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Preliminary Report of Encephalitis Surveillance Study in Rajshahi Medical College Hospital

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Abstract

More than 100 different viruses, bacteria, toxins and drugs can cause acute encephalitis. A prospective, hospital-based study to define the causes of encephalitis in Bangladesh began in June 2003. At Rajshahi Medical College Hospital in one year 105 out of 391 suspected encephalitis patients were enrolled. The specimens were collected from these patients and were tested for a variety of pathogens at twelve laboratories at the Centers for Disease Control and Prevention (CDC) in Atlanta and Ft. Collins, USA. Among the first 105 patients enrolled, the median age of the patient was 18 years; 55% were male. Twenty-four percent (n-25) died in hospital or before completing the follow-up. Thirteen out of 105 (12.38%) patients had Japanese encephalitis; three of the encephalitis patients had a positive test result of having recent infection with dengue virus and one had encephalitis due to alpha virus, another patient had encephalitis due to echovirus. Three (2.8%) were polymerase chain reaction (PCR) or culture positive for *Streptococcus pneumoniae*, and 4 for *Mycoplasma pneumoniae*. No Nipah virus infection was identified among the first 105 serum samples tested. These data suggest that Japanese encephalitis virus is an emerging cause of encephalitis in northern part of Bangladesh.

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Introduction

Acute encephalitis, a severe neurological syndrome, remains a significant public health problem worldwide. More than 100 different viruses, bacteria, toxins and drugs can cause acute encephalitis.[1] The likely pathogens in encephalitis are dramatically influenced by geographic location, traveling history, animal exposures and vaccination.[1] Each year, thousands of patients are diagnosed with viral encephalitis[2]. Amongst them Japanese encephalitis (JE) although under-reported[2] is a serious public health problem with significant morbidity and mortality.[1] An estimated

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50,000 cases and 15,000 deaths (5-35% case fatality rate) and a 75% JE-related disability are annually reported from Asia.[3] Most JE virus infections are mild or apparently symptomless.[2] Only about 1 in 300 infections results in disease, and there is a wide range of presentations from a simple febrile illness to a severe meningo-encephalitis, as well as a newly recognized polio-like acute flaccid paralysis.[4] The virus is transmitted in a zoonotic cycle among mosquitoes and vertebrate-amplifying hosts, chiefly pigs and wading birds. The mosquito vector of JEV differs and it has been isolated from Culex, Anopheles, and Mansonia mosquitoe[5]. Intensification and expansion of irrigated rice production systems in South and South-East Asia over the past 20 years have had an important impact on the disease burden.[3] As Japanese encephalitis is the common mosquito-borne viral encephalitis found in Asia, so there is a strong possibility of patients in Bangladesh suffering from encephalitis being infected by Japanese encephalitis Virus.

But the epidemiology of encephalitis has recently been complicated by a superimposed encephalitic virus previously unidentified.[6] Five outbreaks of Nipah encephalitis are reported from different parts of Bangladesh since 2001 to 2005 where mortality rate was 60-74%[7,8,9] During this five outbreaks 11 sporadic cases were also identified.[10]

Though existence of dengue fever/dengue haemorrhagic fever (DF/DHF) caused by dengue viruses is widespread in South-East Asia Region and its documented occurrence in Bangladesh is known since 1965, and in 2000 epidemic of dengue was identified.[11, 12,13,14] Encephalitis or direct involvement of the brain by dengue virus was thought to be unlikely. But occasionally evidences of neuro-virulent property of the virus have been documented.[15] Considering this situation question arises whether there may be some patients suffering from encephalitis caused by Dengue.

In this preliminary report results of Rajshahi Medical College Hospital will be mainly focused. Though the study is ongoing and the result is preliminary and partial but it gives the reflection of the epidemiology and etiology of encephalitis in northern and western part of Bangladesh.

