Progress in Cerebrovascular Disease

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Current Concepts in Stroke and Vascular Dementia

Editors

J. S. Chopra
K. Jagannathan
I. M. S. Sawhney
H. Lechner
G. L. Szendey

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Preface

Stroke remains the third most frequent cause of death not only in the Western world but also in many other developing countries. Whilst stroke is the most severe manifestation of acute cerebrovascular disease, the chronic forms remain a major medical and socioeconomic problem. The financial and human resources invested in the management of cerebrovascular disease represent a huge burden for both society and family.

The World Federation of Neurology, through its Cerebrovascular Disease Research Group, has undertaken considerable efforts to disseminate the advanced findings amongst both neurologists and internal medicine for whom cerebrovascular disease represent a daily encounter.

One of the most effective instruments has been a series of international symposia on various aspects of cerebrovascular disease organized throughout the world.

Following this principle, the Neurological Society of India, in agreement with the Council of Delegates of the World Federation of Neurology, decided to organize the first day main-theme symposium focusing on cerebrovascular disease at the XIVth World Congress of Neurology.

This volume compiles the papers presented at the sessions on acute and chronic cerebrovascular disease.

The editors wish to thank the convenors of the symposium, namely Professor Praful M. Dalal (Bombay, India) and Professor Helmut Lechner (Graz, Austria) for their dedication and expertise in organizing this state-of-the-art conference.

Introduction

George L. Szendey
Pharmaceutical Division, Hoechst Aktiengesellschaft, Frankfurt am Main, Germany

Although the incidence of stroke has been reduced in a number of countries as the result of better control of hypertension and other risk factors, there is every prospect that the total number of stroke victims worldwide will rise sharply over the next decades.

Reports from a number of countries clearly show that by the turn of the century many more people will live to an age at which cerebrovascular disease is a common occurrence. According to these sources, rising living standards and the conquest of many formerly rampant diseases, especially in the developing world with its young populations, will greatly increase life expectancy. A rise in cerebrovascular disease will be the inevitable result of this development.

Part One of this volume compiles the papers of the session on Acute Cerebrovascular Disease.

Neuroepidemiological studies indicate that transient ischaemic attacks, hypertension, myocardial ischaemic diseases, diabetes and smoking habits are major predicting risk factors for ischaemic stroke, as summarized by B.P.M. Schulte, The Netherlands.

Ischaemic stroke as the most severe manifestation of acute cerebrovascular disease is caused by either thrombosis due to atherosclerosis including emboli from carotid artery plaques, embolic strokes of cardiac origin and lacunar strokes due to arteriolar occlusion or cerebral microangiopathies. The latter includes the impairment of blood flow properties due to pathological changes in haemorheological parameters, particularly in the cerebral microcirculation.

A critical factor in acute cerebrovascular accidents is very often constituted by platelet adhesion on the basis of platelet aggregation and endothelial damage.

K. Kogure, Japan, suggests that sudden cerebral arterial occlusions leading to acute and chronic brain cell damage are characterized by neuronal mechanisms such as energy failure and loss of both structural and functional integrity of the cell membrane.

Acute cerebral ischaemia affects the functional cellular metabolism in the ischaemic territory. At the center of the infarction, tissue damage may occur but in the so-called penumbra, cell integrity may be preserved if reduction of tissue perfusion does not exceed a threshold value. A critical evaluation of the role of haemodilution as well as of haemorheological factors is presented by A. Hartmann, Germany.

J.S. Chopra, India, reports on acute cerebral venous occlusions, a fairly fatal condition common in India among child-bearing women or women who have just given birth. Curiously enough, all the women suffering venous stroke have had their confinements at home where – for traditional reasons – they have been deprived of water for one or two days. This suggests a possible relationship between the steep increase in blood viscosity and cerebral venous thrombosis.

Transient ischaemic attacks (TIA), often ignored by the patient, are increasingly recognized as precursors of serious cerebrovascular events. J.F. Toole, USA, argues that the arbitrary definition of TIA was established at a time when advanced diagnostic techniques such as CAT scan or MRI were unknown. The return of the function of briefly impaired areas after TIA does not mean that there is no permanent brain damage. About 36% of the patients have an infarction within the month and 50% within 12 months after the onset of TIA.

Stroke in the young is a frequent problem in the host country of the XIVth WCN, India. Hypertension, dyslipidaemia, high haematocrits, vasculitis and the use of oestrogenes are named by P.M. Dalal, India, as predominant causes of stroke in people aged 11 to 45.

