RECENT ADVANCES IN THE MANAGEMENT OF CEREBRO-VASCULAR ACCIDENT

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INTRODUCTION

According to the World Health Organization, stroke or cerebro-vascular accident (CVA) has been defined as a syndrome of rapidly developing clinical symptoms and signs of focal (or global) loss of cerebral functions, with symptoms lasting 24 hours or longer or resulting in death with no apparent cause other than of vascular origin[1,2]. Stroke is a major challenge to physicians worldwide, with high incidence, mortality, disability rates, and costs.[3]

It remains the third leading cause of death in the United States and the leading cause of serious long-term disability worldwide[4,5]. It is estimated that 700,000 American residents experience a new or recurrent stroke, with an estimated 500,000 having their first stroke[4]. This disease was thought to be rare in the black Africans five decades ago[6], but strong evidences supports an emerging epidemic of stroke in developing countries following social and economic re-structuring over the next few decades.

Though the situation in sub-Saharan Africa is peculiar as significant mortality accrues to infectious diseases such as human immuno-deficiency virus/ acquired immune-deficiency syndrome (HIV/AIDS) and malaria, there are however reports indicating that stroke had become the leading cause of neurological admissions in most tertiary hospitals in Nigeria, taking over from central nervous system infections reported in earlier studies[7,8,9,10]. Stroke accounted for 0.92 – 4% of hospital admissions and 2.83 – 4.52% of total deaths in Nigeria[11].

The actual incidence of stroke in Nigeria has not been established but there are indications that the incidence is likely to be high and the mortality increasing as in other African countries. In a community study of neurological disorders among Nigerians, Osuntokun *et al* [12] reported a crude prevalence rate of 58 per 100,000 of population, similar to the figure by Matenga[13] in Zimbabwe. More recently, community surveys undertaken in South Africa[14], Togo[15] and Tanzania[16,17] suggest the prevalence of stroke to be between 200 and 300 per 100,000.

In industrialized countries, stroke accounted for 10-12 percent of all deaths, with about 88% of the deaths attributed to stroke occurring among people over 65 years[5]. It appears however that death rates from stroke have been falling dramatically in recent decades in developed nations, with Japan experiencing the most precipitations fall[18]. This change in trend is not

unlikely to be related to the changing risk factor levels over time.

Stroke Types

Stroke is caused by disruption in the flow of blood to part of the brain (ischemic-thrombotic) resulting in hypoxia and eventually necrosis. It may also be due to occlusion of a blood vessel (ischemic-embolic) or rupture of a blood vessel (hemorrhagic). About 80 percent of all acute strokes are caused by cerebral ischemia, usually resulting from thrombotic or embolic occlusion of a cerebral artery, the remaining 20 percent are caused by intra-cerebral or subarachnoid hemorrhage. Categories of ischemic stroke include (a) large vessel disease (atherothrombosis) (b) small vessel disease (microatheromatosis) and (c) cardio – embolic. The large vessel disease comprises 30-35%, the small vessel type 15 – 25%, cardio-embolic 15%, arterial dissection (with vasculitides and hypercoagulable states) contribute 5 -10% while the remaining 20 – 25% are of unknown etiology.

Cost constraints and limited availability of computerized tomography (CT) imaging considerably restrict information on the profile of different pathologic types of stroke in sub-Saharan Africa. In many hospitals, CT scan is only performed in about 50 percent of all patients presenting with stroke, and usually only among those who can afford it[19]. The South African MEDUNSA stroke register[20] showed that cerebral infarction accounted for 71% of stroke cases in South African blacks. On the other hand however, intra-cerebral bleed accounted for 60 percent of strokes in a series of over 900 CT – confirmed cases of stroke in Ghana[21]. Similar trend of high rate of intra-cerebral bleed was reported in Tanzania[22]. Ischemic stroke accounted for 73.8% of all patients with stroke in Nigerians[23]. The ongoing AMMP stroke incidence study in Tanzania with high use of CT will provide more reliable estimates of the proportional frequencies of stroke types within a community setting[22].

Risk Factors for Stroke

The major risk factors for stroke have been extensively investigated and reported. The modification and treatment of these risk factors directly influence incidence and indirectly affect case fatality of stroke, as the natural history of the disease is altered. The identification and understanding of the magnitude of these stroke determinants will go a long way in stroke prevention.

Studies among Nigerians and other populations in developed countries have confirmed hypertension as the most dominant detriment of stroke[24,25,26,27].