Patients and Methods

A prospective, hospital-based study to define the causes of encephalitis in Bangladesh began in June 2003. Every fourth encephalitis patient admitted to Dhaka, Mymensingh and Rajshahi Medical College Hospitals who met the case definition of fever ($T \geq 38^0C$), hypothermia ($T \geq 35^0C$), or history of fever during present illness, indication for a lumber puncture (LP), pleocytosis (>4 cells/mm^3 of cerebrospinal fluid [CSF]), and onset of neurological illness within five days of hospitalization was recruited for the study. Those patients who fulfilled the clinical case definition as well as they themselves or their guardians providing informed consent were enrolled for the study from Rajshahi Medical College Hospital. Clinical and epidemiological data were collected for every patient from the patient him/herself or from the caregiver of the patient along with serum, CSF, saliva, oropharyngeal swabs, urine, and stool sample. Patients were also interviewed at a follow-up visit four to six weeks after recruitment into the study to evaluate short-term neurological and functional outcome and to collect a convalescent serum sample. The specimens were tested for several pathogens at twelve laboratories at the Centers for Disease Control and Prevention (CDC) in Atlanta and Ft. Collins, USA, including alpha viruses, flavi viruses, entero viruses, herpes viruses, influenza, measles, mumps, rubella, Nipah virus, rabies virus, respiratory syncytial viruses, rickettsial agents, and by 16S ribosomal testing for bacterial meningitis.

Results

From the beginning of the study to 10 June 2004, 105 out of 391 patients with symptoms and signs of encephalitis were enrolled. Among them 58 (55%) were male and 47 (45%) were female patients; the mean age of the recruited patient was 20 with a standard deviation of (± 14.65) and the median was 18 years. Twenty-four percent (n=25) died in hospital or before completing follow-up. Half (52%) of the patients were illiterate and a quarter of the patient had primary education. Eighteen percent of these patients were farmer, 29.5% student, 19.1% housewife, 24.8% unemployed and 9% were engaged in other

occupations. Two third (67%) of the patient were poor (monthly income <3000 taka) and the rest of them (32%) belonged to the middle class (earning 3000-6000 taka) of the society. Although the result is partial, it reflects a great diversity as thirteen (13) for JE, three (3) for dengue, one (1) for alpha and one (1) for echovirus were positive. Some patients (3 for streptococcus and 4 for Mycoplasma) were suffering from bacterial meningitis or meningo-encephalitis as well. Case fatality rate was 15% (n=13).

Japanese encephalitis testing was performed to all the serum samples collected from the patients enrolled: 13 out of 105 {12.38% (8 were recently infected, 5 had previous infection and 1 was doubtful} patients had Japanese encephalitis infection demonstrated by a four-fold rise in virus-specific antibody detected in paired acute and convalescent sera by enzyme-linked immunosorbent assay and validated by ruling out dengue through enzyme-linked immunosorbent assay testing and subsequent plaque reduction neutralization testing for virus specificity of the antibody. The mean age of these patients was 21.93 (sd±9.60) and the median was 22 ranging from 8 years to 40 years. Seven (7) patients were male (54%) and 6 were female (46%) patients. Most of the Japanese encephalitis patients resided in Rajshahi (n=4), Chapai Nawabganj (n=4) and Naogaon district (n=3), and other two patients came from Natore and Pabna district. But the incidence of Japanese encephalitis patients was highest (30%) in Naogaon among all the five districts. No patients with Japanese encephalitis had a history of travel outside Bangladesh within 30 days prior to onset of illness.

Three of the encephalitis patients had evidence of a recent infection with dengue virus, i.e. a four-fold rise in dengue virus-specific antibody in paired acute and convalescent serum samples measured by enzyme-linked immunosorbent assay and confirmed by testing virus specificity. One had encephalitis due to alpha virus and another had the disease caused by echovirus.

Among the 105 CSF samples evaluated, 3 (2.8%) were polymerase chain reaction (PCR) or culture positive for *Streptococcus pneumoniae*, and 4 for *Mycoplasma pneumoniae*. There were no Nipah virus infections identified among the first 105 serum samples tested.

