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STROKE AND CEREBROVASCULAR DISORDERS:

NEUROLOGICAL IMPLICATIONS

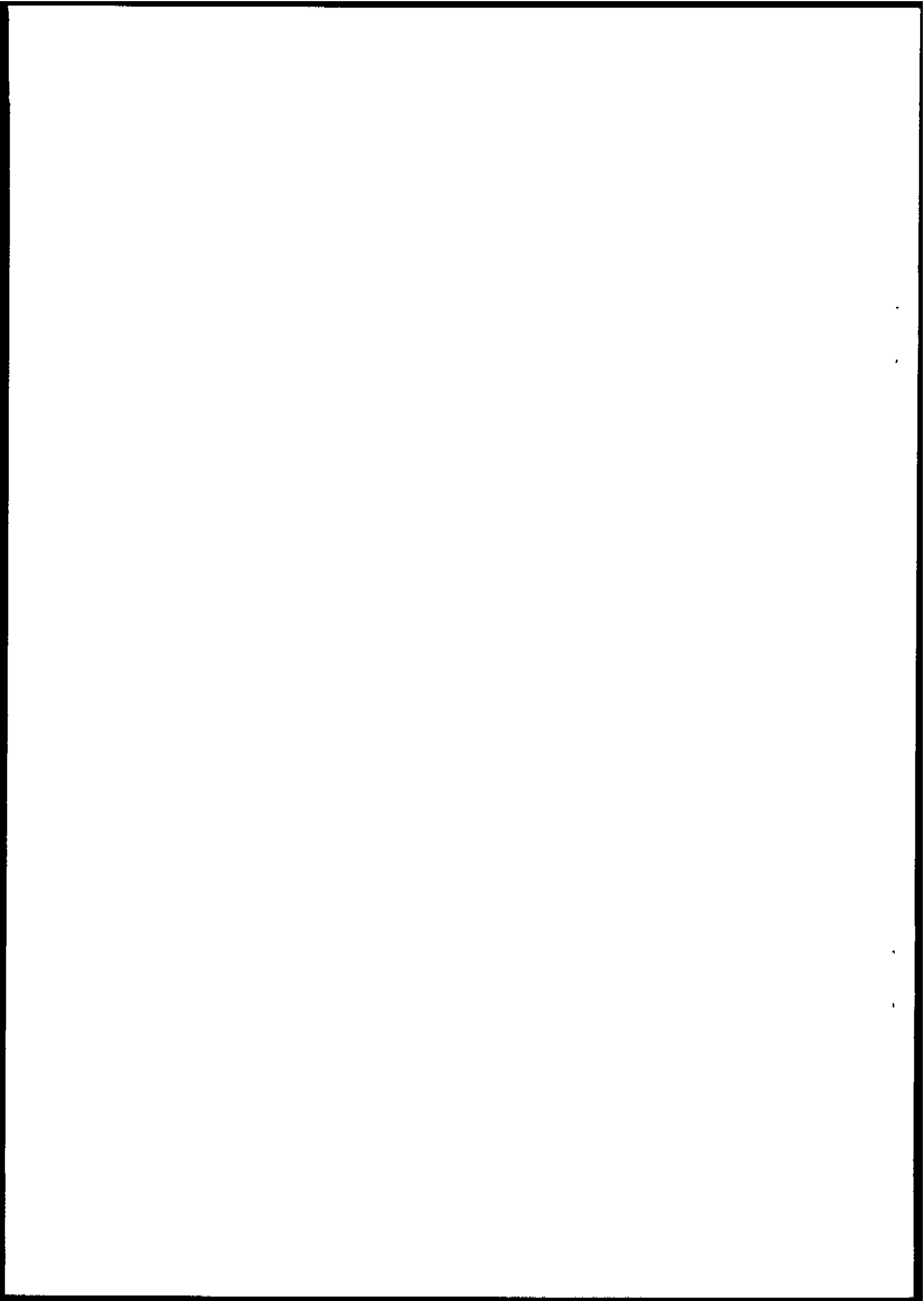


DIVISION OF MENTAL HEALTH

UNIT OF NEUROSCIENCE

WORLD HEALTH ORGANIZATION

GENEVA



STROKE AND CEREBROVASCULAR DISORDERS: NEUROLOGICAL IMPLICATIONS

This document arises from a WHO meeting held in Geneva on 13-15 February 1995. It summarizes the previous work of WHO/MNH in the field of neurology with special reference to cerebrovascular disorders and stroke, as well as materials related to different modern aspects of pathophysiology of stroke and relevant problems.



DIVISION OF MENTAL HEALTH
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GENEVA

1995

This document results from a WHO meeting on Stroke and Cerebrovascular Disorders: Neurological Implications, held at WHO, Geneva, 13-15 February 1995. The following experts participated:

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Further copies of this document may be obtained from

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STROKE AND CEREBROVASCULAR DISORDERS: NEUROLOGICAL IMPLICATIONS

1. INTRODUCTION

1.1 Welcome address

A WHO meeting on *Stroke and Cerebrovascular Disorders: Neurological Implications* was held in Geneva from 13 to 15 February 1995.

Opening the meeting the Director of the Division of Mental Health, Dr J.A. Costa e Silva stressed that the neurological implications of cerebrovascular disorders (CVD) and stroke deserve special attention because of their widespread prevalence and variable etiology.

Dr Prilipko introduced the new Unit on Neuroscience within the Division of Mental Health. Using modern achievements in basic and clinical neuroscience, the Unit will deal with the development and improvement of new methods for prevention, diagnosis and treatment of mental and neurological disorders.

Particular attention will be given to standardizing treatment and research methodology as well as to developing guidelines and consensus statements on controversial issues in psychiatry and neurology. In addition, collaboration between basic and clinical neuroscience will be emphasized strongly. The Unit includes the following sub-units:

1) Applied Neuroscience in Mental Disorders: This sub-unit will assist and coordinate research to develop methods for prevention, diagnosis and treatment of mental disorders, with emphasis on psychopharmacology and biological psychiatry including neuroimaging, neuropathological, neurochemical and molecular genetic investigations, cognitive evaluations and other methods.

2) Applied Neuroscience in Neurological Disorders: This sub-unit will promote and develop approaches to the prevention, diagnosis and treatment of neurological disorders. The frequency and the burden of neurological illnesses in the population calls for the application of public health principles and paradigms. Utilizing relevant diagnostic and therapeutic modalities, such as neuroimaging, neurological and neurosurgical interventions, the goal is to ensure an appropriate spectrum of care for all people with neurological disorders in each country. This however has to go hand in hand with the development of neurological inputs into primary health care programs. To reach this goal, the sub-unit will give priority to neurological problems that are common and amenable to treatment. These include epilepsy, cerebrovascular disorders, infectious diseases, disorders of motor system, headaches and cranio-spinal trauma. Special attention will be paid to the needs of children and the elderly.

The sub-unit will also promote and coordinate educational and training programs on these aspects.

3) Basic Neuroscience: The purpose of this sub-unit will be to provide a programmatic and organizational focus for basic neuroscience research within the WHO Division of Mental Health.

The sub-unit will provide international coordination of basic neuroscience research in humans and animals, in search of fundamental brain mechanisms in health and diseases. Training courses on research methodology will be organized and encouraged.

1.2 Scope of the meeting

Dr Prilipko stressed the purposes of the meeting, as follows:

1. To evaluate the cellular damage and cellular basis of brain energy metabolism;
2. To evaluate the neurological implications of stroke and other CVD in children and young adults;
3. The relevance of infectious and parasitic disorders;
4. Recent data on neuroimaging;
5. Neurosurgical approaches;
6. Related language disorders; and
7. Recommendations.

At the same time, it was suggested that a discussion to review the Special Report from the WHO "Stroke 1989" document should take place.

1.3 Background

Brain injuries have different pathogenesis including prenatal, metabolic, vascular, neurodegenerative, toxic, traumatic and tumoral conditions. The WHO meeting on Stroke and Cerebrovascular Disorders focused on vascular processes. Vascular involvement is a common denominator of most brain injuries, but only selected topics were considered at this Meeting.

