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VIEWS AND REVIEWS

Setting priorities in Asian stroke research

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Abstract

This is a report based on the Asia-Pacific Stroke Stroke Workshop at the Biopolis, Singapore in September 2005. The meeting discussed the priorities, future directions and other issues in stroke research in Asia. Stroke research must occupy a prominent area in Asian neurology as stroke is a leading cause of adult disability and dependency, resulting in substantial demands in individual, family and healthcare resources. There are many problems in stroke research closely related to socio-economic, political and regulatory factors. On the other hand, there are many potential areas for clinical, genetic and epidemiological research in stroke, given the quantity and diversity of patients in Asia.

INTRODUCTION

Stroke is the main cause of adult disability and the 3rd largest cause of mortality in the world. With half of the world's population, stroke in Asia is important globally. With an aging population, there is an expected rise in numbers of stroke and a corresponding increase in the burden of stroke in Asia. Due to the limited economic and human resources available and the enormity of the problem, prioritization of research questions and directions for stroke investigators in Asia is of vital importance. On this background, the 1st Asia-Pacific Stroke Workshop was organized by the Clinical Trials and Epidemiology Research Unit, Singapore. This event was held at the Biopolis Complex, Singapore on 10th September 2005. It was sponsored by the Biomedical Research Council of Singapore and co-funded by several pharmaceutical companies. The present review is based on this successful workshop.

EPIDEMIOLOGICAL AND CLINICAL STUDIES

It is well recognized that stroke prevalence, mortality and incidence vary widely in different populations. Population-based epidemiological studies are lacking in many parts of Asia, some with large populations.[1-2] Available data are often limited to prevalence and mortality. Due to lack of medical certification for deaths, the mortality data are often inaccurate. In Asia, particularly in countries with wide geographical spread, ethnic and cultural diversities as well as large economic disparities, data on prevalence, mortality and stroke incidence are essential but difficult to obtain. Despite these difficulties, salient features of Asian stroke epidemiology have been described.[3]

For instance, the prevalence of stroke in China was recognized to be 3-6 times higher in the north compared to the south. This difference has been attributed to differences in modifiable risk factors such as diet, smoking and alcohol and hypertension.[3-5] Stroke in Asia is different from the West due to a high prevalence of lacunar stroke and a high incidence of intracerebral hemorrhage among men.[5-6] Similar findings were noted in many developed and less developed parts of Asia. However, more recent studies have noted a shift in numbers from intracerebral hemorrhage to cerebral infarction in populations from China and Japan.[7-10]

These basic epidemiological data are important as the basis for appropriate allocation of health care resources for stroke and as basis for stroke prevention strategies. The data will allow for monitoring of trends in a population due to urbanization, change of diet, lifestyles and healthcare facilities. Comparison to trends in the West as well as other populations can also be

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performed. Therefore, every effort should be taken to obtain these basic data for all countries in Asia.

Nevertheless, important information on stroke in Asia have been obtained from hospital-based registries including some recent data from economically more developed parts of Asia.[8-10] Data from economically less developed parts of Asia often have shortcomings from insufficient case ascertainment, imprecise diagnosis and incomplete investigations with variable accessibility to investigative facilities.[11] Case control studies with normal populations as comparison allow risk factors for stroke to be determined. Risk factor determination continues to be important particularly in certain stroke pathologies and in the young stroke population in Asia.[12-14] Monitoring of the risk factors in a population can also reflect the future trends of the incidence of stroke.

Hospital-based registries have been particularly successful in identifying the peculiar clinical features of stroke in Asia. These include the relatively high prevalence of young stroke[12-14], primary intracerebral haemorrhage[11], lacunar infarction[11] and intracranial atherosclerosis.[15-19] On the other hand, extracranial carotid stenosis is less frequent in Asia.[20] Why there is a difference between Asian and Caucasian patients when the risk factors appear to be similar in intracranial and extracranial disease should be an important research question. The prevalence of asymptomatic intracranial atherosclerotic disease in high risk patients[21] and its natural history are also important issues with public health implications. In view of higher prevalence of intracerebral hemorrhage among Asians with stroke, the risks of primary intracerebral hemorrhage in Asian patients with ischemic stroke while on anti-platelet drugs[22-24] should also be investigated.

Etiologies of stroke recognized to be more common in Asia are infections of the central nervous system, cerebral venous thrombosis, rheumatic heart disease, subacute bacterial endocarditis, lupus-related diseases, Takayasu's arteritis and moya-moya disease.[25] These conditions are likely to be given lower priorities in investigations in the West. However, there has been little collective effort in Asia to study these conditions in depth with respect to their epidemiology, clinical presentation, pathophysiology, treatment and outcomes. In these areas respectively, the use of transcranial Doppler (TCD)[26] ultrasound can contribute to the research of patients with stroke in Asia. TCD is an increasingly important, cost-effective and non-invasive investigative modality particularly in less developed parts of Asia for the diagnosis of intracranial atherosclerosis. As such, TCD can help in answering further research questions for instance, in central nervous system infections and strokes.[27-30]

Subcortical ischemic vascular dementia is another condition believed to be relatively common among Asians but has not been studied extensively. The underlying mechanism is said to be cerebral small vessel disease secondary to small, deep infarcts and subcortical white matter changes.[31] Cerebral small vessel disease is believed to be more common in Asia as seen from comparative studies between Asian and Caucasian populations.[6,11] More recent data suggested that the prevalence of subcortical ischemic vascular dementia following stroke was 13.3% based on formal neuropsychological testing.[32] Data from several other studies showed that the prevalence ranged from between 11-27%.[32-36] Overall, these studies were relatively small and there is a necessity for larger studies to clarify the prevalence of these conditions and to address therapeutic strategies in the future.

