contralateral hand could be produced by magnetic stimulation. Several other groups [14-18] have applied constraint-induced therapy, one group even in acute stroke [17]. A multicenter trial is in progress. Two studies [17,18] examined motor activation by functional MRI in conjunction with constraint-induced therapy; one [18] suggested that some of the new activation induced by CIT occurs in the contralateral hemisphere. In practice, patients with neglect of the left arm, but without severe paralysis, may respond best to the therapy. Despite criticism that these experiments simply made use of recovery after cessation of rehabilitative therapies, these experiments have provided hope to stroke patients and evidence that rehabilitative therapies can help the motor cortex reorganize after stroke.

The remodeling of the motor cortex with stroke rehabilitation is just one example of reorganization in the human motor cortex, in response to motor training. String musicians have much larger areas of right hemisphere motor cortex devoted to the left hand than do control subjects [19]. Likewise, blind subjects who learn to read Braille show increases in cortical activation of the fingers of both hands [20,21].

Other cortical areas, including those devoted to higher functions and behavior, may also have a capacity for remodeling with rehabilitative therapies. In acute stroke, language deficits change dramatically with changes in perfusion of the language cortex. Hillis and colleagues [22,23] showed that both aphasia and visuospatial deficits correlate with hypoperfusion of the cortex, as imaged by perfusion-weighted MRI (PWI). Increases in perfusion induced by pressor drugs or by carotid endarterectomy can improve behavioral functioning [22]. Acute stroke represents an opportunity to study the localization of brain functions before compensatory mechanisms, via recruitment of other parts of brain networks and cortical reorganization, come into play [24].

The language cortex also appears to reorganize during recovery after stroke. Some investigators [25-27] have emphasized the activation of right hemisphere cortical sites by PET or fMRI, suggesting that the right hemisphere might mediate recovery of language function. Heiss and colleagues [28,29], however, found that defective PET activation of the left temporal area precludes full recovery; only cases with reactivation of adjacent left hemisphere cortex regain high levels of language function. Activation of right hemisphere areas, in the authors' opinion, represents a "second best" or incomplete effort at recovery. This pattern was also seen with motor recovery [11]. Recovery of neglect and related right hemisphere neurobehavioral deficits has also been documented with improved right hemisphere activation [30-32]. As left hemisphere language deficits and right hemisphere visuospatial deficits improve after stroke, functional neuroimaging shows increased activation of the hemisphere in which the behavioral function (language or visuospatial functioning) is normally localized. What is lacking, in the practical world of stroke rehabilitation, is evidence that speech or cognitive therapy accelerates this cortical reorganization, as has been accomplished in the motor sphere.

CLINICAL STROKE REHABILITATION

In order to succeed in stroke rehabilitation, the patients must be well selected. Patients with mild deficits can be discharged home and receive outpatient therapies, while those with severe deficits may not benefit from intensive, inpatient rehabilitation and may be more appropriate for therapy in subacute or skilled nursing units. Too often, undue rehabilitative efforts are expended on the most severely ill patients, who can benefit least. The best candidates for inpatient rehabilitation are the moderately impaired, who are unable to return home initially but have a good chance of eventual independence. Multivariate models have been created to predict stroke outcome [33,34]. In general, several factors appear to make it unlikely that a patient will regain independence: 1) initial coma; 2) incontinence persisting beyond two weeks; 3) complete

hemiplegia, especially when accompanied by sensory loss; 4) severe unilateral neglect, global aphasia with inability to follow commands, or general confusion; 5) history of multiple strokes; 6) severe cardiac or medical disease with lack of endurance; and 7) lack of a caregiver. Any one of these factors, however, should not exclude a patient from inpatient rehabilitation. Age by itself influences prognosis only little, but it influences endurance, medical stability, and ability to benefit from therapy. In addition to these exclusionary factors, simple bedside measures can aid in prediction. Reding and Potes [35] examined pure motor, versus motor plus sensory, versus motor plus sensory plus visual field deficits. They reported that patients with pure motor hemiparesis walked with assistance at 12 weeks, and 65% were independent in ADL's at 12 weeks. Patients with hemiparesis and either hemisensory loss or hemianopsia did not walk until 22 weeks. Patients with motor, sensory, and visual field deficits did not walk until 28 weeks, and only 10 % regained independence in ADL's. Olsen [36] reported on recovery of 75 stroke patients, based only on degree of arm and leg paresis. 89% of these patients improved in lower extremity motor score, whereas only 52% showed upper limb recovery. Best recovery of leg function occurred in 10 + 4 weeks, upper limb function in 9 + 3 weeks. Maximum recovery occurred by 14 weeks. Only 11% of patients with 0-2/5 strength in the leg recovered independent ambulation during rehabilitation, whereas those with >3/5 strength all regained walking with assistance, and all regained independence or minimal dependence in ADL's. Gompertz and colleagues [37] compiled a G-score (Table 1) for outcome prediction; scores of 1-2 were associated with good, 3-4 intermediate, and 5-7 poor outcome.