One of the most important aspects of such injuries is direct ischemic damage usually secondary to arterial occlusion by thrombus or embolus, and acute tissue compression, and due to parenchymal hemorrhage. Another aspect is the indirect damage caused by compression, such as in head trauma and brain edema resulting from various causes.

Ischemia causes impairment of brain energy metabolism and an accumulation of calcium ions in the intracellular space, raised lactate levels, acidosis, and production of free radicals. Thus, it is critical to examine the cellular and metabolic damage as well as the entire cerebrovascular network. This will enhance our delineation of neuronal damage at the cellular and molecular levels as a background to the design of rational and targeted pharmacological interventions.

Brain and spinal cord injury results in cognitive and neurological impairments, functional incapacities, behavioral changes and overall handicap more severe than any other category of disease. The scope and magnitude of the deficits related to central nervous system (CNS) injury have only recently been fully appreciated, and warrant further studies.

2. PREVIOUS WORK OF WHO/MNH IN THE FIELD OF NEUROLOGY WITH SPECIAL REFERENCE TO CVD AND STROKE

Disorders of the nervous system, as well as of other organs, have various etiologies, *e.g.*: genetic, traumatic, toxic, nutritional, metabolic, infectious/inflammatory, degenerative, vascular, lack of proper nutrition and alcohol or drug abuse. A peculiarity of neurological diseases is that certain manifestations, like epilepsy, can result from any of these diverse etiologies, so that these manifestations are sometimes as important, in terms of management, as the underlying etiologies.

As early as 1954, the World Health Organization (WHO) convened an expert committee on epilepsy, a directory of epilepsy was published and other activities on epilepsy were initiated later: in 1969, WHO convened an international scientific group to discuss how to control neurological disorders and how best to define its priority areas. The group emphasized that neurological disorders represent a significant proportion of human illness, since everyone is at risk of neurological diseases throughout their entire life. These disorders may cause severe disabilities which render life difficult to the individual, their family and hence represent a significant burden to society. Many neurological disorders may be prevented, and for this reason, appropriate intervention measures to identify risk factors and to control through them neurological disorders should be implemented worldwide.

The WHO Neurosciences Program for the Control of Neurological Disorders was established in January 1974 as part of the Division of Mental Health. During the following years, an Expert Advisory Panel on Neurosciences was formed and later several WHO Collaborating Centres for Research and Training in Neurosciences were established in America, Africa, Asia, and Europe. Their mission was to advise the Director-General in developing the WHO Neurosciences Program for the Control of Neurological Disorders as part of the Mental Health Division and in establishing the Program in different parts of the world in order to contribute to an important aspect of WHO's global approach to achieving "Health for All by the Year 2000".

There was a positive response by different institutions in the world, member states and non-governmental organizations (NGOs) towards the implementation of the WHO Neurosciences Program that certainly facilitated its development and encouraged the development of measures to help control neurological disorders.

The Program, during its development, assimilated the results of many studies on the basic mechanisms involved in the etiology of neurological disease, in order to apply all possible measures of prevention and treatment.

The major lines followed were:

- (1) Promotion of basic science research, in order to get specific feedback information for applied clinical research.

- (2) Field research studies on neuroepidemiology in order to have information on the incidence, prevalence and distribution of neurological disorders in different parts of the world. Field studies in specific areas should make it possible to: (a) provide accurate statistics concerning the number of people affected by a particular disease in a selected area; (b) indicate whether the disease is increasing or decreasing in frequency; (c) identify areas of the world with a particularly high or low frequency of disease; (d) provide clues as to the cause of disease; (e) define factors that are important in predicting the outcome of disease; (f) measure the social and economic impact of disease; (g) evaluate the effectiveness of methods of treatment; and (h) predict the needs for programs and facilities to care for the people affected.

These studies are fundamental to better understanding the dynamic distribution of neurological disorders and hence their control. A WHO protocol has been developed for these field studies and suitable areas have been identified in Africa, South America, South-East Asia and some industrialized nations. In this effort, the WHO Collaborating Centres for Research and Training in Neurosciences have been extremely helpful.

- (3) Field research studies in specific areas of neurology, such as epilepsy, peripheral neuropathies (toxic, metabolic, traumatic), neuroendocrinology, behavioral neurology (including Alzheimer's disease and senile dementia), cerebrovascular disorders, infectious diseases of the nervous system and epilepsy. A protocol for community control of epilepsy has been prepared and tested.
- (4) Implementation of training medical personnel to better apply knowledge to prevent and treat neurological disorders, as well as the organization of training courses in different regions.
- (5) Establishment of a two-year fellowship program by WHO and the Fogarty Foundation for neurology training (neuroepidemiology, neuropathology, basic neurosciences, clinical neurology) for doctors mainly from Africa, South-East Asia, and South America: a total of 18 fellowships have been awarded.
- (6) Diffusion of information through study group reports and other documents, organization of international conferences on specific subjects, and cosponsoring of international neuroscience meetings worldwide.
- (7) Collaboration with WHO Regional Offices, EURO, AMRO/PAHO, SEARO, as well as with the WHO Collaborating Centres for Research and Training in Neurosciences and NGOs.
- (8) Preparation of Neurological Adaptations to the International Classification of Diseases: ICD-9 NA (1985-1987) and ICD-10 NA (1994-95).

2.1 International and scientific activities related to stroke and cerebrovascular disease, coordinated by the WHO Neuroscience Program, MNH

- International Symposium on Cerebral Ischaemia, Madrid, June 5-8, 1980.
- International Symposium on New Trends in CVD: Surgical and Medical Aspects, Gardone Riviera, July 2-4, 1981.
- International Conference on Neural Aging Including CVD: Basic and Clinical Aspects, Buenos Aires, August 26-28, 1982.
- International Conference on Neural Aging Including CVD, Buenos Aires, April 14-16, 1983.
- WHO Task Force on Stroke and Other Cerebrovascular Disorders, 1987-1989.

2.2 WHO training courses in cerebrovascular disorders

- Cerebrovascular Disorders: Special Technical Approaches, Marseilles, September 6-7, 1978.
- Training Course on Cerebrovascular Disorders in Latin America, Lima, October 22-27, 1978.
- Cerebral Disorders of the Newborn, Marseilles, September 3-6, 1979.
- WHO Workshop on Primary Management of Common Neurological Disorders Including CVD and Stroke, Ibadan, Nigeria, December 10-14, 1979.
- Training Course on Clinical Neurology, CVD and Stroke, Durango (Mexico), August 4-13, 1980.
- Training Course on "Epilepsie et Cérébrovasculaires Accidents", Marseilles, September 1-4, 1980.
- WHO Training Course on the Control and Management of Common Neurological Disorders including CVD and Stroke, Beijing, October 30 to November 12, 1980.
- Advanced Course on Neuroepidemiology (Including CVD and Stroke): Principles and Clinical Applications, San Miniato (Italy), May 18-25, 1981.
- WHO Training Course on Cerebrovascular Disorders and Transient Ischaemic Attack, Beijing, September 28 to October 6, 1981.

- WHO Training Course on New Methods of Investigation of Neurological Disorders Including CVD and Stroke, Shanghai, September 29-October 10, 1982.

2.3 International Classification of Diseases

- Informal Consultation on the Classification of Neurological Disorders for ICD-10, Geneva, May 1-4, 1984, MNH/MEP/84.2
- Informal Consultation on the Classification of Neurological Diseases for ICD-10, Geneva, September 10, 1984
- Informal Consultation on the Special Adaptation of ICD-9 for Neurological Diseases, Geneva, September 11-14, 1984, MNH/MEP/84.7
- Informal Consultation on the Application of ICD-9 to Neurology, Geneva, January 21-24, 1985, MNH/MEP/85.1
- Meetings of the Presidents of Non-Governmental Organizations: Preparation of the Neurological Adaptation of ICD-10, Geneva, December 1991, 1992, 1993.
- Subsequent preparation of ICD-10 (already published) and ICD-10 NA, which will be published at the end of 1995.