GENETIC STUDIES

Genetic studies are likely to play an important role in the understanding of the pathophysiological basis of stroke among Asians. It is likely that ethnic and genetic factors affect disease pathology and its manifestations in Asia and this is unquestionably applicable in the area of stroke[37], facilitated by the rapid technological improvements in molecular biology.

As previously described, intracranial large vessel atherosclerosis in Asians is a common cause of stroke with poor prognosis among Asians.[15-16] This is an important area for genetic studies.[38] However, genetic studies in the pathogenesis of intracranial stenosis are compounded by the coexistence of multiple risk factors such as hypertension and diabetes.[39] Very large cohorts and samples may be required before successful results can be obtained.

The genetic influence on the pharmacokinetics of various treatments in Asians is another meaningful area to investigate. This can include studies on gene polymorphisms for anti-platelet therapy resistance[40], the genetic differences in the effects of anti-hypertensives[41] and in elucidating the mechanisms of young stroke.[42,43]

Other possible areas are new candidate genes which confer increased risk of stroke such as phosphodiesterase 4D gene[44,45] among Asians.

The genetic basis of thrombophillic tendencies as well as the underlying hematological mechanisms of atherothrombosis in Asian populations is another priority area for research.[46,47] Genetic studies may offer possible explanations for the low incidence of deep venous thrombosis after stroke in Asians compared to Caucasians and in cerebral venous thrombosis. Further laboratory studies can also investigate the differences in haemostatic and fibrinolytic factors[48] associated with insulin resistance and the role of genetic polymorphisms in homocysteine metabolism[49] which may explain the prevalent mechanisms for atherothrombosis in Asian stroke patients.

The objectives can be achieved through a prospective collaborative effort by a consortium of international cohorts across Asia. There should be a series of defined outcomes with the analysis of pooled genetic material and relevant biomarkers. The current successful model, the Asia-Pacific Cohort Studies Collaboration produced numerous publications with international pooled epidemiological data.[50-52] A model which incorporates physiological parameters, biomarkers and genetic material can be another step forward, leveraging upon the ethnic diversity in Asia.

PSYCHO-SOCIAL ISSUES AND COMPLEMENTARY MEDICINE

In Asia, eighty percent of the populations live in rural areas particularly in economically less developed countries. In these countries, there is commonly an underestimation of the importance of stroke, particularly by governments and healthcare planners. Access to stroke services is often limited due to geographical and logistic reasons, inadequate physical and human resources, as well as cultural practices, beliefs and misconceptions.[53]

The impact of stroke on the patients and caregivers' psychological health and well-being has not been given serious consideration in many parts of Asia. Studies on informal care for stroke survivors has been performed in developed countries like Australia and the United States[54,55], but are only starting to gain attention in Asia. A study from Thailand[56] have confirmed that appropriate nursing information and assistance should be given to caregivers to ensure the best possible quality of life for both patients and caregivers.

Another common phenomenon in the management of stroke patients in Asia is the use of complementary medicine particularly in post-stroke setting. There are numerous herbal medications and various traditional modalities of treatment that are likely to vary between different countries and cultures.[57] These are utilized with the rationale that the treatments will improve recovery, assist in secondary stroke prevention, and promote better general health. Ginseng[58] and gingko[59] are among the better known examples of herbal medications. Well designed, randomized controlled trials of these commonly used herbal medications are lacking, although some of these herbs has been subjected to chemical analysis and animal studies.[60]

Acupuncture is another complementary medicine widely used in large parts of Asia. This therapy has been regarded as effective treatment in stroke rehabilitation by most practitioners of traditional Chinese medicine. However, there has been insufficient scientific evidence to confirm its efficacy.[61] Two recent meta-analysis and systematic review have not demonstrated additional effects on motor recovery compared to conventional rehabilitation within 6 months post-stroke.[61,62] Large, well designed randomized controlled trials such as that led by the Chinese Acupuncture for Stroke Study Group[63] will hopefully clarify its role and set a trend for the future studies.

Stroke awareness and public education is another important research area in Asia. It is well known that even in developed countries, public stroke awareness can be improved.[64,65] In developed countries, it has been observed that stroke awareness in populations at risk of stroke were not better than the general population.[66,67] In Asia, public stroke knowledge and awareness appeared to be related to age, educational levels and socioeconomic status.[68-70] In general, the percentage of participants who were able to name at least one risk factor for stroke ranged from 56-79%.[68-70] These findings appeared to be lower when compared to developed countries.[64,65]

Research in this area is useful in order to measure the effectiveness of prevention campaigns and public education programs. It can also identify deficient areas for improvement. Public awareness of stroke can also facilitate greater public demand and access for stroke services. This will in turn allow for greater allocation of funds into the prevention and treatment of stroke.