A recent risk factor analysis[26] among Nigerians revealed hypertension as risk factor in 82.5% of stroke patients with corresponding odds ratio of 3 and the risk of stroke was strongly related to both systolic and diastolic blood pressure. The relationship between blood pressure and risk for first stroke or recurrent stroke appears to be log-linear throughout normal range of blood pressure, with a 10mmHg rise in mean arterial pressure (MAP) conferring about 20% to 30% increase in stroke risk[17]. It is established that stroke risk, especially of the hemorrhagic type, is reduced with optimal control of blood pressure[6].

Increasing age has been reported to be the strongest risk factor for cerebral infarction, primary intra-cerebral and sub-arachnoid bleed[28,29]. The risk of stroke increased from 3 per 100,000 by third and fourth decade to 8 – 9 per

100,000 in the eighth and ninth decade[27]. In sub-Saharan African, most cases of stroke occur in relatively young people (mean age < 60years in most studies), some 10-15 years younger than stroke patients in developed countries[25,30]. The age of occurrence is even younger for hemorrhagic stroke compared with ischemic stroke[17]. These data indicate a high burden of premature stroke in black Africans.

Sex differences in stroke patients have not been consistent but most studies showed higher proportion of deaths from strokes in men than women in all age groups, up to 60-69 years[27]. At older ages mortality is greater for females.

Diabetes mellitus, which has been reported in up to 20 – 37% of patients with stroke, and cardiac diseases especially rheumatic valvular heart disease associated with atrial fibrillation causing embolic stroke, are common determinants of stroke[1,13,20,26,28].

Chronic infection with streptococcal pneumonia has been reputed as a risk factor for ischemic stroke in Cameroon[31]. Dyslipidemia has been reported among stroke patients in South Africa, Burkina Faso and Nigeria[32,33,34]. Other risk factors include cigarette smoking, heavy alcohol consumption, neuro-syphilis, homozygous sickle cell disease (in children), obesity, anemia, dehydration, infection (including HIV infection), under nutrition and congestive heart failure[25,26,35,36].

Limited studies also suggest the contribution of cervical spine hyper flexion, carotid artery stenosis, cocaine abuse, chorionic cancer and hypercoagulable states like anti-thrombin III, protein S and C deficiency, factor V Leiden and prothrombin 202A gene mutation[37]. The presence of anti-phospholipid antibodies and migranous headaches are relatively well established risk factors for ischemic stroke in young females[38]. Transient ischemic attacks and family history of stroke are important precursors of stroke and other vascular ischemic events[26]. Recent studies have highlighted the contributions of high fat and sodium diets[39], and hypokalemia[40] to stroke risk.

Although there may not be a single genetic factor associated with stroke, genes do play a large role in the expression of stroke risk factors such as hypertension, heart disease, diabetes, and vascular malformations. It is also possible that an increased risk for stroke within a family is due to environmental factors, such as a common sedentary lifestyle or poor eating habits, rather than hereditary factors. Vascular malformations that cause stroke may have the strongest genetic link of all stroke risk factors. A vascular malformation is an abnormally formed blood vessel or group of blood vessels. One genetic vascular disease called CADASIL, which stands for cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy. CADASIL is a rare, genetically inherited, congenital vascular disease of the brain that causes strokes, subcortical dementia, migraine-like headaches, and psychiatric disturbances. CADASIL is very debilitating and symptoms usually surface around the age of 45. Although CADASIL can be treated with surgery to repair the defective blood vessels, patients often die by the age of 65[41].

Current Management Strategies

Until recently, treatments for stroke have consisted of supportive care and the prevention of complications. In recent years however evidence has accumulated to justify a more active approach. Experimental and clinical

data show that immediately after occlusion of a cerebral vessel, cells become intensely ischemic leading to infarction. As they die, they release a range of neuro-active substance and enzymes that damage the surrounding area. The zone of secondary damage represents potentially salvageable tissue (penumbra). The process of cerebral infarction may take several hours to complete, creating a 'time window' during which it may be possible to restore blood supply to the ischemic area of the brain and interrupt or reverse the process. If this can be achieved it may be possible to minimize subsequent neurological deficit, disability, and secondary complications. Therefore acute stroke is regarded as a treatable condition that requires urgent specialist attention. Both specific treatments and specialist care have been shown to influence survival and recovery. The approach to management depends on the type of stroke the patient has and the time of presentation.