Acute ischaemic stroke therapy is discussed by F.M. Yatsu, USA. Therapeutic measures are directed towards the thrombus, to the improvement of collateral circulation, particularly in the 'ischaemic penumbra', and to the prevention of secondary metabolic events, resulting from ischaemia and reperfusion which can aggravate the cerebral insult in precipitating irreversible neuronal damage.

Part Two of this volume presents the current concepts of Chronic Cerebrovascular Disease.

Vascular dementia (VD) is one of the most common forms of chronic cerebrovascular disease. It is currently considered as a severely frequent cause of dementia after the senile dementia of Alzheimer type (DAT).

Carlo Loeb of Italy claims that the term vascular dementia seems more appropriate to identify conditions of intellectual impairment due to vascular origin than the term multi-infarct dementia (MID).

The clinical diagnosis should include the identification of the dementia syndrome (history, neurological examination, psychiatric interviews, neuropsychological tests), the exclusion of causes of dementia other than Alzheimer's disease and vascular dementia, and a differential diagnosis between DAT and VD (ischaemic score, modified ischaemic score including CT and MRI, differentiation of clinical features ascribed to DAT and VD and focal EEG-changes, among others).

Memory loss is a feature of all forms of dementia, including those due to multiple cerebral infarctions. M.M. Cohen, USA, reports that the hippocampal formation, in particular, has been implicated as being critical for recent memory deficits in experimental animals and in humans. Bilateral hippocampal lesions disrupt spatial memory or cognitive mapping in lower mammals and lead to rapid loss of newly acquired information. Ischaemic hippocampal necrosis is a delayed rather than acute event.

Clinically, two broad categories are prominent in chronic cerebrovascular

disease. First, patients with severe focal neurological symptoms and often also dementia after a major stroke. Second, patients in whom progressive dementia is the dominant manifestation of cerebrovascular disease.

As it is difficult to distinguish clinically vascular dementia from cases of primary degenerative dementia, N.A. Lassen, Denmark, suggests to add the regional measurement of cerebral blood flow (CBF) and of cerebral metabolic rate of oxygen ($CMRO_2$) to the classical neuroimaging techniques CT and MRI for differential diagnosis.

Here, SPECT provides reliable data indicating that in patients with degenerative dementia either the absence of the cortical parieto-temporal low flow pattern or symmetrical frontal lobe flow can be observed. In vascular dementia, however, asymmetries of cortical CBF occur more frequently.

M.D. O'Brien, United Kingdom, critically discusses the importance of cerebrovascular disease as a cause of dementia as well as the underlying mechanisms. The author urges the need for a more appropriate definition of vascular dementia as the terms multi-infarct dementia and senile dementia might be rather misleading. Besides patients who definitely have a vascular cause of dementia, there exists a group with a mixed type of dementia in which degenerative and vascular pathology co-occur. Such a redefinition will certainly have an influence on the prevalence rate of dementia with vascular pathology.

The author also stresses that cerebrovascular disease causes dementia by a combination of the volume of infarcted tissue, the location of the lesions and, particularly, their bilaterality.

V. Hachinski, Canada, claims that the clinical assessment remains the mainstay and most reliable method of assessing multi-infarct dementia (MID). This involves three overlapping steps, namely determining dementia by clinical history, by physical examination and by mental status scales, determining the type of dementia as well as distinguishing between Alzheimer's disease and MID.

For the latter, the ischemic score remains the single most useful method. Hachinski presents a detailed analysis of the thirteen items and their contribution to the assessment.

The differential diagnosis also comprises the radiological assessment by CT and MRI, as well as the neurophysiological assessment by EEG and short latency somatosensory evoked potentials.

J.P. Blass, USA, outlines the principles of designing clinical trials on vascular dementia. The corresponding clinical criteria were used for a single-centre, double-blind, placebo-controlled trial of pentoxifylline (Trental) in vascular dementia. The patients underwent a treatment with either pentoxifylline or placebo for a period of 36 weeks.

When mean Alzheimer's Disease Assessment Score (ADAS) at the beginning of the trial was compared with the mean score at the end of the trial, there was significant deterioration in the placebo group, while the patients receiving pentoxifylline did not show significant difference from baseline. Pentoxifylline appears to have a positive effect on the course of vascular dementia, significantly slowing the course of deterioration.

The management of chronic cerebrovascular disease is reviewed by H. Lechner, Austria. The underlying strategies focus on the improvement of disturbed cerebral function and the prevention of relapses. Attention should be paid to reducing cerebrovascular risk factors such as smoking habits, arterial hypertension, impaired cardiac function and diabetes. Additionally, a pathological status of haemorheological factors should be corrected by adequate therapeutic measures.