2.4 Publications

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WHO Offset Publication No. 43
- 1981- *Neuronal Aging and its Implications in Human Neurological Pathology*
Technical Report Series No. 665
- 1982- B.O. Osuntokun, B.S. Schoenberg, V. Nottidge, A. Adeuja, O. Kale, A. Adeyefa, O. Basemosi, A. Olumide, A.B.O. Oyediran, C.A. Pearson, C.L. Bolis
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Epidemiology of Cerebrovascular Disease in an Urban Community of Beijing, People's Republic of China
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- 1989- L. Morgante, F. Grigoletto, F. Meneghini, G. Vita, M.A. Coraci, A.E. Di Rosa, C.L. Bolis, R. Di Perri
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Neuroepidemiology, 8: 214-220
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Recommendations on Stroke Prevention, Diagnosis and Therapy
Stroke, 20(10): 1407-1431
- 1990- Rapport du groupe de travail de l'OMS sur les accidents vasculaires cérébraux et autres affections cérébro-vasculaires
Rapport de l'Organisation Mondiale de la Santé
Recommandations pour la Prévention, le Diagnostic et le Traitement des Accidents Vasculaires Cérébraux (première partie et deuxième partie)
Semaine des Hôpitaux, 66: 1789-1802 et 1845-1861.
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Journal of Stroke and Cerebrovascular Diseases, 2: 40-63.
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AIREN-NINDS / NIH - John Hopkins University *Neurological Outcomes After Coronary By-Pass Surgery*, Vancouver, July 30-31, 1991. NINS, Vol. IV, No. 4.
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Neurology, 43: 250-260.
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Application of the 10th International Classification of Diseases to Neurology (ICD-10 NA)
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3. CELLULAR ASPECTS OF STROKE AND CVD

3.1 Acute brain damage

Acute brain damage, particularly when due to stroke, cannot be dissociated from brain energy metabolism; indeed ischemic stroke results directly in an acute metabolic failure. In order to develop preventive strategies and potential therapeutic interventions, it is fundamental to identify the cellular and molecular events that underlie brain energy metabolism.

Recent experimental research has emphasized the role that astrocytes play in brain energy metabolism. Astrocytes constitute at least 50% of total brain volume, and quantitatively astrocytes outnumber neurons in ratios ranging between 10:1 and 5:1. The cytological relationships between astrocytes and other brain cells make them ideally suited to couple neuronal activity with energy metabolism. Indeed, specialized astrocyte processes, the astrocytic end-feet, are wrapped around intraparenchymal capillaries, while other processes ensheath synapses between neurones (Magistretti *et al.*, 1995). This arrangement allows astrocytes to sense synaptic activity and to control the entry of substrates into the brain. The signal that astrocytes recognize as a concomitant of synaptic activity, is the increase in extracellular K^+ and glutamate, while the major energy substrate that is imported from the circulation to sustain activity is glucose (Magistretti *et al.*, 1995).

One of the best characterized functions of astrocytes is to remove K^+ and glutamate from the extracellular space (ECS). Recent experimental evidence indicates that glutamate uptake into astrocytes triggers glucose uptake in these cells, thus providing a mechanism that couples neuronal activity with glucose utilization (Pellerin and Magistretti, 1994). Conversely, glutamate uptake into astrocytes is highly dependent on ATP generated through the glycolytic process (Swanson, 1992). This implies that impaired glucose availability, as it occurs in stroke, will lead to glutamate accumulation in the ECS. It is now well-documented that high extracellular glutamate leads to neuronal damage, and eventually death, via receptor-mediated excitotoxic mechanisms. Thus, failure of the astrocytic glutamate uptake process is likely to be one of the major mechanisms of neuronal death during stroke.

Another level at which astrocytes contribute to brain energy metabolism, is through their capacity to accumulate glycogen, the brain's single largest energy reserve, and to mobilize it following appropriate stimuli (Magistretti *et al.*, 1993). Recent evidence in experimental animals has indicated that pharmacological manipulations to enhance the glycogen content of astrocytes can limit the extent of ischemic damage (Swanson *et al.*, 1990).

This short introduction aims at reminding that any advance in knowledge of the basic cellular and molecular mechanisms of brain energy metabolism, in particular as they relate to neuron-glia interactions, is likely to help identify the pathophysiological mechanisms of acute brain damage, and to possibly identify new pharmacological interventions.

4. IMAGING TECHNIQUE IN THE EVALUATION OF CVD AND STROKE

Cerebral ischemic events account for 70-80% of all types of stroke and cover a wide spectrum of clinical presentations that range from transient ischemic attacks (TIAs) to cerebral infarction. For further management and initiation of appropriate treatment, differentiating between non-ischemic strokes, (*e.g.*, intracerebral hemorrhage, subarachnoid hemorrhage, and venous thrombosis) is essential. Additionally, classifying subtypes of ischemic stroke due to emboli, stenosis/thrombosis of large vessels, small vessels disease, or other causes would be helpful.

4.1 Diagnostic strategy

Diagnostic procedures to evaluate stroke patients must follow a strategy:

- demonstration of the lesion in the tissue, *i.e.*, diagnosis of ischemic or hemorrhagic stroke and differentiation from other brain damage;
- detection of the vascular lesion responsible for the attack;
- assessment of pathophysiological changes which might be accessible for therapeutic strategies and might indicate further course and prognosis.

The order of these three procedures indicates their hierarchical importance in the evaluation of stroke patients. Diagnosis of the lesion is made by brain imaging, especially X-ray computed tomography (CT) and magnetic resonance imaging (MRI), while more complex and sophisticated techniques, such as single photon emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance spectroscopy (MRS), are necessary to assess pathophysiological changes. Contrast angiography is still the "gold standard" for visualizing both the intracranial and extracranial vasculature, but it has the disadvantage of being an invasive test with some risk. Non-invasive techniques utilized to study the cerebral vasculature (*e.g.*, ultrasound imaging, Doppler and duplex scanning, color flow imaging, transcranial Doppler sonography, and magnetic resonance angiography) are gaining importance.

In diagnosing the lesion, CT and MRI are the important procedures to differentiate between ischemic strokes, intracerebral hemorrhages, subarachnoid hemorrhages, arteriovenous malformations and venous/sinus thrombosis. To detect intracerebral hemorrhages CT is still the preferred method, while MRI imaging better reveals early ischemic lesions and is superior in demonstrating small ischemic lesions in the white matter, basal ganglia and especially the brain stem.

A description of the techniques to detect the vascular lesion responsible for a stroke is beyond the scope of this review, which we have restricted to neuroimaging methods. We have also omitted an account of other methods to discover medical causes of strokes. In this context cardiac evaluation of stroke victims is vital, employing non-invasive transthoracic

echocardiography and the minimally invasive transoesophageal echocardiography to locate sources of emboli.

4.2 Assessment of pathophysiology of ischemic stroke

The disturbance of focal blood supply as the cause of ischemic stroke must reach certain threshold values to elicit functional neurologic defects, biochemical changes and morphologic tissue damage. The development of cell necrosis and infarcts depends not only on severity, but also on the duration of flow disturbances. According to the current concepts, complex biochemical and pathophysiological changes, which are triggered during ischemia or even during early reperfusion and continue after restoration of blood supply, additionally contribute to the development of ischemic cell damage.