Table 1. Gompertz et al, g-score (36)

CRITERION	POINT SCORES
Complete paralysis of any limb	1 point
Motor + sensory + cortical deficit	1 point
Initial loss of consciousness	1 point
Drowsiness at 24 hours	1 point
Age <50	1 point
Age 50-75	2 points
Age >75	3 points
Isolated (pure motor) hemiparesis	- 1 point

EVIDENCE FOR EFFICACY OF STROKE REHABILITATION

Although many studies have examined the efficacy of rehabilitative therapies, few are truly randomized or placebo-controlled. Nonetheless, considerable evidence points to a beneficial effect of rehabilitation. Several studies have compared outcomes in patients hospitalized on specialized stroke units to those treated on traditional wards. In Europe and the UK, both acute stroke treatment and rehabilitation therapies take place on a single stroke unit. These studies indicate a better outcome in the specialized units, usually in a shorter time [38,39]. Such findings establish that specialized stroke care is effective, but they do not separate rehabilitation from early management of stroke. Efficacy of inpatient rehabilitation programs has also been reported in two large metaanalyses [40,41]. Ottenbacher and Jannell's [42] review of 3717 stroke patients in 36 studies indicated that patients treated in rehabilitation programs fared better in measures of gait, upper limb function, independence in ADL's, and visuospatial function than those not referred to such programs. The effect was especially strong in younger patients treated soon after stroke onset. Patients undergoing intensive rehab programs also had a higher percentage of home discharge and return to work. Little evidence for cost-effectiveness has been presented [42].

Specific therapy techniques have been less well validated than the general outcome of stroke rehabilitation. Of the traditional therapies, speech therapy has received the most research scrutiny. A major VA study [43] divided patients into an acute therapy group, treated for 12 weeks, and a crossover group in whom therapy was delayed until the 12-24 week period. The early treatment group clearly improved more than the delayed treatment group, but the second group made up much of the difference during weeks 12-24. A smaller study by Lincoln and colleagues [44] was negative, but the amount of therapy actually provided was very limited. A recent analysis of treatment trials for aphasia found that intensity of therapy was a major factor in predicting positive outcome; those studies that provided intensive therapy tended to show improved outcomes, whereas those with less intensive therapy did not [45]. Several studies have evaluated speech therapy provided by trained volunteers, and the efficacy has generally been comparable to that of formal speech therapy [46,47]. Two large metaanalyses [48,49] have supported the facilitation of language recovery with speech therapy. Again, cost effectiveness has not been extensively

documented, and newer, less expensive forms of speech therapy, such as group programs and computer-assisted language training, are being developed.

In practical terms, third party payors dictate early discharge of stroke patients from the acute hospital, and the inpatient rehabilitation unit provides an interim placement for the patient and family to prepare for care at home. Inpatient rehabilitation has become the standard of care for stroke treatment [50]. Two current trends threaten the future of inpatient rehabilitation. First, subacute units and skilled nursing facilities offer rehabilitation at roughly half the price of inpatient rehabilitation, and this arrangement is especially attractive to Medicare HMO's. One comparative study found that patients in inpatient rehabilitation improved faster than subacute patients, but the overall cost was twice as high, and the relative cost per gain in functional independence measures (FIM) was 1.5 [51]. A more recent study found that inpatient rehabilitation resulted in better outcome as compared to subacute rehabilitation in stroke patients, but not in hip fracture patients [52]. The intensity of rehabilitation [53] may thus be a predictor of outcome. Further research is needed in this area.

Another practical trend in stroke rehabilitation is the recent switch to a prospective payment system (PPS) in the U.S.A. in January, 2002. Mandated, single lump-sum payments have shortened stays on rehabilitation units, especially for more severely affected patients. Whether these funding changes have affected outcomes is not currently known.