Patients with acute ischaemic stroke or vascular dementia due to multifocal ischaemic lesions represent a heavy burden for the family and society. Although the experimental and clinical investigational tools and diagnostic techniques presently available have reached a most advanced and sophisticated level, the therapeutic measures are still limited and are subject to critical debate.

It was therefore an essential contribution to the XIVth World Congress of Neurology to provide a venue for this state-of-the-art symposium on cerebrovascular disease, documenting facts and shaping the vision of progress.

Contents

Part One

Acute Cerebrovascular Disease

Neuroepidemiology of cerebrovascular disease: An overview*

Bento P.M. Schulte
Institute of Neurology, Catholic University, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands

In developed countries, stroke is the third leading cause of death (after heart disease and cancer), and in many surviving patients, it is the devastating endpoint of cerebrovascular disease (CVD). To date, the best approach to CVD in general, and stroke in particular, is prevention. Rational prevention measures are derived from the data of well-conducted neuroepidemiological studies. During the last three decades, considerable literature describing the epidemiology of CVD has been published. The following is an overview of the neuroepidemiology of CVD for clinical neurologists [1].

Neuroepidemiology is the study of the distribution and determinants of neurological disease in human populations and the factors affecting those characteristics [2]. In designing studies, the most important considerations are representativeness of the population selected for investigation and accuracy of the diagnoses in that population. To correctly analyse the results of epidemiological investigations, one must be familiar with the complete definition of the disease entity being studied. Many but not all studies have defined stroke according to the criteria of the World Health Organisation (WHO) as 'rapidly developing clinical signs of focal (at times global) disturbance of cerebral function, lasting more than 24 h or leading to death with no apparent cause other than that of vascular origin. Transient episodes of cerebral ischaemia were excluded by definition' [3]. The last sentence of the WHO definition is especially important. For proper analysis of the results of epidemiological studies, it is also necessary to know how the subtypes of CVD and stroke were coded. In successive revisions of the WHO International Classification of Diseases (ICD), the same subtype of stroke is sometimes given different three-digit codes [4]. Moreover, in the current 9th revision of the ICD [4], CVD is still listed under the circulatory system, as it may well be in the upcoming 10th revision.

Disease frequency is measured by the following epidemiological indices: mortality, incidence, and prevalence. Descriptive studies using these three indices for CVD provide important information for formulating aetiological hypotheses. These hypotheses are tested using the techniques of analytic epidemiology (case-control or prospective studies). Thus, risk factors associated with CVD are identified. The fact that exclusion of risk factors is beneficial to preventing or reducing

* This paper is written in memory of the late Bruce S. Schoenberg, M.D., Dr P.H., F.A.C.P.

the frequency of CVD can be tested in experimental studies with controlled clinical trials.

Descriptive studies

Mortality

Mortality data have yielded information for large populations worldwide for many years. An official death certificate is required by the government in most nations. Thus, mortality data are collected relatively uniformly, and are available for analysis by age, sex, race, or geographic origin. Despite this advantage, using mortality statistics for establishing the frequency of CVD poses several dilemmas. In such tabulations, those strokes having high case fatality ratios are over-represented. A major problem is the uncertain accuracy of the diagnosis appearing on the death certificate. The death certificate is often rapidly filled out by a poorly informed physician, who may have only been called on to pronounce the patient dead. Diagnoses of stroke subtypes seem correct in only a minority of cases, except for those coded as subarachnoid haemorrhage [5]. Even in the Framingham study, considerable errors for stroke as a whole were made [6]. Another problem is that only one disease per person as the underlying cause of death is allowed on the death certificate. After analysing mortality data from the United States for deaths due to and related to 20 neurologic diseases for 1971 and 1973 through 1978, Chandra et al. [7] concluded that stroke as a single underlying cause of death was under-represented on death certificates.