Various physiological variables including regional cerebral blood flow (rCBF), regional cerebral blood volume (rCBV), and regional cerebral metabolic rates of oxygen (rCMRO₂) and glucose (rCMR_{glc}) can be measured noninvasively and repeatedly in the human brain by PET and/or SPECT of various tracers (Tables 1 and 2); and some pathophysiological

Table 1 PET Tracers used in Ischemic Cerebrovascular Disease

Variable	Abbreviation	Tracer	Isotope	Half Time
Cerebral Blood Flow	CBF	H ₂ ¹⁵ O	¹⁵ O	2 min
Cerebral Blood Flow	CBF	C ¹⁵ O ₂	¹⁵ O	2 min
Cerebral Blood Flow	CBF	¹⁵ O-Butanol	¹⁵ O	2 min
Cerebral Blood Flow	CBF	¹⁸ F-CH ₃	¹⁸ F	110 min
Cerebral Blood Volume	CBV	C ¹⁵ O	¹⁵ O	2 min
Cerebral Blood Volume	CBV	¹¹ CO	¹¹ C	20 min
Cerebral Metabolic Rate of Oxygen	CMRO ₂	¹⁵ O ₂	¹⁵ O	2 min
Cerebral Metabolic Rate of Glucose	rCMR _{glc}	FDG	¹⁸ F	110 min
Tissue H ⁺ -Concentration	pH	¹¹ CO ₂	¹¹ C	20 min
Tissue H ⁺ -Concentration	pH	¹¹ C DMO	¹¹ C	20 min
Blood-Brain Barrier	BBB	⁶⁸ Ga-EDTA	⁶⁸ Ga	68 min
Protein Synthesis	PS	¹¹ C-Methionin	¹¹ C	20 min
Hypoxic Tissue		¹⁸ F-Misonidazole	¹⁸ F	110 min
Activated Ca ²⁺ -Channels		¹¹ C-Nimodipine	¹¹ C	20 min

mechanisms leading to tissue damage can be studied by these methods. However, the necessary equipment is expensive, and the logistics involved are complex and necessitate a specifically trained interdisciplinary team. The studies are time consuming since it is usually obligatory to prepare, execute, and evaluate multitracer investigations. Therefore, these studies are restricted to special centers and the number of patients investigated is still limited.

Table 2 Main CBF-tracers used for SPECT

Inert lipophilic gases:

¹³³Xenon (¹³³Xe, PHL = 5.3 days; MEP = 81 keV)

Molecules labelled with ¹²³Iodine (PHL = 13.2 hours; MEP = 159 keV)

N-isopropyl (¹²³I)-p-iodoamphetamine (IMP)

N,N,N'-trimethyl-N'-[2-hydroxyl-3-methyl-5-[¹²³I]-iodobenzyl]-1,3-propanediamine (HIPDM)

Molecules labelled with ²⁰¹Thallium (PHL= 3.1 days; MEP = 167 keV):

[²⁰¹Tl]-Diethyldithiocarbamate ([²⁰¹Tl] DDC)

Molecules labelled with ^{99m}Techneium (PHL = 6.0 hours; MEP = 140 keV) :

^{99m}Tc-Hexamethyl-propyleneamine-oxime (HMPAO)

^{99m}Tc-ethyl cysteinate dimer (ECD)

Isotopes used for the labelling of red blood cells and plasma

^{99m}Tc pertechnetate: Mainly used for *in vivo* labelling of RBC (indicator of CBV) after preinjection of stannous chloride or stannous fluoride. Human serum albumin (indicator for plasma volume) can also be labelled with this isotope.

¹¹¹Indium (¹¹¹In, PHL = 2.83 days; MEP = 171 and 245 keV): due to the long half life, RBC kinetics can be studied over a longer period, however, its high gamma energy produces a considerable amount of scatter radiation and leads to severe degradation of image quality.

PHL = physical half life

MEP = main energy peak

Despite all technical achievements, functional neuroimaging can only assess a few steps - namely initial changes of perfusion and energy metabolism - in the complex biochemical and molecular cascade leading to ischemic cell damage. Functional neuroimaging, especially PET, however, may also yield important information on the extent of damage, compensatory mechanisms and the reserve capacity of the tissue to cope with a focal lesion, and therefore can be utilized to estimate prognosis and to evaluate therapeutic modalities. The applications of PET in ischemic stroke are summarized in Table 3.

Table 3 Applications of PET and SPECT in Ischemic Stroke

Acute ischemia:

- Thresholds of ischemia and infarction
- "Viable tissue" and "Penumbra"
- Pathogenetic mechanisms (misery perfusion, anaerobic glycolysis)

Postacute changes in tissue

- Growing infarcts
- Dynamic penumbra
- Postischemic hypo-/hyperperfusion

Chronic deficiencies

- Deactivation of remote tissue ("diaschisis")
- Hemodynamic reserve
- Metabolic reserve

Estimation of prognosis

- Subacute state and outcome
- Functional rerouting and recovery
- Functional reserve capacity (activation)

Evaluation of treatment effects

- Therapeutic window
- Long-term effects of revascularization procedures
- Early intervention focusing on disturbances of blood flow or energy metabolism

It should be decided which imaging methods are essential for stroke management for differential analysis and which technical procedure is necessary to decide therapeutic intervention; furthermore, which procedures may help improve our knowledge of the pathophysiologic mechanisms involved, and thereby may be used to indicate therapeutic strategies and to assess prognosis.

5. CLINICAL ASPECTS

This includes: 1) clinical presentation of the various types of stroke; 2) clinical findings which help identify the mechanism and etiologies, and 3) the strategy of laboratory investigations which derive from the clinical findings on the one hand, and from the management options under consideration on the other hand.

Stroke is diagnosed 500,000 times annually in the U.S., representing the most common single neurological cause of hospital admission. Each year approximately 150,000 persons in the U.S. die as a consequence of an acute stroke. Similar figures have been reported in other industrialized countries while data from other countries are scarce. Most strokes are due to cerebral infarction usually secondary to arterial occlusion by thrombus or embolus. Thrombotic stroke is due to either large or small artery occlusive disease, while embolic stroke is due to either cardiogenic, aortogenic or arteriogenic sources. Ischemic stroke is a major cause of death and disability. Despite its high incidence, acute management remains controversial. Most current forms of therapy are designed to reduce complications of a recent stroke or to prevent recurrences.

Early diagnosis and management in the first few hours after stroke are critical. Proper management begins with an accurate diagnosis. Stroke is a clinical diagnosis and, as such, the differential diagnoses must be considered. Differentiation between cerebral infarction and cerebral hemorrhage is paramount. Other disorders mimicking acute cerebrovascular disease must be excluded. CT is essential to differentiate an ischemic from a hemorrhagic stroke, and to help exclude tumors, abscesses, or subdural hematomas, which may masquerade as acute stroke. Physicians without easy access to CT may resort to a scoring system that can assist in the clinical diagnosis of acute stroke.

Ideally, stabilized patients identified as having possible ischemic stroke should have immediate screening blood work, including a complete blood count with differential, platelet count, prothrombin time, partial thromboplastin time, erythrocyte sedimentation rate, VDRL, serum glucose, blood-ureous-nitrogen, serum creatinine, serum sodium, potassium, chloride, carbon dioxide, cholesterol, triglycerides, lipoprotein electrophoresis, as well as urinalysis, plain chest X-ray, 12-lead EKG, and unenhanced brain CT. Intravenous enhanced CT studies are rarely needed unless a primary or metastatic brain tumor is suspected. If posterior fossa pathology is suspected, thin cuts through this area should be obtained. The physical examination should focus on the vital signs and cardiac, neurological, and neurovascular examinations. Blood pressure should be measured in both arms and in the supine, sitting, and standing position if hemodynamically acceptable.

5.1 Clinical presentation

The acute syndromes of cerebrovascular disease are characterized by a sudden (within seconds) or rapid (within minutes) onset of neurological deficits suggestive of damage to a localized structure of the brain. Hemiplegia, hemisensory (somatosensory or visual deficits) and impairment of language (aphasia) or other cognitive functions are the very frequent result

of stroke. Recovery before 24 hours qualifies the event as a transient ischemic attack (TIA), recovery after 24 hours or lack of recovery qualifies the event as a complete stroke (WHO Task Force on Stroke, 1989).

TIAs are recognized on clinical criteria only, which enable differentiation between vertebrobasilar or carotid TIAs in most cases. The clinical utility of recognizing TIAs lies in the possibility of adapting specific measures of prevention to avoid stroke recurrence.