NEW APPROACHES TO STROKE REHABILITATION

In addition to "constraint-induced therapy", several new techniques have been reported. A new approach is regional anesthesia to deafferent the affected arm proximally, to improve distal motor function [54]. Use of robotic devices [55,56], treadmills with harnesses for partial weight support [57,58], electrical stimulation [59], and transcranial magnetic stimulation [60-62] all promise to aid in the rehabilitation of stroke patients. Transcranial magnetic stimulation (TMS) can be used to map areas of the cortex [13], or to interfere with or enhance the function of the cortex. Stimulation over the left prefrontal region actually reduced response latencies in an analogical reasoning task in normal subjects [60], suggesting that TMS may be useful in rehabilitation. TMS has been reported to reduce visuospatial neglect in right hemisphere stroke patients [62]. Hyperbaric oxygen (HBO) has been tested as an acute stroke treatment, with mixed results. HBO has been promoted on the internet for chronic stroke patients, but evidence-based studies are lacking. Transplantation of neural cells is another promising avenue for stroke rehabilitation [63]. Recent evidence suggests that the normal brain contains some stem cells, but these do not appear to be able to repopulate infracted brain to bring about recovery. Experimental methods to facilitate stem cell migration or survival are in an early stage [64].

Another new area of stroke rehabilitation is the use of drugs to facilitate neurologic recovery. Bromocriptine has been used with some success in patients with nonfluent aphasia [65], though a randomized clinical trial [66] failed to support its efficacy. Amphetamines have been used experimentally in stroke patients to promote motor [67,68] or language [69] recovery. A multicenter trial of amphetamine for stroke rehabilitation is currently in progress. Many rehabilitation physicians use amphetamines or methylphenidate in patients with large strokes whose somnolence interferes with rehabilitative therapies. Attention should also be paid to avoidance of medications that may impede recovery, including benzodiazepines, barbiturates, phenytoin, antihypertensive agents such as clonidine or prazocin, and neuroleptics [70].

MEDICAL COMPLICATIONS OF STROKE

One of the major roles of the rehabilitation physician is the prevention and treatment of medical complications following stroke. Medical complications include: 1) dysphagia and aspiration pneumonia; 2) deep vein thrombophlebitis (DVT) and pulmonary embolism; 3) incontinence, urinary tract infections, constipation, and sexual dysfunction; 4) skin breakdown; 5) musculoskeletal complications such as shoulder-hand syndrome and falls; 6) post-stroke pain; 7) spasticity; 8) seizures; and 9) post-stroke depression. Several reviews of medical complications of stroke have been presented [71-76]. We shall review the complications in abbreviated form, citing only a few, key references.

40-50% of stroke patients have dysphagia, and not only those with brainstem or bilateral strokes [77-79]. Stroke patients may silently aspirate, without coughing, and aspiration pneumonia can result. Dysphagia in stroke patients correlates both with the incidence of pneumonia and the associated complications of malnutrition and dehydration [77]. Neglect of swallowing dysfunction and subsequent aspiration are more common in patients with

right than left hemisphere strokes [78]. Prevention of aspiration pneumonia rests on the identification of patients with dysphagia. Bedside evaluation alone, e.g. watching the patient swallow 3 ounces of water, can miss up to 20% of patients with silent aspiration [80,81]. Videofluoroscopy of swallowing and related techniques can help not only to identify patients with dysphagia, but also to designate the most favorable consistencies of food and liquids and the optimal position for feeding [78,79]. A test of airway protection or cough reflex, in response to the inhalation of an irritant such as tartaric acid, has been promoted as a bedside test that might obviate the need for videofluoroscopic methods. Controlled trials have not yet been reported. The therapeutic implications of swallowing assessment involve changes in diet and positioning for feeding. Diet can be modified to emphasize soft solids and thick liquids, often with restriction of thin liquids or use of thickeners. Patients should generally be upright, with the head turned to the weak side. The patient is taught the "supraglottic swallow" technique, meaning swallowing small bites, separated by coughs and small liquid sips. One randomized study of dysphagia therapy failed to confirm a difference between formal speech pathologist therapy and simpler counseling [82]. Clinically, however, it seems that early attention to swallowing dysfunction in stroke patients has helped to prevent aspiration pneumonia. Stimulation techniques are being tested for efficacy in swallowing dysfunction after stroke. The use of feeding tubes interferes with the quality of life for a stroke patient, and ethical issues concerning the use of percutaneous endoscopic or nasogastric feeding tubes continue to cause controversy.