The management of stroke patients is practically divided into phases; the acute phase which includes ambulance service and care, emergency room care, neuro-intensive care and stroke unit management; (2) the sub-acute phase management which is mainly supportive and takes place in the stroke care ward and physiotherapy unit, and (3) chronic phase which takes place in the community (patient's house and environment) and the outpatient clinics[11].

The acute phase is usually in the first week and focuses on assessment and early supportive care. The sub-acute phase, which is between second and fourth week, focuses on prevention of complications, early rehabilitation, psychological support and prevention of recurrence. The chronic phase focuses on long term rehabilitation, psychological and social support, and prevention of recurrence. The management will be discussed based on the stroke types because of the peculiarities in the approach to acute intervention in the emergency room and intensive neuro-critical care.

Management of ischemic stroke

The main goal of acute ischemic stroke therapy is to reduce infarct size which can translate to improved clinical outcome and better quality of life. The major advances include the use of tissue plasminogen activator, the establishment of stroke unit, the use of neuro-protective agents and neuro-endoscopic surgery and transplantation of germ cells. Thrombolytic therapy is a major step in the acute stroke care. It comprises the use of thrombolytic agents like rtPA, which is administered within 3 to 4.5hours of onset of symptoms. Prourokinase is another alternative that is used and is given within a 6 hour window trial. Neuro-protective agents are aimed at intracellular calcium, free oxygen radicals and excitotoxicity (glutamate).

Stroke Care Unit

This is a specialized unit with a multi-disciplinary approach to care of stroke patients. It comprises the neurologist, neurosurgeon, psychiatrist, physical therapist, speech therapist, occupational therapist, urologist and social worker. The aim of the unit is to render holistic care to stroke patients, and it has been documented from several meta-analyses that the stroke unit presence improves the survival of patents and significantly reduces disability.

Stroke units are known to improve outcome by concentrating patients in a unit with appropriate expertise.[42]

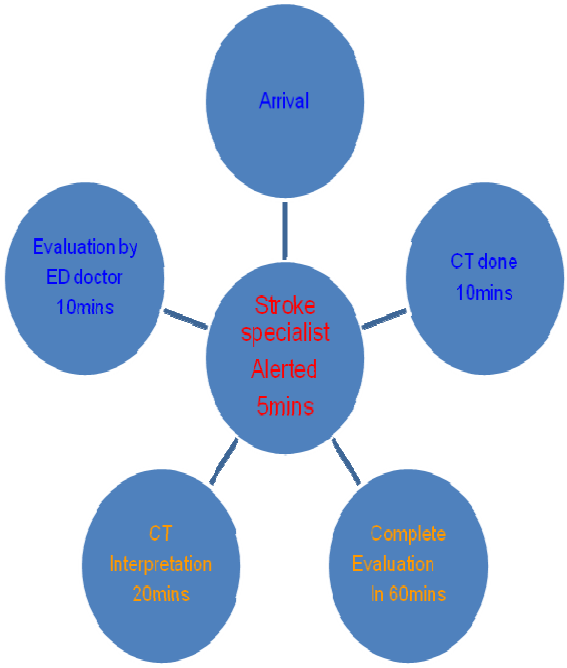
Following the dismal and disturbing report of the Royal Society of Physicians in 2001 revealing the failure of the NHS in the United Kingdom to provide adequate numbers of beds in stroke units, the national clinical guidelines for stroke are unequivocal in stating that "the evidence in support of stroke unit is overwhelming and achieving this should be the highest priority of clinicians and managers."[43] The national service framework explicitly recommends that "All patients who may have had a stroke should be treated by specialist stroke teams within designated units."[44] This effectively means treatment in a stroke unit for every person with a stroke. Provision of care in a stroke unit is not only the practice of evidence based medicine but a matter of clinical governance. Milestones in the UK national service framework specify that all general hospitals in United Kingdom introduce this model of care from 2004, integrated with a stroke prevention service, and specialist community rehabilitation teams.

With the implementation of this guideline, overall mortality reduced by a third, and the 30 day case fatality rate fell from 27%[45] to 15%.[46] Other gains have been a low rate of institutionalization, a high rate of discharge from the acute hospital site, and a rolling educational programme for staff.[46] Key to the success of a unit is influencing bed managers to give the stroke unit beds the same kind of priority as the coronary care unit, and persuading management to increase capacity to match need, with flexible bed reconfiguration within the pool of beds. The number of beds actually used for people with strokes should meet demand.

