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EDITORIAL

Viruses and "epidemic brain attacks": new agents, new challenges

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The last decade has seen a surge of interest in viral infections amongst neurologists everywhere. This has been prompted by outbreaks of viral encephalitis in many regions of the world associated with high case fatality and morbidity.

The first was an outbreak of Enterovirus 71 (EV71) in 1997, in the state of Sarawak in Malaysia (1). This was followed in the next year by a larger outbreak in Taiwan (2). During these outbreaks children developed acute pulmonary edema and many died with hours of admission to hospital. Postmortem showed brainstem encephalitis and normal cardiac muscle (3). A pathogenesis similar to what was seen in polio outbreaks in the fifties was postulated to be the cause of neurogenic pulmonary edema in these children (4). As yet no satisfactory treatment is available for these cases, once pulmonary edema has set in.

Just as the region was recovering from the shock of EV71, in September 1998 another state in Malaysia experienced an outbreak of encephalitis. This time the victims were adult pig handlers. A new paramyxovirus, the Nipah virus, named after the village, Kampong Sungai Nipah, where the first outbreak occurred, was discovered and shown to the causative agent. This virus was then traced to flying foxes. These bats had fed on the fruits above the pigsties which, when they fell to the ground, were fed to the pigs. The pigs developed respiratory symptoms and in turn transmitted the disease to the animal handlers. The humans rapidly developed an encephalopathic illness with a 40% case fatality rate (5).

Meanwhile, across the globe, New York City experienced an outbreak of West Nile encephalitis. This virus, thought to originate from birds in East Africa, caused fatal illness both in avian species and humans in New York. In subsequent years the virus spread sequentially to most parts of North America. The pattern of illness also changed to include acute flaccid paralysis (6).

In this issue of the journal yet another virus is implicated in neurological disease. Rao et al. (7) from Andra Pradesh in India report on what is probably the first epidemic of stroke, or "brain attack". This epidemic appears to be epidemiologically linked with Chandipura virus (CHPV) (7). Three hundred and twenty two cases of stroke, or "brain attack" were seen over a period of 73 days, of whom 55 fulfilled the inclusion criteria for their study. Both groups had a high fatality rate, 177 (55%) of 322 cases and 28 or 51% of their selected sample.

What is particularly interesting about the report by Rao et al. (7) is that the children who developed neurological complications of the disease did not have any evidence of direct central nervous system (CNS) invasion of the virus as shown by normal cerebrospinal fluid (CSF) analysis. The actual interval between infection with CHPV and the onset of neurological signs and symptoms appears to be uncertain. Although the authors mention a 2 day interval between a heavy rain after a hot summer and the onset of cases, their cases spanned a period of 73 days and were all confined to the same state where presumably the rainy season would have started at the same time.

Neurological involvement appears to have been limited to the middle cerebral artery (MCA), either unilaterally or bilaterally. Computerized tomographies done early (<1 day) were normal, as were 82% of those done late (>6 days). The majority of patients (28/55) either died, apparently from complications of raised intracranial pressure, or recovered fully (23/55). However four children developed persistent hemiplegia on follow-up and their follow-up magnetic resonance imaging showed evidence of established ischemic damage confined to the corresponding MCA territory. This implies that the children were exposed to the full range of vascular involvement from near total occlusion leading to sufficient cerebral edema to cause death

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to fully reversible ischaemic events.

Many possibilities come to mind. Was the involvement of the MCA due to a vasculitis induced by CHPV? Such a mechanism has been postulated for both varicella infection and Mycoplasma pneumonia infections (8,9). The reversibility of the edema demonstrated both clinically and radiologically in some cases make thromboembolic events precipitated by infection less likely as the sole pathogenetic mechanism. These are, generally, more common in bacterial infections. However viral illness either in conjunction with underlying metabolic disorders or thrombophilic tendencies may cause thromboembolic phenomenon. The authors have attempted to address these concerns.

As not all the inflammatory mediators (10) implied in the pathogenesis of stroke in acute inflammation have been excluded, this remains a likely explanation for those children who succumbed to the illness.

As the authors rightly point out stroke is now considered an inflammatory process and recent infection has been shown to be an independent risk factor for stroke especially among the young (10,11). They go on to postulate that there was direct viral invasion of the middle cerebral artery presumably causing endothelial damage, spasm or both. Such a mechanism has not been previously postulated in stroke. In cases of varicella zoster encephalitis with large or medium vessel vasculopathy, distinctive Cowdry-A intranuclear viral inclusions are rare (12).

Cytokine and chemokine mediated inflammation induced by infection is now thought to be a major cause of perinatal stroke especially in near term babies (13). Such a mechanism is still possible in this series, given the absence of CSF changes of acute encephalitis. Unfortunately no post mortems were available to help us resolve this issue.

As the authors have pointed out, CHPV has been present in India at least since 1955, so why is it now causing an epidemic of "brain attacks"? They speculate the possibility of a second virus playing a role in the pathogenesis of stroke in these children. This has also been postulated to be the reason for the EV71 outbreak in Sarawak when adenovirus was isolated from the myocardium of fatal cases. The presence of the adenovirus is thought to have modified the virulence of EV71 (14).

Another very interesting and indeed very useful observation, was the efficacy of mannitol in reversing the raised intracranial pressure and improving outcome. Mannitol is easily available in most district hospitals of the developing world, and this observation will allow doctors in the periphery to initiate treatment prior to transferring children to larger centers. Mannitol has many postulated modes of action including being a scavenger of free radicals. It has been shown to attenuate increase in regional cerebral blood flow in experimental meningitis (15). More recently it has been shown to ameliorate the EEG changes in acute stroke (16). Recent reviews on the management of arterial ischemic stroke have tended to concentrate on low molecular weight heparin and tissue thromboplastin activator (17). Both of these are not readily available in many centers. Although the data on mannitol was not subjected to statistical analysis, the results of this report will hopefully rekindle interest in the use of osmotic agents in childhood stroke.

As they have themselves observed, the report of Rao et al. (7) raises many issues in the pathogenesis and treatment of "brain attacks" associated with viral illness. These will have to be addressed systematically, hopefully before the next virus causing neurological disease surfaces.

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