ECONOMIC IMPACT OF STROKE

Stroke, similar to many other areas of internal medicine, economic concerns are increasingly important and affects research funding decisions. There are three main categories when measuring the cost of stroke. The first is the *direct cost* including acute stroke therapy with relevant primary and secondary prevention strategies. The second is the *indirect cost* encompassing loss of productivity and income for both the patient and caregiver. The third is *intangible cost* concerning the change in quality of life.

Much of the direct cost is borne by society particularly in the developing countries. While the West has performed many studies, the results should not be directly extrapolated to Asia due to differences in health care financing and delivery systems. Aspects of direct cost that have been studied in some Asian countries include costs of acute stroke care and treatment[71], cost-effectiveness of stroke units[72], as well as the feasibility of thrombolytic treatment.[73-5] These can be models for similar studies by other countries in Asia. On the other hand, cost of rehabilitation has not been studied in Asia.

Similarly the indirect cost has also not been addressed sufficiently in the region. In many traditional Asian societies, the burden of post-stroke care often falls on the family, particularly the female members.[56] On the other hand, with increasing industrialization, rural to urban population shift, and change of the family structure and dynamics, there is change in how the burden of post-stroke survivors is being born. For example, the frequent use of foreign maids in the care of elderly parents with stroke has become the norm in some Asian cities. These changing practices are important considerations in assessing the indirect cost of stroke.

Inequitable distribution of resources for management of stroke is a common phenomenon in many countries in Asia. This is partly because in many of these countries, the cost of stroke treatment is largely born by the patients and their families. It is thus not surprising that the stroke specialists, stroke units, neuroimaging and rehabilitation facilities are largely concentrated in the capital cities and large urban centers. However, in some countries, this inequitable distribution of resources is also seen within the public sector. For example, in Malaysia, 80% of the neurologists from the Ministry of Health and public university hospitals are located in Kuala Lumpur, whereas the Klang Valley only accounts for a fifth of the country's population. The distribution of stroke resources in relation to the population spread in Asia should be carefully documented to ensure a more equitable distribution of resources in the future.

BARRIERS IN STROKE RESEARCH AND FUNDING ISSUES

Bureaucratic difficulties are important factors in the success of stroke research in many countries in Asia. These are related to political, administrative and regulatory factors. For example, many areas in India are under different political control with different languages used in administration. Stroke research also occupies low priority in the political agenda. In Japan, prohibitive regulatory requirements in the licensing of new drugs can be most frustrating. In China, regulatory bodies do not allow the export of genetic material.

Limited funding for stroke research is an issue not just in Asia, but elsewhere in the world. Possible funding sources include the WHO, a network of investigators associated with the International Stroke Society, the Wellcome Trust, and the National Institutes of Health (NIH) of United States of America. NIH funding is difficult to obtain for non-US based programs unless the research cannot be done in US but has to be carried out in Asia. The NIH application can be strengthened with a good US-based partner. Other possible funding sources are the national governments, non-governmental organizations, professional bodies, patient-based stroke organizations, academic institutions and pharmaceutical industries. Currently, most Asian stroke researchers receive funding from central national research councils and national professional organizations whereas patient-based organizations provided very small funding for minor projects only. Private funding in Asia is limited.

The Stroke Trials' Network consisting of various centers in Australia, New Zealand, Singapore and Hong Kong is a good model of research collaboration in the region. It is also successful in attracting funding to various centers of excellence to maintain and expand stroke research. Further information regarding this collaboration can be accessed via the website *http://www.astn.org.au/home.html*

DEVELOPMENT OF COMMON MEASUREMENTS AND TRAINING

Common research tools for communication are another important issue to facilitate stroke research in Asia. There is a need for common measurements such as widely accepted stroke scales optimized for regional use. This will prevent disparities between countries when reporting data. A common language for the exchange of findings will enhance further cooperation from different centers. Examples of widely accepted stroke scales to be adapted locally are the NIH stroke scale, the TOAST criteria and MMSE. International multi-centered pharmaceutical sponsored trials may be a valuable resource for translated and modified scales for regional validation and use.

Training is also an important issue to facilitate stroke research in Asia. Through training, researchers can build up local technical capabilities and infrastructure. A dual training scheme for a higher degree where one year is spent in an overseas training center of excellence, and the rest of the time is spent doing research of local importance in the home country may help to minimize brain drain from extended overseas training. This will also facilitate Asian stroke research. Short workshops with specific themes such as research methodology, use of certain investigatory tools for researchers and allied health personnel may also be useful.

In *conclusion*, with limited resources, investigators of stroke in Asia should clarify their priorities. However, progress is also dependent on overcoming various bureaucratic, regulatory and funding issues. Tactical partnership between various neurological and stroke centers, international organizations, funding bodies, pharmaceutical industry, and individual stroke specialists may be an important key to future development.

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