5.2 Cardiovascular examination and history

History and physical examination aim at screening some major risk factors. A history of hypertension and diabetes, cigarette smoking, previous TIAs or strokes, coronary artery disease, or intermittent claudication, are major determinants for the occurrence, short term prognosis and recurrence of a stroke. Hypertension is the most important risk factor for all strokes and for ischemic strokes and is the direct cause of deep small infarcts called lacunar (Orgogozo and Bogousslavsky, 1989).

5.3 Prevention of complications

During the first days after stroke blood pressure reduction must be accomplished carefully to avoid exacerbating cerebral ischemia and careful management of fluids and electrolytes balance is mandatory. Prevention of complications due to immobilization in patients with acute ischemic stroke is the first stage of rehabilitation. The patient's position should be checked at least every two hours to avoid decubitus ulcers. Patients are generally not allowed to eat for the first twenty-four hours, and sometimes longer if they have difficulty swallowing, so that naso-gastric tube feeding is indicated. Venous thromboembolism is a common complication in patients with acute ischemic stroke and should be prevented in a systematic manner. Physical therapists, occupational therapists, neuropsychologists and psychiatrists are consulted, when needed, for these patients.

6. INFECTION AND PARASITES

The relative importance of the role of infections in the etiology of stroke is largely unknown because community- and hospital-based studies of stroke usually exclude infections. Nevertheless a wide variety of infections (bacterial, spirochetal, fungal, viral, rickettsial, parasitic) have been shown to be risk factors for all strokes, especially in the developing countries, and particularly in children. However, in these developing countries, as in the developed countries, the most important risk factor for stroke is high blood pressure.

6.1 Pathogenesis

The pathogenesis of stroke from infections includes vasculitis by direct spread through the lymphatics, adjacent tissues, or the blood stream, embolic occlusion as in bacterial or parasitic (*Trypanosoma cruzi*) diseases, occlusion of small vessels by parasitized red cells as in cerebral malaria, by schistosomal ova and by migratory adult worms (*Gnathostoma spinigerum*). Mycotic aneurysms may rupture. Gastroenteritis causing dehydration and hypernatraemia may predispose to stroke (especially in patients with sickle cell disease). Systemic infections may result in a hemorrhagic state with disseminated intravascular coagulation which may cause intracranial hemorrhage or cerebral venous thrombosis.

6.2 Infections and stroke

Endemic and epidemic acute bacterial meningitis, common in Sub-Saharan Africa, and tuberculous meningitis are complicated by stroke, usually ischemic infarction in about 10% of patients. About 20% of patients with infective endocarditis, will develop stroke (Valtonen *et al.*, 1993). Rheumatic heart disease is still highly prevalent in the young in Africa and infective endocarditis is a frequent complication. In developing countries endocarditis due to *Staphylococcus aureus* frequently involves normal aortic valves. Prosthetic valves, especially the mechanical types, may be affected by endocarditis. Meningovascular syphilis is an important cause of stroke in some Sub-Saharan countries (Osuntokun, 1979). Stroke may also be a complication of brucellosis, Lyme disease, Chagas disease, mycoplasma pneumoniae infections, infections with herpes viruses (Martin *et al.*, 1990) and human immunodeficiency virus (Philippot *et al.*, 1994; Perriens *et al.*, 1992) and critical medical illness (Bleck *et al.*, 1993). Stroke which occurs in about 5% of patients with sickle cell disease, which may afflict 1% of some communities in Sub-Saharan Africa, is usually precipitated by infections. A growing amount of clinical and experimental evidence suggests a link between infection and atherosclerotic diseases including both myocardial and cerebral infarction (Valtonen, 1991). The risk of stroke is increased in septicemic patients with and without endocarditis, and about 10% of bacteremic patients without endocarditis will develop stroke within one month of onset of bacteremia (Valtonen *et al.*, 1993). Seasonal variations of plasma fibrinogen and factor VII activity associated with more frequent infections in the winter may account for the increase in ischemic heart disease and stroke in winter (Woodhouse *et al.*, 1994).

6.3 Prevention

There is great opportunity to reduce the frequency of stroke caused by infections by promptly treating the common ones such as cerebral malaria, bacterial meningitis, endocarditis, and gastroenteritis especially in children. It is important to suspect infections as risk factors for stroke in young patients, particularly in developing countries, and appropriate diagnostic facilities should be available to direct appropriate treatment.

7. ISCHEMIC STROKE IN YOUNG ADULTS

Stroke is considered a disorder of middle-aged or elderly adults. However, young adults are also subject to stroke. The young stroke patient is a diagnostic challenge, since the list of causes is extensive and the diagnosis is often more difficult than in adults. Overall, 3-5% of cerebral infarctions affect young adults between the ages of 15 and 45 years. One study of young adults with ischemic stroke showed a 30-day mortality of 6.6% which is less than mortality reported with older adults. Ischemic stroke in young adults frequently results from atherosclerotic cerebrovascular disease, non-atherosclerotic cerebral vasculopathies, cardiac embolism and prothrombotic states.

7.1 Atherosclerosis

Although uncommon before age 40, atherosclerosis has its onset in infancy and childhood. It tends to affect the large and medium-sized arteries such as the aorta, iliac, superficial femoral, coronary and cerebral arteries. Positive independent predictors of atherosclerosis include cigarette smoking, advanced age, male gender, diabetes mellitus, systolic blood pressure, serum lipids and lipoprotein, and obesity. Smoking may be a particularly important risk factor for premature atherosclerosis in young adults. Clearly, smoking cessation has a major impact in limiting the cumulative effects of smoking.

7.2 Non-atherosclerotic vasculopathies

Many different categories of non-atherosclerotic vasculopathies may produce cerebral infarction. Cervicocephalic arterial dissections are an important cause of stroke in children and young adults, with most involving the extracranial carotid artery. Vertebrobasilar and intracranial carotid dissections are less common. Cervicocephalic arterial dissections are often underdiagnosed and underevaluated. Dissection should be considered in the differential diagnosis of stroke in any young adult, particularly when traditional risk factors are absent. Diagnosis is based on arteriographic findings. High-resolution magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) provide valuable information in the evaluation of these patients and may replace conventional cerebral angiography in the future. B-mode ultrasound and Doppler, although non-specific, can be helpful. Moyamoya is a chronic noninflammatory occlusive intracranial vasculopathy of unknown etiology. While it has been most commonly noted in Japan, it does occur in North America and has been seen in both children and adults, especially women in their first or third decades of life. Diagnosis is based on a distinct arteriographic appearance. MRI and MRA provide valuable information in the evaluation of these patients. Fibromuscular dysplasia (FMD), also known as fibromuscular hyperplasia, is a segmental, non-atheromatous, noninflammatory angiopathy of unknown etiology affecting medium- and small-sized arteries. The diagnosis of cervicocephalic FMD is made on the basis of cerebral angiography. Many infectious and multisystem noninfectious inflammatory diseases can cause cerebral vasculitis. Cerebral vasculitis can be considered in children and young adults with ischemic or hemorrhagic stroke; patients with ischemic or hemorrhagic stroke associated with encephalopathic changes, and patients with stroke accompanied by fever, multifocal neurological events, unexplained

skin lesions, glomerulopathy, or elevated sedimentation rate. Angiography is typically performed after an abnormal MRI to confirm the diagnosis; focal areas of irregular narrowing are demonstrated in the intracranial circulation, with variable branch occlusions. Although migraine has been implicated as a cause of stroke in many patients, migraine-induced cerebral infarction is a rare occurrence.

7.3 Cardiac etiologies

A definite or presumed cardiac etiology of cerebral infarction is found in 14-35% of young adults. While nonvalvular atrial fibrillation and ischemic heart disease are the most common causes of cardioembolic stroke in older individuals, the number of causes in young adults is more diverse, and unusual disorders need to be more seriously considered. Detection of these abnormalities requires a detailed history, cardiac examination and often extensive cardiological diagnostic studies. Imaging evaluation of the heart is accomplished primarily with echocardiography. Transoesophageal echocardiography is superior to transthoracic echocardiography in demonstrating potential cardiac or aortic sources of emboli.