Deep vein thrombophlebitis (DVT) may occur in as many as 75% of paretic limbs in stroke patients [83]. Pulmonary embolism is one of the most common and devastating complications of stroke. In one study, pulmonary emboli occurred anytime between 3 and 120 days after a stroke, with a median of 20 days. Approximately 50% of post-stroke pulmonary embolism cases were fatal [84]. Measures to prevent DVT and pulmonary embolism include elastic stockings, compression devices, exercise, subcutaneous heparin, low molecular weight heparins such as Lovenox^{R}, or low-dose warfarin. Clearly all stroke rehabilitation patients should be on at least one, and perhaps two or more of these treatments. One early study [85] found a trend towards greater benefit of low molecular weight heparin than unfractionated subcutaneous heparin in stroke patients. Low molecular weight heparins cost several times as much as unfractionated heparin, and no FDA indication specific to stroke patients exists. A large study with enoxaparin (Lovenox^{R}) is currently planned.

Many stroke patients have bladder dysfunction [86]. Bladder dysfunction is one of the prognostic indicators predicting poor recovery after stroke [33,87,88]. Urinary tract infections are a frequent cause of morbidity and even life-threatening sepsis in stroke patients. Urinary sepsis can be prevented by intermittent catheterization, avoidance of anticholinergic and other drugs which cause urinary retention, and early treatment of urinary tract infections [86]. Constipation is almost universal in stroke patients, and preventive treatment with stool softeners, fiber, and laxatives is strongly recommended. Sexual dysfunction is also common after stroke; most stroke patients of both genders remain interested in sex, but ability to perform declines [89,90]. In one study, male stroke patients' ability to achieve erection declined from 75% to 46% after stroke, ejaculation decreased from 88% to 29%, and female orgasms dropped from 45% to 9% [89]. One series found that right hemisphere strokes are more likely to affect male sexual functioning than left hemisphere strokes [91]. Many stroke patients fear that sexual activity will be harmful, or that the spouse will not desire it. Counseling, teaching of behavioral techniques, and use of sildenafil (Viagra^{R}) or referral to a urologist for penile injections or implants should be offered.

Prevention of pressure sores and skin breakdown involves frequent turning of patients; air mattresses, wheelchair cushions, and boots, attention to adequate nutrition, and prevention of incontinence [92,93]. Avoidance of pressure over bony prominences is essential. When skin breakdown continues to worsen, circulatory insufficiency may be present. Wet-to-dry dressings, semipermeable dressings, antibiotics either topically or systemically, and surgical debridement are used for established pressure sores [93].

Musculoskeletal problems after stroke are common. Shoulder subluxation occurs in many hemiplegic stroke patients [94-96]. Support of the paretic arm by armrests and pillows is essential; slings are used during ambulation but may promote neglect of the weak limb. Staff and family members must be instructed not to lift the patient by the affected arm. The shoulder-hand syndrome is a combination of a painful, subluxed shoulder and an edematous hand, often with associated sympathetic signs of blue discoloration, cool skin temperature, atrophic changes, and sensitivity to touch. These changes suggest a

sympathetically-mediated mechanism. Massage, exposure to warm and cool baths, steroids and nonsteroidal antiinflammatory agents, and sympathetic blocks may be helpful [95]. Corticosteroids [96] may be beneficial in patients with shoulder-hand syndrome. Prevention of falls is a major goal of rehabilitation facilities [97]. Close supervision, wheelchair seatbelts, bed alarms and Vail beds are all helpful. Posey vests and wrist restraints are used only when absolutely necessary [97,98].

A common problem after stroke is neuropathic or "dysesthetic" pain. Classically described in patients with thalamic infarctions (the "Dejerine Roussy" syndrome), this syndrome can develop after any stroke affecting the sensory radiations. Dysesthetic pain involves unpleasant tingling and burning sensations in areas of partial sensory loss, often beginning weeks after a stroke. Sometimes the pain is episodic enough to suggest transient ischemic attacks or seizures. A host of medications have been used in this condition, including tricyclic antidepressants and antiepileptic drugs such as carbamazepine, gabapentin, and topiramate. Amitriptyline brought about more relief than carbamazepine in one study [99]. Refractory cases can be referred for intravenous lidocaine [100], baclofen or morphine intrathecal pumps or even deep brain stimulation.

