bodies to white matter glial or myelin antigens in acute disseminated encephalomyelitis.[29] The field of antibody-mediated CNS disease is only in gestation; more antibody-associated syndromes may yet be identified amongst the many encephalitis cases of unknown cause. Rapidity of testing for antibody-associated encephalitis will be considerably assisted with the development of commercial assays. It is hoped that these will soon be available.[29]

Other developments

The recent HPA study led to the development of published clinical and aetiological case definitions, which informed how cases were classified.[18] These present the UK perspective on aetiological case definitions for acute encephalitis; they include immune-mediated causes. Wide usage of these definitions is encouraged to facilitate better comparison between studies. They are the basis for an International Working Group that aims to determine by consensus an optimal set of criteria/case definitions to recommend for use in clinical practice, public health, and research internationally.

Within the UK a major practice development is the recent publication of National Guidelines for the Management of Suspected Viral Encephalitis in Adults and Children, briefly referred to above.[14,30] The guidance covers initial investigation of all patients with suspected acute encephalitis; it includes specific management advice for the viral encephalitides, particularly HSV, VZV and enteroviral encephalitis; as well as advice for assessment of encephalitis in the immunosuppressed and returning traveller. A management algorithm is included modelled on the successful guidance for management of suspected bacterial meningitis. It can be downloaded from: http://www.braininfectionsuk.org/resources/documents/YJINF2823.pdf.

Whilst high dose intravenous acyclovir is well established as treatment for HSV encephalitis the role of other treatments, such as steroids, are not.[31,32] There is circumstantial and animal model evidence to suggest that corticosteroids with acyclovir might improve clinical outcome in HSV encephalitis.[33] The German trial of Acyclovir and Corticosteroids in Herpes-simplex-virus-Encephalitis (GACHE) is a multicentre, multinational, randomised, double-blind, placebo-controlled trial that aims to assess the efficacy of acyclovir and corticosteroids in the treatment of HSV encephalitis; it is recruiting at present.[34]

Challenges ahead

Despite numerous advances in the field of encephalitis, many challenges remain. Cases of unknown aetiology still form the largest subgroup. Virus discovery methods, which sought to amplify nucleic acid sequences of novel pathogens, did not prove fruitful in the HPA study. However, almost a quarter of unknown cases were shown to have intrathecal synthesis of IgG, for which antigenic specificity was not found following screening against of battery of microbial antigens.[25] The presence of intrathecal IgG gives weight to an inflammatory or infective pathogenesis in these cases – they are less likely to be non-inflammatory syndromic mimics. Studying the antigenic specificity of intrathecal IgG could provide clues to the cause in these cases.[35] Future studies could use peptide libraries to seek putative antigenic targets for CSF antibodies: such a technique might reveal novel infectious or autoimmune aetiologies.

For sporadic and epidemic causes of infectious encephalitis it is not understood why only a minority of individuals exposed to an infection develop encephalitis – the majority of encephalitic patients are not immunosuppressed. Host and pathogen-related factors are likely to be important. It has been shown in horses that a naturally occurring variation in a single amino acid position of the viral DNA polymerase enzyme results in differing pathogenic potential of a herpesvirus.[36,37] Whether distinct strains of human HSV differ in their pathogenic capacity has yet clearly to be established in cases of HSV encephalitis. Host factors are increasingly implicated in encephalitis. Alleles in the innate immune effectors TLR3 and UNC93B have been identified that mediate susceptibility to herpes encephalitis in children.[38,39] Further studies to address both pathogen neurovirulence and host susceptibility could increase our understanding of the pathogeneses of encephalitis, perhaps even providing potential targets for novel treatment strategies.

The HPA study showed that rigorous and systematic laboratory testing in a prospective study reduced the proportion of cases of unknown aetiology. Now a standard diagnostic algorithm for laboratory investigation is needed incorporating testing for infectious and antibody-associated causes. Such a development should be combined with improved access to specialist diagnostic tests performed in centres participating in rigorous quality control programmes.

Research and development programmes are currently underway in the UK addressing some of these issues. A major new NIHR programme grant on "Understanding and improving the outcome of encephalitis" is being co-ordinated by the Brain Infections Group in Liverpool. Further research co-ordinated by the HPA is underway to better define associations between neuroimaging results and specific encephalitis aetiologies, and to assess specific post-encephalitic morbidities in the UK. Furthermore, multicentre prospective studies in other parts of the world, including Australia, are underway to study aetiology seeking emerging infections.

Conclusions

Encephalitis has only recently become a priority for researchers, funders and policy makers. Recent research, particularly the emerging field of antibody-mediated CNS disease, has decreased the proportion of cases of unknown aetiology. But the proportion of encephalitic patients for whom no aetiology is found remains unacceptably high. Both novel infectious aetiologies and new antigenic targets for immune-mediated encephalitis could underlie these cases. Recent advances are encouraging but there is still a way to go. ◆

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