7.4 Hematologic conditions

Several hematologic conditions may be associated with ischemic strokes. Hypercoagulable disorders account for 1% of all stroke patients, and for 2-7% of young patients with ischemic stroke. These disorders should be suspected in patients with recurrent episodes of deep venous thrombosis, recurrent pulmonary emboli, family history of thrombotic events, unusual sites of venous and arterial thromboses, or in patients with thrombotic events occurring during childhood, adolescence or early adulthood.

Brain and retinal ischemia in association with antiphospholipid antibodies has been frequently reported in this population. Antiphospholipid antibodies occur in patients with systemic lupus erythematosus, Sueddon's syndrome, acute and chronic infections, neoplasms, drugs and in individuals without demonstrable underlying disorders.

Stroke is a major cause of morbidity and mortality in sickle cell disease. The risk of cerebral infarction is higher in children under 15 years of age.

Cerebral arterial and venous occlusive disease should be considered in women of childbearing age on oral contraceptives, or during pregnancy and postpartum.

In spite of extensive investigation, many cases of stroke in children and young adults are classified as stroke of undetermined etiology. In some of these cases, genetic and metabolic causes of stroke may be overlooked and underdiagnosed.

8. LANGUAGE DISORDERS AND COGNITIVE DISORDERS

"Any description and classification of aphasic syndromes must begin with the question of what aspects of language are impaired" (Jakobson, 1956). An examination of the cognitive deficits that result from focal lesions of the brain (in the left hemisphere regarding language and other cognitive abilities such as mathematical and logical analysis; in the right brain regarding musical tone, spacial perception, etc.) however, can help to provide information on normal function just as an understanding of normal language and cognition helps to understand the resultant disorders. There is converging evidence that focal damage to the left cerebral hemisphere does not lead to an across-the-board reduction in language ability and that lesions in different locations in the left hemisphere are selective in the language disorders that result. That is, following damage to different parts of the left hemisphere, syntax (the way words are combined to form phrases and sentences) may be impaired with phonology (the sounds of the language) retained, for example, or vice versa as is the case of **jargon aphasia** (Buckingham, 1981). Fluent or Wernicke's aphasics (Wernicke, 1874) often produce neologisms or jargon which are correctly inflected so that the sentences are syntactically grammatical but uninterpretable.

8.1 Description

Agrammatism (Kean, 1985) was originally defined as a disorder of sentence production in which some aphasic patients typically delete grammatical formatives such as auxiliaries, pronouns, determiners and some prepositions, as well as inflectional affixes. Agrammatics are characterized as producing 'telegraphic speech' in which there is a proliferation of content words with an absence of grammatical affixes and words with their sentences lacking complex structure with few embeddings, dysprosody, and other difficulties in speech production. For many years agrammatism and Broca's aphasia (Broca, 1861) were synonymous terms but today there is general agreement that not all patients with lesions in Broca's area are agrammatic nor can all agrammatics be clinically classified as suffering from Broca's aphasia. An early view of agrammatism as purely an expressive deficit was revised in the 1970s when controlled experiments were conducted to test comprehension abilities (Caramazza and Zurif, 1976). Comprehension was found to be compromised when it depended on inflectional affixes and syntactic structure. Thus, agrammatics have difficulty in assigning thematic roles (who did what to whom) in reversible passive sentences such as *The dog was chased by the cat.*

Lesions that include the entire posterior portion of the first temporal gyrus, *i.e.*, Wernicke's area, produce the language disorder referred to as **fluent aphasia** or **Wernicke's aphasia**. The symptoms seem to be almost the direct opposite of those with lesions to Broca's area. Such patients speak fluently, with good intonation and prosodic contours, but with numerous instances of lexical errors (word substitutions) and neologisms. Unlike agrammatics whose syntax is disrupted, the phonological and semantic components of the mental grammars of fluent aphasics are affected.

Other linguistic deficits are also found following left brain damage. Among these are various forms of acquired dyslexia in patients who, prior to the lesions, were able to read and write (Newcombe and Marshall, 1984). One category of acquired dyslexics make many word substitutions in reading content words, *e.g.* HYMN may be read as *bible* but are unable to read grammatical words like *him, our, would* at all. Another group of acquired dyslexics can read words but not nonsense forms. Other reading deficits occur in these patients, *e.g.*, inability to provide a meaning from the written form and the ability to understand a wording from its pronunciation. Thus a word like PAIR will be understood as meaning either *pear* or *pair*.

One also finds category specific deficits, some patients have difficulty in naming man-made objects but not animate objects and vice versa.

It must be noted that the above-mentioned disorders are language rather than speech disorders such as **hypophonia** -- a pathologically reduced voice volume often resulting from deep anterior subcortical lesions involving the basal ganglia, a feature commonly found in Parkinson's -- or **dysarthria**, an articulatory deficit resulting from motor difficulties or impairments of the articulatory apparatus. The crucial evidence that it is language rather than speech disorders that result from specific brain lesions comes from studies of the sign language deficits following damage to the left hemisphere of deaf aphasics who prior to injury were native or fluent signers. Aphasia for sign language similar to the language breakdown in hearing aphasics result. Furthermore, the language impairments of these patients contrast markedly with their relatively intact capacities to process non-visual spatial relationships, further enforcing the fact that the left hemisphere has an innate predisposition for language, not speech or the physical ways in which language is expressed (Poizner, Klima, and Bellugi, 1987).

9. VASCULAR DEMENTIA: PERSISTING CONTROVERSIES AND QUESTIONS

Vascular Dementia (VD) implies the existence of a clinical state of dementia assumed to be caused by cerebrovascular disease. It has been recognized as a distinct form of dementia since the work of Kraepelin, Binswanger and Alzheimer 100 years ago.

The concept of dementia linked to cerebrovascular disease has evolved over time. Initially, the proposed pathophysiological mechanism emphasized "chronic cerebrovascular insufficiency". Then, a volumetric mechanism was proposed (damage to over 100 ml of brain tissue), and an aggregate and restrictive mechanism was suggested (multi-infarct dementia). These facts have led to either overdiagnosis or underdiagnosis of VD.

Recently the term "vascular cognitive impairment", was proposed but remains controversial. Also, the term "vascular dementia" has been criticized, because it represents largely an end-stage of post-stroke cognitive impairment and because the term "vascular" covers several different physiopathological mechanisms.

Indeed, controversies in the diagnostic criteria for VD persist. The Ischemic Score (IS) (Hachinski *et al.*, 1975) has shown to be an excellent tool to exclude a cerebrovascular lesion in patients with Alzheimer's disease, but is not useful to identify patients with pure vascular dementia. Operational difficulties in the definition of dementia, the absence of causal relationship between cerebrovascular disorders and dementia, and criteria limited to ischemic vascular lesions have been major problems in the proposed diagnostic criteria (DSM-III, DSM-IV, criteria of the State of California Alzheimer's Disease Diagnostic and Treatment Center - SCADDTC).

More recently, an operational definition of dementia emphasizing a causal and temporal relationship between cerebrovascular lesion and dementia, with several diagnostic sub-categories, has been proposed by the NINDS-AIREN working group (1993).

Although VD is considered the second most common cause of dementia, epidemiological data in VD are scarce and reflect the controversies of the concept. A prevalence of 15% of all dementias has been reported from European studies. In at least 10% of patients Alzheimer's disease and vascular dementia may coexist (Jellinger *et al.*, 1990). Age, arterial hypertension, diabetes mellitus, prior stroke, history of myocardial infarction, and cigarette smoking have been identified as risk factors for VD (Tatemichi *et al.*, 1993), but they do not differ from risk factors for stroke in general.

Many pathophysiological mechanisms are associated with VD (Leys and Bogousslavsky, 1994): 1. Large-vessel disease; 2. Small-vessel disease (Lacunar infarcts); 3. White matter changes including the rare entity "Binswanger's Disease"; 4. Potential cardiac sources of embolism; 5. Alzheimer's disease: LA and cerebral amyloid angiopathy (CAA) may be associated with Alzheimer's disease; 6. Hereditary causes: the most common being the Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and

Leukoencephalopathy (CADASIL); 7. Cerebral hemorrhage. 8. Combination of various mechanisms.