Evidence from randomised controlled trials shows that even the most disabled patients gain from management on a stroke unit, with less time spent in hospital and more patients going home.[47] For patients with a mild stroke, stroke units have a role in secondary prevention, an area where the evidence continually changes and needs to be interpreted by a specialist. Current evidence shows that there is no substitute for management of all strokes in a stroke unit. The patients are already in the hospital, so what is needed is simply reconfiguration of beds and training of staff to deliver the care.

What about the community? The sentinel audit shows that only 31% of trusts have specialist community stroke teams.[48] Evidence from randomised controlled trials shows that a focused community rehabilitation team with adequate resources, linking with a state of the art stroke unit, reduces length of stay and, in moderately and severely disabled patients, reduces disability and institutional care, compared with management by a stroke unit alone[49].

The time plan for acute stroke care is illustrated below;



Source: author's presentation

Physicians have several diagnostic techniques and imaging tools to help diagnose the cause of stroke quickly

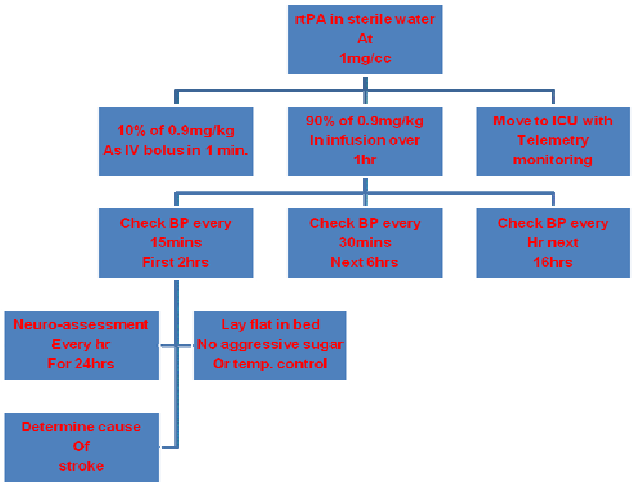
and accurately. The first step in diagnosis is a short neurological examination. When a possible stroke patient arrives at a hospital, a health care professional, usually a doctor or stroke nurse, will ask the patient or a companion what happened and when the symptoms began. Blood tests, an electrocardiogram, and CT scans will often be done. One test that helps doctors judge the severity of a stroke is the standardized National Institute of Health (NIH) Stroke Scale, developed by the National Institute for Neurological Diseases and Stroke (NINDS). Health care professionals use the NIH Stroke Scale to measure a patient's neurological deficits by asking the patient to answer questions and to perform several physical and mental tests. Other scales include the Glasgow Coma Scale, the Hunt and Hess Scale, the Modified Rankin Scale, and the Barthel Index. In the emergency room, the following steps must be taken:

a. detailed neurological evaluation
b. assess deficit using the National Institute of Health Stroke Scale (NIHSS)
c. check blood sugar
d. give oxygen 2 – 4L by nasal cannula or prongs
e. administer dextrose in saline or normal saline by intravenous route
f. obtain continuous ECG monitoring
g. Thereafter an urgent neuro – imaging investigative modality is sought.

For patients that present within 3 hours of stroke onset, there is need to determine tPA eligibility. The criteria for tPA eligibility Include;

a. Clinical and CT evidence of ischemic stroke
b. No history of recent trauma or major surgery (within the last 2weeks), Gastro-intestinal or Genito-urinary bleed (within the last 3 weeks) and no serious head injury, brain surgery or stroke (within the last 3months)
c. No evidence of rapidly improving symptoms (this suggests a possible Transient Ischemic Attack)
d. No seizure at onset (to suggest Todd's paralysis)
e. Blood pressure greater than 185/110mmHg without major intervention
f. No CT evidence of intra-cerebral hemorrhage
g. Normal glucose concentration of between 50 and 400mg/dl
h. Prothrombin time less than 15 seconds
i. Platelet count greater than 100,000/mm^3.

Schedule for administration of rtPA



Source: Author's presentation

The non-contrast CT is the cornerstone of investigation as it detects 90% of intra-cerebral hemorrhages

(ICH) in the first 24hours. It is the preferred diagnostic technique for acute stroke because of its unique diagnostic benefits[50]. It will quickly rule out a hemorrhage, can occasionally show a tumor that might mimic a stroke, and may even show evidence of early infarction. Infarctions generally show up on a CT scan about 6 to 8 hours after the start of stroke symptoms. Hemorrhage is the primary reason for avoiding certain drug treatments for stroke, such as thrombolytic therapy, the only proven acute stroke therapy for ischemic stroke. Thrombolytic therapy cannot be used until the doctor can confidently diagnose the patient as suffering from an ischemic stroke because this treatment might increase bleeding and could make a hemorrhagic stroke worse[51].