Spasticity after stroke can also lead to painful spasms and interference with movement. Exercise is the primary treatment of spasticity, but pharmacotherapy with baclofen or tizanidine (Zanaflex [R])[101] can be helpful in reducing clonus and painful spasms. Injections of botulinum toxin have been shown beneficial for wrist and finger spasticity after stroke [102]. For refractory cases, phenol nerve blocks, intrathecal baclofen pumps [103], and surgical procedures such as tendon transfers can be considered.

Post-stroke seizures are one of the more common complications of stroke. Early seizures, defined as those occurring in the first week after a stroke, occur in 4-6% of acute stroke patients [104]. Most occur within the first 24 hours, before patients enter a rehabilitation facility. Delayed seizures are more common, occurring in as many as 20% of patients with cortical strokes, less than 10 percent of subcortical strokes [105]. Delayed seizures may occur from weeks to months after a stroke, but they can occur even a year after onset. Early seizures do not generally predict late seizures [104, 105]. Seizures do not appear to affect rehabilitation outcome [106]. Prophylactic therapy to prevent seizures is not recommended, since the likelihood of adverse effects is greater than the expected benefit. Treatment of seizures is undertaken with one antiepileptic drug. Since phenytoin, carbamazepine, and phenobarbital may slow stroke recovery [70], valproic acid and gabapentin may be favored antiepileptic drugs.

Post-stroke depression is a major impediment to successful stroke rehabilitation. Studies have shown an increased incidence of depression in patients with left as opposed to right hemisphere strokes, especially anterior left hemisphere strokes [108,109]. Not all studies have confirmed these findings [110-112]. Right hemisphere stroke patients may have indifference rather than depression in the early post-stroke period, but later they become dysphoric and depressed. The interhemisphere difference in depression may cease to exist by four months after stroke [113]. Early identification of post-stroke depression and treatment with antidepressant medications and supportive counseling is essential. Reding and colleagues [114] found that the antidepressant trazodone was more effective than placebo in improving ADL's in depressed stroke patients. Robinson and colleagues [115] reported that nortriptyline was superior to fluoxetine in the treatment of post-stroke depression. In general, however, the selective serotonin reuptake inhibitors such as fluoxetine, sertraline, paroxetine, citalopram, and excitalopram are better tolerated than traditional tricyclic antidepressant drugs and less likely to cause sedation. Emotional lability, or pathological laughter and crying, is also frequently seen in stroke patients [116,111]. Occasionally, behavioral problems such as mania [117,118], aggressive behavior [119], and delirium [120] are problematic in stroke patients and must be treated.

CONCLUSION

More than 500,000 patients survive strokes each year in the United States, and increasing resources are being devoted to stroke rehabilitation. Basic neuroscience insights into cortical reorganization after injury are increasingly shaping new rehabilitative therapies, and new techniques are developing rapidly. Practical evidence favors intensive rehabilitation programs for patients who are alert and able to cooperate but have moderate stroke deficits, while more severely affected patients should probably be treated in subacute or skilled nursing facilities until their progress justifies transfer to an inpatient unit. Medical complications of stroke are important determinants of the success of rehabilitation. Studies of the efficacy of specific therapy techniques, with measurement of cortical remodeling by brain imaging parameters, are strongly needed in stroke rehabilitation.

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CURRICULUM VITAE
Howard S. Kirshner, M.D.

Present Position
Professor of Neurology, Psychiatry, and Hearing and Speech Sciences Vice Chairman, Department of Neurology Vanderbilt University School of Medicine
Director, Vanderbilt Stroke Center Program Director, Stroke Service, Vanderbilt Stallworth Rehabilitation Hospital Staff Neurologist, Nashville Veterans Administration Medical Center
Consultant, St. Thomas Hospital

Past Positions
Associate Professor, Neurology and Hearing and Speech Sciences 1983-1987
Assistant Professor, Neurology 1978-1983
Assistant Professor, Division of Hearing & Speech Sciences 1980-1983 Vanderbilt University School of Medicine

Born
Bryn Mawr, Pennsylvania July 11, 1946

Military Service
U.S.P.H.S., Active Duty July 1973-June 1975
Reserve, July 1975-1980