The laboratory investigations in a patient with a dementia suspect of vascular origin will be those of stroke. Neuroimaging studies may show vascular cerebral lesions in up to 90% of patients with VD, mainly ischemic.

Stroke prevention strategies may reduce by at least one-third the risk of vascular dementia, but no other specific treatment is available.

10. THERAPEUTIC APPROACHES - NEUROSURGERY

10.1 Stroke and cerebrovascular disorders

Surgical treatments for stroke and cerebrovascular disease are highly technical and considering the entire spectrum of the disease process, relatively limited in their application.

10.1.1 Carotid endarterectomy

For patients with cerebral or retinal TIAs or minor stroke due to advanced focal athero-thrombotic disease in the extracranial carotid artery, carotid endarterectomy has proven effective in reducing the risk for stroke in three randomized trials (European Carotid Surgery Trialists' Collaborative Group, 1991; North American Symptomatic Carotid Endarterectomy Trial Collaborators, 1991; Mayberg *et al.*, 1991). Recently carotid endarterectomy was also shown to effectively reduce stroke in asymptomatic patients with advanced carotid stenosis. However, the absolute reduction is small compared to that accrued in symptomatic patients. (Hobson *et al.*, 1993; The National Institute of Neurological Disorders and Stroke, 1994). In each of these situations, the benefit of surgical therapy was achieved by careful attention to patient selection and maintenance of low perioperative morbidity and mortality at or below established guidelines (Beebe *et al.*, 1989). Therefore it is mandatory that each surgical team monitor the results of their surgery particularly with attention to perioperative morbidity and mortality.

10.1.2 Extracranial-intracranial (EC-IC) bypass

Recent studies of patients with chronic cerebral hypoperfusion due to carotid occlusion or extreme intracranial carotid or middle cerebral stenosis suggest that there is a small group of patients who are symptomatic with hemodynamic transient ischemia who have an increased risk for subsequent stroke. Physiologic studies showing a diminished cerebrovascular reserve capacity have further defined this small group of patients (Yonas *et al.*, 1993; Schmiedek *et al.*, 1994). In those with progressive ischemia despite optimal medical therapy, an EC-IC bypass procedure is a rational therapeutic alternative; although unsupported by the findings of a single randomized trial (McCormick *et al.*, 1991; Schmiedek *et al.*, 1994). EC-IC bypass is also indicated in treatment of certain complex cases of giant aneurysm requiring parent artery occlusion (Sundt *et al.*, 1986).

10.1.3 Aneurysmal subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) due to intracranial aneurysm is a lethal disease in nearly one-half of the patients afflicted. Aggressive treatment of good condition patients as well as those in poor condition with promising neurological signs has resulted in improved management outcomes (Haley *et al.*, 1992). Important measures in this management strategy include early surgery to definitively repair the aneurysm causing the hemorrhage and hypervolemic therapy, and calcium channel blocking drugs to reduce the risk for delayed vasospasm. Endovascular treatments for obliteration of aneurysms and treatment of

vasospastic arterial segments are proving to be valuable treatment modalities (Moret, 1994; Newell *et al.*, 1989; Nichols *et al.*, 1994).

10.1.4 Cerebral arteriovenous malformations (AVM)

Cerebral AVMs carry a definite risk for hemorrhage at approximately 4% per year with accompanying major risk for morbidity and mortality. It is especially desirable to eliminate the risk of hemorrhage in younger patients by obliterating or removing the AVM. In selected cases of AVM, especially those of smaller size and in non-eloquent regions of the brain, surgical removal of the AVM is the treatment of choice. (Sisti *et al.*, 1993). For small, surgically inaccessible lesions under 3 cm in diameter, treatment with stereotactic radiosurgery can eliminate the lesions in most cases within 2-3 years with low morbidity (Friedman *et al.*, 1995). Preliminary treatment of the AVM with endovascular methods may facilitate open or radiosurgical therapy. In certain cases of large or very diffuse AVMs, there may be no viable alternative treatment because of inherent risks.

10.2 Hypertensive intracerebral hemorrhage (HICH)

HICH is one of the most common types of cerebral stroke. Despite a wealth of literature spanning over 100 years of vigorous research into the etiology and treatment of HICH, its mortality remains high and the majority of the survivors are left with moderate to severe disability (Ducker, 1985). A conventional method of treatment for HICH is medical and conservative, but this is not always satisfactory. CT has revolutionized HICH management. The size and location of the hematoma can be defined precisely by CT; this combination of clinical manifestations and CT findings allows a more rational approach to treatment.

Although clear cut indications for surgery have not yet been established, the following principles may be accepted:

1. For patients showing a secondary deterioration after the onset of hemorrhage, operation is often indicated.
2. In cases of cerebellar hematoma, the role of surgery should be emphasized except for those patients who are alert, without hydrocephalus and with hemorrhage volume < 10 ml. Generally, the results of surgery for cerebellar hemorrhage are good even for those patients showing evidence of brain stem compression (Crawell, 1986; Ducker, 1985; Zhao, 1993).
3. For selected patients in whom the etiology of bleeding is uncertain, exploratory surgery may be indicated to treat an underlying occult AVM or aneurysm.
4. Rarely is surgery for brain stem hemorrhage indicated. Cases combined with hydrocephalus and intraventricular hemorrhage may be best treated with ventricular drainage and, if necessary, delayed shunting.

Level of consciousness is the most important clinical criteria in selecting surgical candidates because it reflects the degree and extent of brain injury. It is widely accepted that an alert patient does not require surgery and most of those in a deeply comatose state will not benefit owing to severe primary brain damage (Chen, 1994; Zhao, 1993).

Conventional large craniotomy has the disadvantage of being time consuming and more invasive; therefore, in many cases it has been replaced by a small craniectomy (so-called key-hole surgery) utilizing microsurgical techniques (Zhao, 1993). Open craniotomy is recommended for patients with large lobar and putanimal hemorrhage to accomplish rapid decompression and complete removal of the hematoma. Bleeding points can be arrested under direct vision.

Hematoma cannulation with aspiration is less invasive, has a lower risk, and is better suited for deep-seated hematomas, *e.g.*, thalamic hemorrhage. It has been more widely used in elderly patients and those in poor condition. The modern aspiration technique is accomplished with a CT or MRI compatible stereotactic frame. Solid components of the clot can be morselated using various mechanical devices such as a screw, spiral steel wire or nucleotome (Chen, 1994; Jia, 1994; Kaufman, 1993). Also, clot fibrinolysis with urokinase has been used with success. Disadvantages of this method include rebleeding (0-3%) and incomplete clot removal (Chen, 1994; Jia, 1994; Kaufman, 1993; Zhao, 1993).

In conclusion, surgery has a place in the management of HICH, and imaging and technical advances have significantly reduced the mortality rate (Kanno, 1993). However, the patient's functional outcome is often unsatisfactory because of the primary brain injury. Criteria for patient selection need further study, and ultra early surgery appears beneficial in many cases (Chen, 1994; Kaneko, 1983; Zhao, 1993).

10.3 Endovascular treatment of stroke

The introduction of endovascular techniques for treatment of intracranial aneurysm, arteriovenous malformation, dural fistulae, etc. has significantly affected therapy. During the last decade, an extensive experience has been accumulated worldwide, and it is agreed that endovascular treatment has benefits, but it remains to be shown if the treatment results for aneurysms and AV fistulae will be as effective as those achieved with conventional open microsurgical methods.

The development of new techniques such as angioplasty, with or without local use of fibrinolytic agents, for treatment of ischemic stroke is still being explored; more experience to evaluate the possibilities of this treatment compared to more classical approaches such as carotid endarterectomy is necessary.

