Encephalitis: recent advances and challenges ahead

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Introduction

Coma accompanying fever, which now would be termed encephalitis, was described by Sydenham as early as the 17th century, although associations between fever and brain dysfunction were recognised even earlier.[1] Since then, much progress has been made in understanding the causes, biological mechanisms, epidemiology and treatment of encephalitis; however, numerous gaps still exist in our knowledge: there is still a long way to go.

One reason for the increased interest in encephalitis is the recognition that it is a sentinel condition for new and emerging infections (Table 1). Consequently numerous national studies have been implemented in different continents to investigate its aetiology and epidemiology.[2-5] The recent discovery of antibody-associated forms of encephalitis has given added impetus to this effort. Other reviews have described what is already known about encephalitis.[6,7] This paper will focus on the challenges faced in studying encephalitis and recent advances of direct clinical relevance that have occurred in the field.

Importance

Although considered a rare syndrome in resource-rich settings, the incidence of encephalitis is likely to be higher than previously estimated. It was estimated that only 700 cases of encephalitis occur per year in England;[8] however, new data suggest that this is an underestimate and that the occurrence of encephalitis is substantially higher (Granerod et al., submitted). Outcomes remain poor: over one-third of encephalitis patients recruited to a multicentre prospective study of encephalitis in England either died or were left with severe disabilities.[2] The median age of patients in this study was only 30 years; 34% of cases occurred in children <18 years of age. Other studies have shown similarly poor outcomes. In a contemporary French study 10% of patients died in the acute phase of the illness.[3] After three years follow-up of 167 surviving patients, a further nine patients had died of encephalitis-related causes and 15% were severely impaired or in a vegetative state.[9] It is estimated that ~70,000 cases of Japanese encephalitis (JE), considered the most important of the viral encephalitides in Asia, occur annually in the 24 JE-endemic countries.[10] This is predominantly a disease of children; approximately 20–30% of cases are fatal and 30–50% of survivors have significant neurological sequelae.[10] Survivors who make a seemingly good recovery are often left with milder impairments that impact upon quality of life. Encephalitis has significant implications not only for patients directly but also wider economic and public health implications.

Current problems

Encephalitis is challenging to diagnose, manage and study. It is a syndrome of multiple aetiologies and pathogeneses. Pathogenetic mechanisms for the parenchymal inflammation of encephalitis range from direct infectious to immune-mediated; however, specific mechanisms within each of these groups are diverse and often incompletely understood. For example, *Mycoplasma pneumoniae* is increasingly implicated in encephalitis; however, its exact role (i.e. whether through direct infection or as a trigger for immune-mediated disease) remains controversial due to incomplete understanding of the biology of the organism and host immune response to it, and inherent limitations of its specific microbiological diagnostic test in the context of central nervous system (CNS) disease.[11-13]

Despite greater than 100 known causes, in most cases of encephalitis neither a pathogenetic mechanism nor aetiology is identified. Accurate and complete case ascertainment of encephalitis cases is made difficult by the complexity of the syndrome, difficulties in distinguishing it from non-encephalitis mimics, and the lack of standard clinical case definitions. There is no standard laboratory diagnostic algorithm for encephalitis in the United Kingdom (UK); although most laboratories test for herpes simplex virus (HSV), varicella zoster virus (VZV) and enteroviruses nucleic acid sequences in the cerebrospinal fluid (CSF) of immunocompetent patients. This practice is supported in the recently published National Guidelines for the Management of Suspected Viral Encephalitis in the UK.[14] Testing beyond this varies greatly between centres. To complicate matters further, the test specificity following detection of some viruses, such as lymphotropic herpes viruses (EBV; CMV; HHV-6), in CSF is much lower than for the neurotropic herpesviruses (HSV; VZV). For certain viruses, such as EBV, calculation of the CSF EBV viral load can be helpful: higher values are more likely indicative of aetiological significance.[15] However, one pitfall for the diagnostician and researcher is HHV-6. A minority of patients have chromosomal integration of HHV-6 DNA; such patients have consistently high levels of HHV-6 DNA in CSF, blood and plasma.[16,17] For other agents, such as West Nile Virus (WNV), detection of an acute serological response in CSF or serum provides strong evidence for causality. Although written primarily for epidemiological studies proposed diagnostic criteria for infectious aetiologies of