Education
Williams College, Williamstown, Massachusetts 1964-1968, B.A. Summa Cum Laude
Harvard Medical School, Boston, Massachusetts 1968-1972, M.D. Cum Laude

Postgraduate
Massachusetts General Hospital Training Intern in Medicine 1972-1973
Laboratory of Perinatal Physiology National Institute of NICDS (Neurological and Communicative Disorders and Strok Staff) Associate 1973-1975
Massachusetts General Hospital Resident in Neurology 1975-1978
Clinical Fellow in Neurology Harvard Medical School 1975-1978

Research Support
"Modality Analysis of Aphasic Deficits Following Stroke" National Institute of Neurological and Communicative Disorders and Stroke, Teacher Investigator Award #5K07NS00429-04 1979-1984
Co-Investigator "Prospective Randomized Study of Asymptomatic Carotid Artery Disease"
HL14 192-12 Project 4, Project No. 281
Co-Investigator "Swallowing Disorders in Neurologic Disease" University Research Council 1983-1984
Principal Investigator, Genentech multicenter Trial of tPA in acute stroke; ATLANTIS trial, Phase IV tPA trial
Co-Investigator, "Pilot Evaluation of Nimodipine to Delay Progression of Cerebrovascular Dementia", NINDS
Principal Investigator, Stroke Treatment with Ancrod Therapy (STAT), Knoll Pharmaceuticals
Principal investigator, Warfarin Aspirin Recurrent Stroke Study (WARSS), NINDS
Principal Investigator, Tirilizad trial in acute stroke, Upjohn Pharmaceuticals
Principal Investigator, Clomethiazole in acute stroke, Astra Pharmaceuticals
Principal Investigator POST trial, Bristol Myers Squibb
Principal Investigator, Stroke Prevention with Aggressive Cholesterol Lowering (SPARCL), Parke-Davis, Pfizer
Principal Investigator, African American Antiplatelet Stroke Prevention Study, NIH
Principal Investigator, Warfarin Aspirin Stroke and Intracranial Stenosis Study, NIH
Principal Investigator, Pfizer Acute Stroke Study
Principal Investigator, Artist Study (Yamanouchi)
Principal Investigator, MATCH study, Sanofi
Principal Investigator, Warfarin Aspirin Low Cardiac Ejection Study FRACTION (WARCEF), NIH

Reviewer
NINCDS site visitor 1983, 1986. Special Study Section, 1986, 1990. VA special reviewer.
American Heart Association, Stroke grant reviewer, 1999
NICHD, Special Study Section reviewer, 8/2002
Reviewer for Archives of Neurology, Southern Medical Journal, Neurology, Annals of Neurology, Dysphagia, Neurocase, New England J Med

Editorial Board
Neurology, 1996-2001 Emedicine (editor, managing editor)

Honors
Phi Beta Kappa Alpha Omega Alpha

Societies
American Academy of Neurology
Junior Member 1975-1980
Active Member 1980-1983
Fellow, 1984-present
Member, AAN Essay Award Subcommittee 1991-97
Course Director: Speech and Language Disorders, 2000

annual meeting, 2002 annual meeting
American Neurological Association Fellow, 1986-present
National Aphasia Association Medical and Scientific Board, 1987-present
Aesculapian Club of Harvard Medical School 1972-present
Nashville Academy of Medicine 1978-present
Tennessee Medical Association 1978-present
Delegate to the Tennessee Medical Association 1987-1989 and 1998-2000, Alternate Delegate 2001-
American Medical Association 1982-present
Academy of Aphasia 1979-present
Local Arrangements Chairman for Nashville Meeting, October 1986
Fellow, American Heart Association Stroke Council 1981-present
Representative to Tennessee Division of American Heart Association, 1994-1997;
Member, 5-state Southeast Regional Board, 1998-2000
Operation Stroke, Nashville, Director of Professional Advisory Board 2000-present
The American Society for Neurological Investigation 1981-present;
Emeritus 1986-present Behavioral Neurology Society 1981-present
Multiple Sclerosis Society, Middle Tennessee Chapter, Board Member 1985-2000
National Stroke Association

Licensure
Tennessee #11196, 1978

Board Certification
American Board of Psychiatry and Neurology, 1980
American Board of Neurorehabilitation, 1992

Committees
Faculty Senate, Vanderbilt University, 1994-96 Medical School Advisory Council 1979-81 VPPP committee 1980-1990 Departmental committees on medical student and Resident education, Clinical practice committee, Promotions committee, Resident interview committee

Clerkship director
Medical Student Clerkship Director, Neurology, Vanderbilt University School of Medicine, 1981-

CURRICULUM VITAE
Howard S. Kirshner, M.D.