Further development of technology (new materials for embolization, intravascular laser techniques), laboratory experimentation, and more clinical experience will allow us to evaluate the usefulness of these minimally invasive treatments for stroke and intracranial hemorrhagic and occlusive lesions.

11. STROKE REHABILITATION

Rehabilitation involves retraining a victim following a stroke with a neurologic deficit to their previous level of function. Persons with neurologic deficits, usually hemiparesis or hemiplegia can be trained to use their retained normal function to allow as near normal daily function as possible. The problem of physical disability after stroke is increasing throughout the world. Populations are aging, and stroke is an age-related disease with incidence doubling with each decade after age 50. Although stroke incidence appears to be decreasing in most populations, decreasing mortality will increase the number of stroke victims surviving with significant physical disability (Bonita *et al.*, 1990; Broderick *et al.*, 1989). The prevalence of stroke victims in most societies will increase.

Rehabilitation programs for stroke victims are not universally applicable because of the initial mortality. Some individuals recover completely with return to normal function as their neurologic deficits resolve. On the other hand, some victims have such severe intellectual loss that they are unable to learn what is required, while others have such severe comorbidity from heart and lung disease that they are physically unable to endure rehabilitation programs. Rehabilitation should begin at the time of stroke onset. In most countries this means when the patient is first admitted to hospital and for others at home when the diagnosis of stroke is first made. Initial therapy is designed to prevent problems of immobility such as joint contracture, muscle shortening and venous thrombosis (Bromfield and Reding, 1988). This can be done by passive range of motion of the paralyzed parts, proper placement of the paralyzed limbs at rest and early ambulation. With stroke, sitting balance is impaired but with practice sitting patients learn to maintain balance and sit without support and falling. When patients are able to sit with good balance, they begin standing. Early standing is important because it prevents venous thrombosis and pulmonary embolus. Initially victims are fearful of placing weight on their weakened leg. Usually some bracing of the paralyzed or weakened leg is needed to stabilize the ankle and at times the knee. When the leg is stabilized, patients are encouraged to begin taking steps and attempting to walk. This process requires endless repetition and assurance from the therapist but with practice most patients can learn to walk either with no or with minimal assistance.

At the same time patients are taught new ways to carry out daily activities using their non paralyzed or weaker arm and hand. They quickly learn to use the functional arm to clean their teeth, bathe, dress and eat. These techniques can be taught by trained therapists but can also be taught by family members and friends at home who have had initial instruction. With practice, confidence is gained and the stroke victim has greater independence.

Victims who are initially incontinent are rarely so at the time of completing a rehabilitation program. Incontinence is handled by regular toileting procedures and taking the stroke victim to the toilet where the usual physiologic position for defecation and urination is possible. Training in transfer techniques from chair to toilet and back are usually possible when patients can stand and take a few steps.

The skill levels of those helping patients achieve these goals can vary from experts to those with limited training. Family members are always brought in to the program to see how it is implemented, so that the program can be continued at home or begun at home.

Motivation of the patient to try to develop new skills is essential. The most common reason for lack of motivation is depression. Depression is very common following stroke and most studies report that at least 50% of all stroke victims are depressed (Reding *et al.*, 1986). When depression is suspected, it must be treated with antidepressants, preferably nontricyclic antidepressants because of their anticholinergic action. Such treatment can improve the outcome of rehabilitation programs and shorten the length of the entire process. A role model of someone who has had a stroke and has been able to make progress in self-care and ambulation is desirable to help patients understand what can be done if effort is made.

The length of time required to complete a rehabilitation program is greatly influenced by the severity of the stroke. Those patients who have only motor involvement as the residua of their stroke have better outcomes and shorter lengths of stay in programs. Those who also have deficits in sensory perception or loss of visual fields have poorer outcomes. Such individuals often do not regain full independence in self-care and may be unable to walk without assistance. Even those with more severe brain damage, as evidenced by motor, sensory and visual deficits, can usually achieve some degree of independence with minimal assistance and be able to go home.

Language problems, expressive or receptive dysphasia, can influence the outcome of a rehabilitation program. If expressive dysphasia is the dominant language problem, it usually does not interfere with a successful outcome. Receptive dysphasia with lack of understanding directions and instruction can greatly impair a good outcome and may make it impossible to carry out a rehabilitation program. Stroke victims with expressive dysphasia are more often depressed than those with other types of dysphasia. Programs to help victims overcome language impairments are a continuous evolutionary process. Professional help is important but where it does not exist, non-professionals can be instructed to carry out many of the steps needed to restore useful communication.

Natural recovery from neurologic deficits following stroke usually occurs in the majority of patients within the first two weeks following the stroke. Recovery of function with improved self-care and ambulation can occur over many weeks and months following stroke. It is important to disassociate return of neurologic function from improved daily function. Although neurologic recovery may not occur or may become static, daily function may continue to improve.

Personnel to help carry out rehabilitation programs can vary from highly trained professionals to those with minimal education in the process. Results with motivated patients and motivated personnel can make impressive gains in outcome, despite the absence of a professional background.

12. CONCLUSIONS AND RECOMMENDATIONS

On the basis of comprehensive discussion the participants unanimously agreed that recent advances in clinical and basic neurosciences have led to greater understanding of the pathogenesis, diagnosis and management of cerebrovascular disease (CVD) and stroke. To address the different aspects of CNS injuries the following actions are recommended:

- I. The establishment of a WHO Task Force on Stroke and other Cerebrovascular Disorders.
- II. The organization of WHO meetings, training seminars, and/or reports on:
 - 1) Mechanism(s) of cellular death in CVD.
 - 2) Cellular and metabolic aspects of CVD and stroke.
 - 3) Molecular mechanisms of neuronal protection and synaptic plasticity as they relate to recovery of function.
 - 4) Advances in neuroimaging in CNS injuries.
 - 5) Surgical advances in the treatment of cerebrovascular disorders.
 - 6) Neurobiology, assessment and treatment of language and other cognitive disorders - relevance to CVD and stroke.
 - 7) Pathophysiology and management of CNS trauma.
 - 8) Assessment of new drugs for CVD and stroke in the light of new basic neuroscience findings.
 - 9) Evaluation of cost-effectiveness of current therapeutic measures and management options in stroke and cerebrovascular diseases.
 - 10) Molecular genetics of cerebrovascular disorders.
- III. Training programs should be developed:
 - 1) Expansion of the WHO Fellowship programs.
 - 2) Establishment of training workshops, at primary and secondary health care levels, in prevention and management of stroke and brain injury.

WHO may consider bringing together another expert group on "Chronic brain damage", to address the issue of neurodegenerative disorders (dementias, Parkinson's disease, motor neurone disease) and potential pharmacological interventions thereof.

Other topics that may be considered for WHO symposia or training seminars:

- Role of neurotrophins as therapeutic agents in neurodegenerative disorders: a critical assessment.
- Molecular genetics of cerebrovascular and neurodegenerative disorders.

The spectrum of cognitive deficits which result from head injury or stroke is vast. It is important that an interdisciplinary group composed of neurologists, neuropsychologists, and linguists form a task force to exchange information and data that has been collected worldwide in order to develop a new taxonomy of specific language and cognitive deficits. The traditional divisions into Broca's, Wernicke's, transcortical, conduction, etc. do not help to determine the specificity of either the disorder or the lesion sites.

Aphasiologists, neuropsychologists, neurolinguists from one country to another and within a single country use different protocols, different tests, different controls and it is difficult to compare results. We recommend that tests be shared, data be published, and researchers and clinicians begin to use unified tests that are linguistically and cognitively sophisticated. There is a major need to insure that these tests do not depend on reading and writing ability, so that they may be used with the large number of persons in the world who speak languages that are primarily oral.

A databank of aphasic and cognitive errors should be developed and made available to anyone requesting its use.

Every effort should be made to establish post-doctoral fellowships to enable cross-fertilization among disciplines in the study of aphasia and other cognitive disorders. Linguists should be supported to train in neurology departments or aphasia clinics; neuropsychologists and neurologists should be supported to learn basic linguistics, etc.

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