Other investigations that may be useful include computed tomography angiography CTA), magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), carotid duplex, cerebral angiography, electro-cardiography, trans- esophageal echocardiography (especially in patients suspected to have patent foramen ovale - PFO) and coagulation profile. MRI uses magnetic fields to detect subtle changes in brain tissue content. One effect of stroke is an increase of water content in the cells of brain tissue, a condition called *cytotoxic edema*. MRI can detect edema as soon as a few hours after the onset of stroke. The benefit of MRI over CT imaging is that MRI is better able to detect small infarcts soon after stroke onset. Arteriography is an X-ray of the carotid artery taken when a special dye is injected into the artery. The procedure carries its own small risk of causing a stroke and is costly to perform. The benefits of arteriography over MR techniques and ultrasound are that it is extremely reliable and still the best way to measure stenosis of the carotid arteries.

Management of hemorrhagic stroke

In the management of intracerebral bleed, there are two major options; (a) medical and (b) surgical. The surgical modalities employed are craniotomy or neuro-endoscopic surgery. The management of intra-cerebral hemorrhage (ICH) remains heterogeneous across institutions and suffers lack of proven effectiveness making its management remains an enigma. Mortality is still as high as 30 – 40% (i.e. 30 day mortality rare)[52].

In LUTH, Lagos, a mortality of 72% was reported[53], which was similar to the rate in Benin, with acute phase mortality of 66.78% and a 3-month mortality rate of 79%[23]. The predicting factors for mortality include volume of hematoma, neurological states of patients at admission (using the Glasgow Gama Scale), presence of intra-ventricular or sub-arachnoid extension, the presence of cerebral oedema[23,54,55] and if patient is on anti-coagulation therapy[56]. The goal of management is to reduce intracranial pressure (i.e. reduce mass effect) and potential stimulus for edema and cell death[54].

Medically, the cardio-pulmonary status of patient is optimized, optimal blood pressure control is important and measures are taken to reduce intra-cranial pressure. The following measures are instituted in the stroke care unit:

(i) Patient positioning: the patient with ICH should have the head elevated to 30 degrees and place in neutral position.

(ii) Measures to reduce elevated intracranial pressure – the use of

hyperosmolar solutions, barbiturate overdose (coma) and hyperventilation.

(iii) The blood glucose should be optimally stabilized non-aggressively.

(iv) Specific measures taken to reverse coagulation defects.

Surgery can be used to prevent stroke, to treat acute stroke, or to repair vascular damage or malformations in and around the brain. There are two prominent types of surgery for stroke prevention and treatment: carotid endarterectomy and *extracranial/intracranial (EC/IC) bypass*. The NINDS has sponsored two large clinical trials to test the efficacy of carotid endarterectomy: the North American Symptomatic Carotid Endarterectomy Trial (NASCET)[57] and the Asymptomatic Carotid Atherosclerosis Trial (ACAS)[58]. These trials showed that carotid endarterectomy is a safe and effective stroke prevention therapy for most people with greater than 50 percent stenosis of the carotid arteries when performed by a qualified and experienced neurosurgeon or vascular surgeon. Currently, the NINDS is sponsoring the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST)[59], a large clinical trial designed to test the effectiveness of carotid endarterectomy versus stenting. The procedure involves inserting a long, thin catheter tube into an artery in the leg and threading the catheter through the vascular system into the narrow stenosis of the carotid artery in the neck. Once the catheter is in place in the carotid artery, the radiologist expands the stent with a balloon on the tip of the catheter. EC/IC bypass surgery is a procedure that restores blood flow to a blood-deprived area of brain tissue by rerouting a healthy artery in the scalp to the area of brain tissue affected by a blocked artery. The NINDS-sponsored EC/IC Bypass Study[60] tested the ability of this surgery to prevent recurrent strokes in stroke patients with atherosclerosis. The study showed that, in the long run, EC/IC does not seem to benefit these patients. The surgery is still performed occasionally for patients with aneurysms, some types of small artery disease, and certain vascular abnormalities. One useful surgical procedure for treatment of brain aneurysms that cause subarachnoid hemorrhage is a technique called *"clipping."* Clipping involves clamping off the aneurysm from the blood vessel, which reduces the chance that it will burst and bleed. A new therapy that is gaining wide attention is the *detachable coil* technique for the treatment of high-risk intracranial aneurysms. A small platinum coil is inserted through an artery in the thigh and threaded through the arteries to the site of the aneurysm. The coil is then released into the aneurysm, where it evokes an immune response from the body. The body produces a blood clot inside the aneurysm, strengthening the artery walls and reducing the risk of rupture. Once the aneurysm is stabilized, a neurosurgeon can clip the aneurysm with less risk of hemorrhage and death to the patient.