Mevcut Görevi
Nöroloji Profesörü, Psikiyatri ve İşitme ve Konuşma Bilimleri Profesörü,
Başkan Yardımcısı, Nöroloji Bölümü Vanderbilt Üniversitesi Tıp Fakültesi,
Direktör, Vanderbilt İnme Merkezi, Nashville, TN, ABD,
Program Direktörü, İnme Servisi, Vanderbilt Stallworth Rehabilitasyon Hastanesi,
Uzman Nörolog: Nashville Veteran Tıp Merkezi,
Danışman: St. Thomas Hospital.

Geçmiş Görevler
Doçent, Nöroloji ve İşitme ve Konuşma Bilimleri 1983-1987
Yardımcı Doçent, Nöroloji 1978-1983
Yardımcı Doçent, İşitme & Konuşma Bilimleri Bölümü 1980-1983
Vanderbilt Üniversitesi Tıp Fakültesi

Doğum Yeri & Tarihi
Bryn Mawr, Pennsylvania 11 Temmuz 1946

Askerlik hizmeti
U.S.P.H.S.,
Aktif Görev Temmuz 1973-Haziran 1975
Yedek, Temmuz 1975-1980

Eğitim
Williams Koleji, Williamstown, Massachusetts 1964-1968, B.A. Summa Cum Laude
Harvard Tıp Okulu, Boston, Massachusetts 1968-1972, M.D. Cum Laude

Mezuniyet Sonrası Eğitim
Massachusetts Kamu Hastanesi, Nöroloji asistanı, Dahiliye 1972-1973, rotasyon
Perinatal Fizyoloji Laboratuvarı, rotasyon
Nörolojik Bozukluklar, İletişim Bozuklukları ve İnme Enstitüsü (NINCDS) Uzman Yardımcısı 1973-1975
Massachusetts Kamu Hastanesi Nöroloji Asistanı 1975-1978
Nöroloji Klinik Uzmanı Harvard Tıp Okulu 1975-1978

Araştırma Desteği
"Modality Analysis of Aphasic Deficits Following Stroke" National Institute Nörolojik Bozukluklar ve İletişim Bozuklukları ve İnme Ulusal Enstitüsü Eğitmen Araştırmacı Ödülü #5K07NS00429-04 1979-1984
Ortak Araştırmacı "Prospective Randomized Study of

Asymptomatic Carotid Artery Disease" HL14 192-12 Proje, Proje No. 281
Ortak Araştırmacı "Swallowing Disorders in Neurologic Disease" Üniversite Araştırma Konseyi 1983-1984
Ana Araştırmacı, Genentech multicenter Trial of tPA in acute stroke; ATLANTIS çalışması, Faz IV tPA çalışması
Ortak Araştırmacı, "Pilot Evaluation of Nimodipine to Delay Progression of Cerebrovascular Dementia", NINDS
Ana Araştırmacı, Stroke Treatment with Ancrod Therapy (STAT), Knoll Pharmaceuticals
Ana Araştırmacı, Warfarin Aspirin Recurrent Stroke Study (WARSS), NINDS
Ana Araştırmacı, Tirilizad trial in acute stroke, Upjohn Pharmaceuticals
Ana Araştırmacı, Clomethiazole in acute stroke, Astra Pharmaceuticals
Ana Araştırmacı POST çalışması, Bristol Myers Squibb
Ana Araştırmacı, Stroke Prevention with Aggressive Cholesterol Lowering (SPARCL), Parke-Davis, Pfizer
Ana Araştırmacı, African American Antiplatelet Stroke Prevention Study, NIH
Ana Araştırmacı, Warfarin Aspirin Stroke and Intracranial Stenosis Study, NIH
Ana Araştırmacı, Pfizer Acute Stroke Study
Ana Araştırmacı, Artist Study (Yamanouchi)
Ana Araştırmacı, MATCH study, Sanofi
Ana Araştırmacı, Warfarin Aspirin Low Cardiac Ejection Study FRACTION (WARCEF), NIH

