Neurology Asia 2005; 10 : 7 – 11

Epidemiology of central nervous system infections in Asia, recent trends

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Abstract

Infections of the central nervous system are important because of the endemicity of many of pathogens, the emerging and reemerging of new infections, the heavy burden they impose on the health care system, the confusing numbers of pathogens involved, the difficulty in arriving at exacting microbiological diagnosis and the significant mortality and morbidity rates in the affected patients. These are particularly so in Asia. The epidemiology of central nervous system infection in Asia exhibits significant differences from the rest of the world. Although the causes of bacterial meningitis are relatively uniform in many parts of the world, in some parts of Asia, gram negative bacilli and tuberculosis, not commonly found to be important as causes of bacterial meningitis elsewhere, assume far greater importance. The spread of enterovirus 71 and Japanese encephalitis virus from their previously geographically limited locations and the emergence and reemergence of new pathogens exemplify the dynamics of the changes in epidemiology induced by interaction between ecological factors, human activities and weather changes. Yet there is a disconcerting lack of epidemiological data from this region. More epidemiological studies and cooperation between centres to facilitate disease surveillance, pathogen transmission characterization and formulation of clinical management are urgently needed in Asia.

INTRODUCTION

Infections of the central nervous system are an important aspect of neurology practice worldwide. On a global scale, not only are many of these infections endemic, epidemics of meningitides and encephalitides, including emerging and reemerging infections, have also occurred with alarming frequency in many places of the world. As a whole, central nervous system infections impose a heavy burden on the health care resources in many nations. In the United States alone, for example, there were nearly 19,000 hospitalization annually for encephalitis, resulting in 230,000 hospital days stays, 1,400 deaths with an annual cost of US$650 million.[1] To the individual health care provider, central nervous system infections often present in such diverse manifestations that they could easily be confused with other disorders. Added to this is the fact that there is a long list of infective agents that are responsible, and often even at discharge, many of these agents are not identified. In only a third to half of the causes of encephalitides are the pathogens identified even with the best laboratory facilities.[2] Yet central nervous system infections are important because they are neurological emergency with significant mortality and morbidity rates. Epidemiological data, therefore, are indispensable in helping the clinicians to make diagnosis, and the policy-makers in combating the illness on a wider scale.

In Asia, central nervous system infections are of particular interest and importance, because of the endemicity of many of these infections, such as Japanese encephalitis[3,4] and tuberculosis, as well as the fact that it recently witnessed the emergence and reemergence of some deadly pathogens. Yet there is a dearth of epidemiological data on the topic from Asia. This article aims to review three broad epidemiologic trends on central nervous system infection in the region, namely the differences in the causative pathogens, the spread of pathogens previously known to be confined geographically to other areas, and the emergence and reemergence of new pathogen.

DIFFERENT PATHOGENS – BACTERIAL MENINGITIS

The commonest causes of bacterial meningitis worldwide are *Haemphilus influenzae*, *Streptococcus pneumoniae* and *Neisseria meningitides.*[5-21] In developed countries with effective vaccination programs, the incidence of *H. influenzae* and *N. meningitides* showed decreasing trends. In the United States, for

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example, after the introduction of *H. influenzae* type b vaccination, the commonest causes of bacterial meningitis in all age groups are pneumococcal, meningococcal, group b streptococci, *Listeria monocytogenes* and *H. influenzae* type b, in decreasing order of incidence.[22] Among children in England and Wales, the commonest causes are meningococcal, *H. influenzae* type b, pneumococcal, group B streptococci, *Escherichia coli*, *Listeria* species and staphylococci.[23] The causes of bacterial meningitis in many parts of Asia are the same, in places as diverse and different as the United Arab Emirates, Bangladesh, China, Vietnam, Korea and Japan.[10-16, 21] In other places in Asia however, the causes of bacterial meningitis are different. In Hong Kong, the commonest cause of non-viral meningitis is tuberculous meningitis, accounting for more than 15% of meningitis in children. Bacterial meningitis, on the other hand, is uncommon. *H. influenzae*, the commonest cause of bacterial meningitis, showed an annual incidence of only 1.1/100,000, even in the absence of an effective vaccination program.[24] In comparison, the incidence of *H. influenzae* meningitis is 2.2 – 4.3/100,000 in the United States[25] and 1.6/100,000 in United Kingdom[26] before the introduction of vaccination, 2/100,000 in Spain,[27] and 6/100,000 in Korea.[16] In the same study, meningococcal meningitis was only seen in Vietnamese children and in none of the indigenous Hong Kong Chinese children.[24] In Indonesia, gram negative bacilli are important cause of bacterial meningitis. In a study quoted by Pusponegoro *et al*, the commonest causes of pediatric bacterial meningitis were *Salmonella* species and *Acinetobacter* species.[28] In Taiwan, gram negative bacilli showed similar importance. In a survey of 263 adults with community acquired bacterial meningitis, the commonest cause was *Klebsiella* species. Staphylococcal species were the third commonest; and these two bacteria accounted for 26% and 14% of all bacterial meningitis respectively.[29] Similarly, *Streptococcus agalactiae* was the commonest cause in adult bacterial meningitis in Singapore and Hong Kong, accounting for 38% of all the meningitis in the two hospitals surveyed.[30]