Preventive strategies

Drug therapy is the most common treatment for stroke. The most popular classes of drugs used to prevent or treat stroke are *antithrombotics* (*antiplatelet agents* and *anticoagulants*), *thrombolytics*, and *neuroprotective agents*. Antithrombotics prevent the formation of blood clots that can become lodged in a cerebral artery and cause strokes. Antiplatelet drugs

prevent clotting by decreasing the activity of platelets, blood cells that contribute to the clotting property of blood. These drugs reduce the risk of blood-clot formation, thus reducing the risk of ischemic stroke. In the context of stroke, physicians prescribe antiplatelet drugs mainly for prevention. The most widely known and used antiplatelet drug is aspirin. Other antiplatelet drugs include clopidogrel, dipyridamole and ticlopidine. Anticoagulants reduce stroke risk by reducing the clotting property of the blood. The most commonly used anticoagulants include *warfarin* and *heparin*. The Stroke Prevention in Atrial Fibrillation (SPAF) trial[61] found that, although aspirin is an effective therapy for the prevention of a second stroke in most patients with atrial fibrillation, some patients with additional risk factors do better on warfarin therapy. The Trial of Org 10127 in Acute Stroke Treatment (TOAST) [62] tested the effectiveness of low-molecular weight heparin (Org 10172) in stroke prevention. TOAST showed that heparin anticoagulants are not generally effective in preventing recurrent stroke or improving outcome.

Neuroprotectants are medications that protect the brain from secondary injury caused by stroke. Although only a few neuroprotectants are FDA-approved for use at this time, many are in clinical trials. There are several different classes of neuroprotectants that show promise for future therapy, including calcium antagonists, glutamate antagonists, opiate antagonists, antioxidants, apoptosis inhibitors, and many others. One of the calcium antagonists, nimodipine, also called a calcium channel blocker, has been shown to decrease the risk of the neurological damage that results from subarachnoid hemorrhage. Calcium channel blockers, such as nimodipine, act by reducing the risk of cerebral *vasospasm*, a dangerous side effect of subarachnoid hemorrhage in which the blood vessels in the subarachnoid space constrict erratically, cutting off blood flow.

Rehabilitation Therapy

Stroke disability is devastating to the stroke patient and family, but therapies are available to help rehabilitate post-stroke patients. For most stroke patients, physical therapy (PT) is the cornerstone of the rehabilitation process. A physical therapist uses training, exercises, and physical manipulation of the stroke patient's body with the intent of restoring movement, balance, and coordination. The aim of PT is to have the stroke patient relearn simple motor activities such as walking, sitting, standing, lying down, and the process of switching from one type of movement to another. Another type of therapy involving relearning daily activities is occupational therapy (OT). OT also involves exercise and training to help the stroke patient relearn everyday activities such as eating, drinking and swallowing, dressing, bathing, cooking, reading and writing, and toileting. The goal of OT is to help the patient become independent or semi-independent.

Speech and language problems arise when brain damage occurs in the language centers of the brain. Due to the brain's great ability to learn and change (called brain *plasticity*), other areas can adapt to take over some of the lost functions. Speech therapy helps stroke patients relearn language and speaking skills, or learn other forms of communication. Speech therapy is appropriate for patients who have no deficits in cognition or

thinking, but have problems understanding speech or written words, or problems forming speech. A speech therapist helps stroke patients help themselves by working to improve language skills, develop alternative ways of communicating, and develop coping skills to deal with the frustration of not being able to communicate fully. With time and patience, a stroke survivor should be able to regain some, and sometimes all, language and speaking abilities.

Many stroke patients require psychological or psychiatric help after a stroke. Psychological problems, such as depression, anxiety, frustration, and anger, are common post-stroke disabilities. Talk therapy, along with appropriate medication, can help alleviate some of the mental and emotional problems that result from stroke. Sometimes it is also beneficial for family members of the stroke patient to seek psychological help as well.

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