Değerlendirici

NINCDS ziyaretçisi 1983, 1986. Özel Çalışma Bölümü, 1986, 1990. VA special reviewer.
American Heart Association, Stroke grant reviewer, 1999
NICHD, Özel Çalışma Bölümü Değerlendiricisi, 8/2002
Archives of Neurology, Southern Medical Journal, Neurology, Annals of Neurology, Dysphagia, Neurocase, New England J Med dergilerinde değerlendirici

Editoryal Kurul

Neurology, 1996-2001
Emedicine (editör, yönetici editör)

Mezuniyet Dereceleri

Phi Beta Kappa Alpha Omega Alpha

Dernekler

American Academy of Neurology (Amerikan Nöroloji Akademisi)
Yeni Üye 1975-1980
Aktif Üye 1980-1983
Fellow, 1984- halen sürüyor
Üye, AAN Essay Ödülü Alt komitesi 1991-97
Kurs Direktörü: Konuşma ve Dil Bozuklukları, 2000 ve 2002 yıllık toplantısı
American Neurological Association (Amerikan Nöroloji Derneği) Fellow, 1986-halen sürüyor
National Aphasia Association (Ulusal Afazi Derneği) Medikal ve Bilimsel Kurul, 1987- halen sürüyor
Aesculapian Club of Harvard Medical School (Harvard Tıp Okulu Eskülap Klübü) 1972- halen sürüyor
Nashville Academy of Medicine (Nashville Tıp Akademisi) 1978- halen sürüyor
Tennessee Tıp Derneği 1978- halen sürüyor
Tennessee Tıp Derneği Temsilcisi 1987-1989 ve 1998-2000, Temsilci Vekili 2001-halen sürüyor
American Medical Association (Amerikan Tıp Derneği) 1982- halen sürüyor
Academy of Aphasia (Afazi Akademisi) 1979- halen sürüyor
Nashville Toplantısı Lokal Düzenlemeler Başkanı, Ekim 1986
Fellow, Amerikan Kalp Derneği İnme Konseyi 1981- halen sürüyor
Amerikan Kalp Derneği Tennessee Bölümü Temsilcisi, 1994-1997; Üye, 5-state
Güneydoğu Bölgesel Kurulu, 1998-2000
İnme Operasyonu, Nashville, Profesyonel Danışma Kurulu Direktörü 2000- halen sürüyor
Amerikan Nörolojik Araştırma Derneği 1981-halen sürüyor; Emeritus 1986- halen sürüyor
Davranışsal Nöroloji Derneği 1981- halen sürüyor
Multipl Skleroz Derneği, Orta Tennessee Bölüm, Kurul Üyesi 1985-2000
Ulusal İnme Derneği

Meslek Ruhsatı

Tennessee #11196, 1978

Kurul Sertifikası

American Board of Psychiatry and Neurology (Amerikan Psikiyatri ve Nöroloji Kurulu),
1980 American Board of Neurorehabilitation (Amerikan Nörorehabilitasyon Kurulu), 1992

Komiteler

Fakülte Senatosu, Vanderbilt Üniversitesi, 1994-96
Tıp Okulu Danışma Konseyi 1979-81
VPPP komitesi 1980-1990
Tıp öğrencisi ve Asistan (Resident) eğitim departmanı komiteleri, Klinik uygulama komitesi,

Terfi komitesi, Asistan mülakat komitesi

Yazmanlık direktörü

Tıp Öğrencisi Yazmanlık Direktörü, Nöroloji, Vanderbilt Üniversitesi Tıp Fakültesi, 1981-halen sürüyor

BİBLİYOGRAFİ

Howard S. Kirshner, M.D.

1. Mezuniyet Tezleri

1. Kirshner HS (1968). Endocrine Effects on hepatic glycogen metabolism in Rana Pipiens. B.A. Honors Thesis in Biology, Williams College. Williamstown, MA.
2. Kirshner HS (1972). Matching-to sample tests, eye movement studies, and analysis of behavior in patients with vascular brain lesions. M.D. Honors Thesis, Harvard Medical School, Boston, MA.

2. Akran Değerlendirmesi yapılan makaleleri

1. Kirshner HS and Sidman M (1972). Scanning patterns in aphasic patients during matching-to-sample tests. Neuropsychologia 10: 179-184.
2. Kirshner HS, Blank, WF Jr., and Myers RE (1975). Brain extracellular potassium activity during hypoxia in the cat. Neurology 25: 1001-1005.
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