The usual causes of bacterial meningitis – *H. influenzae*, pneumococcal and meningococcal – are important worldwide. However, in parts of Asia, especially part of East and Southeast Asia, a variety of gram negative bacilli are proportionately more important.

SPREAD OF PATHOGENS – THE ENCEPHALITIDES

Enterovirus 71 was first isolated in California in 1969. It was known to cause febrile illness and in a small minority of patients, a mild aseptic meningitis. In 1975, it caused an outbreak in Bulgaria affecting 705 patients with poliomyelitis-like paralytic illness with 44 deaths; and 93% of these patients were children under 5 years of age. In 1986, it caused another outbreak of hand-foot-and-mouth disease in Southeast Australia, again affecting children under 5 years of age. In this outbreak, however, half of the patients had severe neurological complications. Though previously unknown in Asia, the first EV71 outbreak occurred in Sarawak, Malaysia in 1997. The virus then spread from here to other parts of Malaysia, then to Taiwan, Singapore, Western Australia, Japan and Korea. In Taiwan alone, it was estimated that over a million patients were affected with over 400 admissions and 78 deaths. The strain that spread through the region was obviously more virulent from the one first isolated in 1969.[31,32]

Japanese encephalitis has caused major outbreaks in Asia every 10 years or so.[33] The virus is believed to have originated from Malaysia – Indonesia.[34] It was first isolated in the 1870's in Japan. Since then it has spread relentless throughout Asia and Asia Pacific. It spread to China in around 1935, and was first isolated there in 1940. In 1938, it reached the far eastern states of Russia; and in the Western Pacific island of Guam in 1947. In 1949, large epidemics were first reported in Korea. In 1965, epidemics were reported in Northern Vietnam, and in 1969, in Chiang Mai, Northern Thailand. In India, the first reported cases were confined to Southern India in 1955. In the 1970's, large epidemics have broken out in the eastern and northeastern states and cases were reported in Bangladesh and Myanmar. In 1990 it was reported in Saipan, Western Pacific, in 1995 the virus spread from Papua New Guinea, where it is endemic now, to the Torres Strait Island of Australia. In 1998, the first clinical case in mainland Australia was reported to occur in southwestern Cape York. Today, all over Asia, there are probably 50,000 cases with 15,000 deaths annually.[33-35]

Both enterovirus 71 and Japanese encephalitis viruses were previously limited in their geographically distribution. Over the last century, Japanese encephalitis has spread throughout the larger parts of Asia, affecting more than 2.5 billion people and enterovirus 71 has caused

affected a large part of the Asia Pacific region. The spread of Japanese encephalitis virus is probably related to the gradual spread of the mosquito-animal cycle, probably due to changing agricultural practice such as increasing irrigation with subsequent increase in mosquito breeding, change in animal husbandry and perhaps weather conditions that produce strong northerly winds that carry infected mosquitoes from the New Guinea mainland to the Torres Strait and Cape York in Australia.[33,35] The spread of enterovirus 71 is less well studied, but may be related to increasing ease in international travels and the high population density in many urban cities of Asia that facilitates human to human spread.