Discussion

This study suggests that Japanese encephalitis virus is an emerging cause of encephalitis in Bangladesh. Because JE is endemic in many countries of Asia[3] and outbreaks occur frequently in 14 Asian countries, as a consequence a total of about 3060 million people live at risk of infection[16] and about 50,000 cases and 15,000 death are reported every year for this entity.[17] Recently the disease has been spreading to other non-Asian regions; in 1995 to Torres strait islands[18] and in 1988 to the Australian mainland.[19] Japanese encephalitis tends to be endemic, and cases occur sporadically throughout the year with a peak after the start of the rainy season.[20] In South-East Asia the virus is transmitted by (C*ulex tritaeniorhynchus* and *Culex vishnui* groups of mosquitoes, which breed particularly in flooded rice fields[21]. Mosquitoes are unavoidable in rural Asia as a result almost everyone becomes exposed to the virus.[16] The flooding of the fields at the start of each cropping cycle leads to an explosive build-up of the mosquito population. This may cause the circulation of the virus to spill over from their usual hosts (birds and pigs) into the human population. Bangladesh is a low lying agro-based (30% of GDP is earned and 60% of the labor force are employed to agriculture sector) geographic area which posses all the criteria of being a JE endemic country but Japanese encephalitis infection has not been recognized in Bangladesh since an outbreak in 1977 Madhupur near Mymensingh[13]. No new cases were documented in that area for two years following the outbreak. So, the outbreak was thought to be due to local introduction of the virus from an endemic area. Most of the Japanese encephalitis cases in the current study were found in Rajshahi Division mainly from three districts, which are bordered by the areas of India where Japanese encephalitis virus is endemic. For example, in West Bengal several percentage of patients were found with JE infection in a surveillance study conducted from 1996-1999.[22]

In Rajshahi though the occurrence of DF/DHF is negligible, 3 of the patients had serological evidence of acute dengue infection, which coincided, with their episode of clinical encephalitis. It is still not clear whether dengue was the cause of the encephalitis or not. Further evaluation of these patients' CSF for dengue virus or dengue antibodies is planned.

Bacterial meningitis was not common in our recruited patients. In the current study 3 patients were found suffering from meningitis caused by *Streptococcus pneumoniae*, and 4 from meningitis due to *Mycoplasma pneumoniae*; none of the patient had meningococcal meningitis. Though the June 2004 issue of the *Health and Science Bulletin*, ICDDR, B has reported that patient of meningococcal meningitis has dramatically increased in the past five years.[23] This result suggests that, *Neisseria meningitides* may be confound to Dhaka and its surroundings but not common in Rajshahi. Again one thing that draws attention is, presence of *Mycoplasma pneumoniae* meningitis because the organism as well as the disease is not a usual one and two of the patients who were positive for Mycoplasma were also positive for JE as well.

Though recent outbreaks of Nipah virus (a paramyxovirus, first identified in Malaysia; closely related to Hendra virus) in Bangladesh has complicated the picture of the disease and we also expected Nipah encephalitis patients, but no Nipah virus infection was identified in the first 105 serum samples tested. One possible explanation is that Nipah patients did not meet the study inclusion criterion of pleocytosis. During recent Nipah outbreaks, only 50% of laboratory-confirmed Nipah patients who received a lumbar puncture had evidence of pleocytosis in the CSF (ICDDR, B: unpublished data).[24]

There are no difference of Japanese encephalitis patients and other encephalitis patients regarding age, sex, education, occupation and income. These suggest that male and female are equally susceptible to the disease. However, Surveillance for encephalitis is an ongoing study and part of the preliminary result is published here. The result is partial because we do not have the results of those specimens tested in Thailand till now. Again results for all the samples cannot be provided as there is logistic difficulty in transportation of specimens and there are some entities of the diseases of which we are not aware.

In Bangladesh, the diagnostic facilities for viral encephalitis are limited. Rapid diagnosis and early treatment of viral encephalitis are vital to reduce mortality and disability. Specific treatment is available for certain viral encephalitis, but for others like JE or Nipah only supportive therapy is available. Control must be based on rapid recognition of early cases, subsequent immunization of persons or animals at risk, or immunization of persons or animals with the potential to be at risk, such as travelers, laboratory personnel, and attending clinicians should be given priority.

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