Fratiglioni et al. [8], using data from 1967 through 1973 for 33 countries, calculated average annual CVD mortality rates, age-adjusted to the 1950 U.S. population. Of these nations, 27 were from Europe and America, only 2 were in Asia (Japan and the Philippines). Rates ranged from 35.8/100,000/year for the Philippines to 196.7/100,000/year for Japan. There was also considerable variation among European and North American countries, with most nations having annual rates close to 100/100,000 (Fig. 1). In the same paper, the rates from 1967 through 1973 were compared to age-adjusted rates from 1951 through 1958, previously calculated for the same 33 countries [9]. Approximately two-thirds of the nations for which data were available showed a marked decline in mortality rates. Of the 22 countries showing such a decline, 11 had a total percentage change of more than 20%. Several other studies reported major decreasing trends in mortality rates from CVD [10–14]. It is suggested that changes in coding conventions and inaccuracies on the death certificate explain the downward trend in mortality rates but this has not been verified. Garland et al. [15] described the trends in mortality rates from CVD in Baltimore, Maryland, during 1950–1970 with reference to all information found in the medical records. Overall accuracy of death certificate diagnoses did not change markedly during the study period. These investigators concluded that the decline of death rates could not be solely attributed to errors in death certificate diagnoses (Fig. 2).

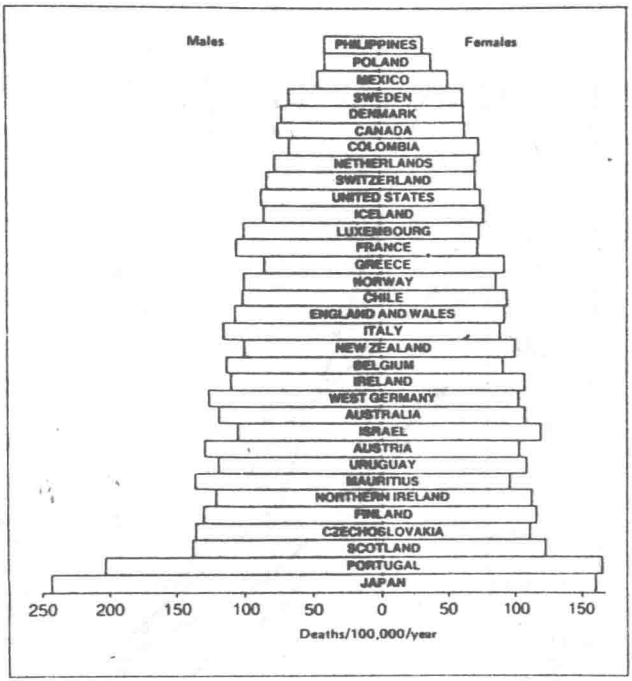

Fig. 1. Average annual age-adjusted (to 1950 United States population) mortality rates (per 100,000), by sex, for cerebrovascular disease, 1967–1973. Reproduced from Fratiglioni et al. [8], by courtesy of the Publishers.

Yatsu et al. [16] found lower mortality rates in three community hospital-based stroke programs in the United States during 1979–1980 than in the National Survey of Stroke during 1975–1976 [17]. It appeared that stroke severity was less in the former than in the latter study. This finding agreed with the hypothesis that the national decline in stroke mortality may be partly due to a decline in stroke severity rather than simply to a decline in incidence. Strong evidence exists, however, that the decline in stroke mortality should be attributed to better control of severe and moderate, and even mild, hypertension [18–20]. The phenomenon of a downward trend in stroke mortality even before hypertension was pharmacologically treated may be explained in the United States by changes in lifestyle [21] and by lower salt intake since the early decades of this century [22].

For all types of CVD, some general characteristics are applicable. Age-specific mortality rates rise steeply with increasing age [5,23]. Mortality rates analysed by sex revealed only a slight male excess for stroke in contrast to the strong male preponderance in mortality from ischaemic heart disease [8]. Before age 55, the male: female ratio for all stroke subtypes is high, at least in Sweden [24]. Although it has long been recognised that blacks in the United States have higher stroke death rates than whites of the same age and sex living in the same geographic