EMERGING AND REEMERGING INFECTIONS

From September 1998 to June 1999, an outbreak of fatal encephalitis occurred in several pig farming villages in Malaysia, affecting mainly the farmers. By the end of the outbreak, some 256 people were affected, with 105 deaths.[36,37] A retrospective serological study on pig farmers with encephalitis from one of the first outbreak village admitted into the local hospital a year earlier showed that the patients had positive serology to Nipah virus.[38] Though initially suspected to be due to Japanese encephalitis, a new paramyxovirus was subsequently isolated, named Nipah virus, after the village of the patient from whom the virus was first found. The virus was subsequently grown from the fruit bats which inhabit much of South and Southeast Asia.[39] Follow up studies showed that up to 9% of survivors and 3.4% of asymptomatic patients suffered relapsed encephalitis up to 53 months after the initial illness.[40,41]

The emergence of the Nipah virus in Malaysia is believed to be due a series of complex interplay of ecological factors, weather changes, changing agricultural practices and deforestation process. Severe deforestation and industrial plantation over the past two decades in Peninsular Malaysia and Sumatra, Indonesia, have severely reduced the habitat of the fruit bats *(Pteropus vampyrus* and *P. hypomelanus*), the natural hosts of the Nipah virus. Slash-and-burn deforestation practice and the drought caused by the El-Nino Southern Oscillation led to acute reduction in the availability of flowering and fruiting forest trees in the shrunken bats habitat. In the same time, intensive pig farming practice, with planting of fruit trees within pig farms to maximize land utilization lured the flying foxes into unprecedented encroachment into the pig farms. The bats probably transmitted the virus to the pigs via secretion. The pigs then acted as amplifying hosts and transmitted the virus to human. After the demise of the pig farmers, the left over pigs were fire-sold by surviving family members and transported illegally to other pig farms in Malaysia, transmitting the virus to other pig farms.[42]

After a hiatus of 2 years, four outbreaks of encephalitis in Bangladesh over 4 years were found to be caused by Nipah virus. The outbreaks occurred in Meherpur in 2001 and Naogoan in 2003, Rajbari, Faridpur, Golpagonj, Manikganj, Joypurhat, Naogoan in January 2004, and again in Faridpur in April 2004.[43] The significant differences between the Bangladesh outbreaks and the Malaysian outbreak were many. Though the natural host of the virus in Bangladesh is fruit bats as well (*Pteropus giganteus*), unlike the outbreak in Malaysia, the virus was believed to be transmitted directly from bats to human via the date palm juice, collected under the trees overnight, and drank unboiled. Bats were believed to feed on the fruit of the trees and their secretion contaminated the juice collected (personal communication, M. Faiz). Direct bats to human transmission was previously shown not to be important in Malaysia.[44] Human to human transmission is also thought to be important in the Bangladesh outbreaks as family members and relatives caring for the sick contracted the virus as well, a phenomenon shown in the Malaysian outbreak involving three health care workers but was not the prominent mode of transmission.[45] Contact with sick cow was the only other important risk factor in acquiring the infection in Bangladesh. During the outbreaks, patients in villages 20 to 40 km away from the epicenters of the outbreaks were admitted with serological-proven Nipah encephalitis, showing that the virus was more widespread than previously thought. Clinically, the patients in Bangladesh did not have segmental myoclonus, a feature seen in more than half of the patients in Malaysia.[36,37] On magnetic resonance imaging (MRI) of the brain, Bangladeshi patients with acute Nipah encephalitis did not show evidence of vasculitic lesions, another well-described features among the Malaysian patients, even the asymptomatic ones.[36,46,47]

The widespread distribution of Nipah disease in Bangladesh and the absence of Nipah host importation from Malaysia suggest that the virus

is indigenous in Bangladesh. The dissimilarities in clinical and MRI features, the ease of bat-to-human transmission and human-to-human transmission, which were shown not to be so in Malaysia, may suggest differences in the Nipah virus found in Bangladesh from that which was first discovered in Malaysia. The recurring outbreaks over vast part of Bangladesh could mean that the virus is endemic in Bangladesh, and are likely to cause more human infections in future.

SUMMARY

Central nervous system infections in Asia show distinctive features from other parts of the world. The differences in the underlying microbiologic cause in bacterial meningitis, an infection which otherwise has been shown to have relatively uniform causes throughout the world, demonstrate that findings from elsewhere cannot be generalized to Asia, and spell a need for original research into the causes of infections here. The rapidly spreading of previously well established infections, such as Japanese encephalitis and enterovirus 71 illustrates how rapidly epidemiology may change. The emergence and reemergence of new infections warns us that sudden, yet deadly outbreaks of serious infection may occur any time, such as that of Nipah encephalitis. The emergence of Nipah virus over the past 4 years in Bangladesh also means that the virus is likely to be endemic in Bangladesh, and its distribution is wider than previously thought. On the other hand, there is a dearth of epidemiological data from this region, especially for viral meningitides and encephalitides. This calls for more epidemiology studies, disease surveillance programs, and cooperation between centres to better characterize the transmission cycles, clinical features and managements of central nervous system infections.

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