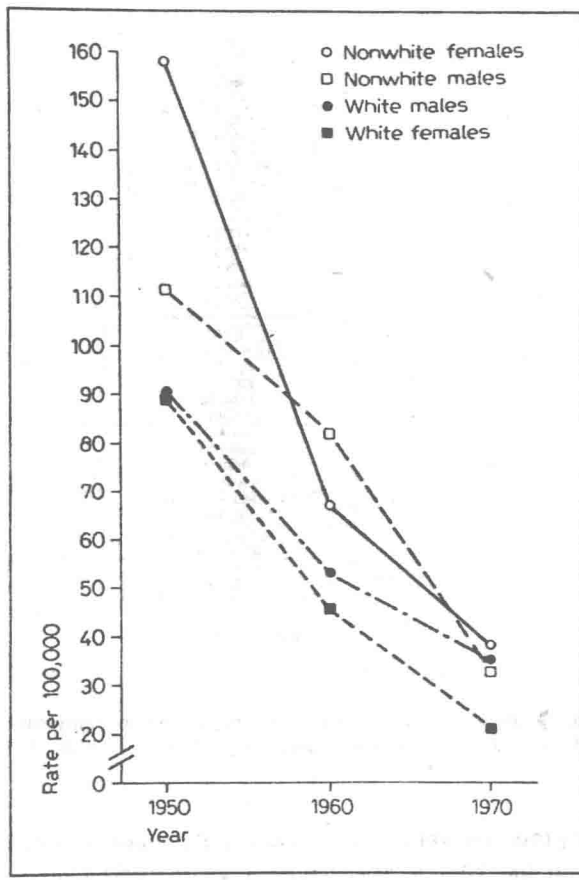

Fig. 2. Annual age-adjusted (to 1960 United States population) mortality rates per 100,000 population for cerebral hemorrhage (ICDA 8th revision, code 431), Baltimore, Maryland, 1950, 1960 and 1970. Reproduced from Garland et al. [15] by courtesy of the Publishers.

region, the reason for this discrepancy is still unknown [7,25]. There are geographic differences in mortality from stroke in the United States, Japan, the People's Republic of China, and France. In the United States, stroke mortality maps for three 7-year periods between 1962 and 1982 for U.S. whites aged 35–74 years showed an east-west gradient of high-to-low stroke mortality rates [26]. In Japan, age-adjusted mortality rates for CVD are higher in northeastern areas than in the southwestern part of the country [27]. In the People's Republic of China, age adjusted mortality rates from urban areas are highest in the northeast and lowest in the southwest [28]. The geographic pattern of stroke mortality in France did not change during 1962–1982; the highest rates were always found in the southwestern part of the country and in Bretagne for both sexes [29].

Incidence and prevalence

As has been mentioned, stroke mortality data contain many potential biases. The best measure of stroke risk is incidence. Because of differences in experimental design worldwide, data from incidence studies must be cautiously compared. Hospital-based investigations cannot precisely identify a population at risk, and it is impossible to calculate rates [30,31]. Furthermore, hospital-based studies may not be representative of all cases of CVD in the community. Since patients with severe strokes are more likely to be admitted to hospital, the distribution of stroke subtypes in the population may be incorrectly reflected [32]. Incidence rates derived from hospital data may underestimate the frequency of first completed stroke by 25–30% [33]. In a well-designed population-based incidence study such bias is excluded. But even in population-based investigations, there are differences that must be considered before making any comparisons. While some studies include all forms of CVD, others include only completed strokes; some count all episodes of stroke, and others exclude all but the first-ever stroke. Many community-based stroke incidence studies have been carried out in Europe, North America, Asia, Africa, and Australia. Recently, in a survey of CVD, Kurtzke [34] compared incidence rates of first completed stroke based on community studies from North America, western Europe, and Australia. After age-adjusting the incidence rates to the 1960 U.S. population, the resulting figures ranged from 100–250 new cases/100,000/year. Because many stroke incidence studies differ in design, comparisons between them may be invalid. In order to improve this situation, Malmgren et al. [35] proposed criteria for the 'ideal' stroke study. These criteria include the following: standard diagnostic criteria (according to the WHO); complete case ascertainment; prospective study design; definition of incident cases of those patients with their first-ever stroke; classification of a pathological type of stroke; rates given for all pathological types of stroke combined; well-defined denominator; representative and large population; rates calculated for similar time periods; cases collected for whole years; standard presentation of rates by age, sex, and race. Fifty-six published stroke incidence studies failed to meet these criteria. Nine comparable incidence studies remained: 5 in Europe, 1 each in the United States, New-Zealand, Japan, and Libya [36–44]. Only three time-trend studies came close to the ideal [38,43–45].

The percentages of the specific stroke subtypes in stroke incidence studies must be carefully evaluated, especially those performed before the introduction of computed tomography (CT). Wherever population studies of completed stroke have been carried out, cerebral infarction accounts for the majority of the incident cases. In a community-based study of a Caucasian population, Kurtzke [46] estimated that 8% of strokes are due to subarachnoid haemorrhage; 12% to intracranial haemorrhage; 69% to thromboembolic infarction; and 11% to ill-defined strokes. In the Harvard Cooperative Stroke Registry, 6% of all strokes are due to subarachnoid haemorrhage; 10% to intracranial haemorrhage; and 82% to thromboembolic infarction [47]. In population-based studies from Japan [42] and